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MEASURING REWARD WITH THE CONDITIONED PLACE PREFERENCE PARADIGM: A COMPREHENSIVE REVIEW OF DRUG EFFECTS, RECENT PROGRESS AND NEW ISSUES

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Abstract—This review gives an overview of recent findings and developments in research on brain mechanisms of reward and reinforcement from studies using the place preference conditioning paradigm, with emphasis on those studies that have been published within the last decade. Methodological issues of the paradigm (such as design of the conditioning apparatus, biased vs unbiased conditioning, state dependency effects) are discussed.

Results from studies using systemic and local (intracranial) drug administration, natural reinforcers, and non-drug treatments and from studies examining the effects of lesions are presented. Papers reporting on conditioned place aversion (CPA) experiments are also included. A special emphasis is put on the issue of tolerance and sensitization to the rewarding properties of drugs.

Transmitter systems that have been investigated with respect to their involvement in brain reward mechanisms include dopamine, opioids, acetylcholine, GABA, serotonin, glutamate, substance P, and cholecystokinin, the motivational significance of which has been examined either directly, by using respective agonist or antagonist drugs, or indirectly, by studying the effects of these drugs on the reward induced by other drugs.

For a number of these transmitters, detailed studies have been conducted to delineate the receptor subtype(s) responsible for the mediation of the observed drug effects, particularly in the case of dopamine, the opioids, serotonin and glutamate.

Brain sites that have been implicated in the mediation of drug-induced place conditioning include the 'traditional' brain reward sites, ventral tegmental area and nucleus accumbens, but the medial prefrontal cortex, ventral pallidum, amygdala and the pedunculopontine tegmental nucleus have also been shown to play important roles in the mediation of place conditioning induced by drugs or natural reinforcers.

Thus, although the paradigm has also been criticized because of some inherent methodological problems, it is clear that during the past decade place preference conditioning has become a valuable and firmly established and very widely used tool in behavioural pharmacology and addiction research.

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ABBREVIATIONS

5-HT	5-hydroxytryptamine
6-OHDA	6-hydroxydopamine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid
CCK	cholecystokinin
CPA	conditioned place aversion
CPP	conditioned place preference
DA	dopamine
GABA	γ-amino-butyric acid
ICV	intracerebroventricular
IP	intraperitoneal
IV	intravenous
mPFC	medial prefrontal cortex
NAS	nucleus accumbens septi
NMDA	*N*-methyl-D-aspartate
PAG	periaqueductal gray
PCP	phencyclidine
PPTg	pedunculopontine tegmental nucleus
SC	subcutaneous
SN	substantia nigra
SP	substance P
THC	Δ(9)-tetrahydrocannabinol
VP	ventral pallidum
VTA	ventral tegmental area

1. INTRODUCTION

The last few years have seen an enormous increase in published studies using the conditioned place preference (CPP) paradigm (Fig. 1). Several reviews of this literature have been published over the years, but since the number of studies employing this paradigm is still increasing from year to year, a new survey of this literature seemed warranted.

Two comprehensive and now widely cited reviews of the literature on CPP were published in 1989 (Carr *et al*., 1989; Hoffman, 1989). A cross-indexed bibliography covering the literature until 1991 became available in 1993 (Schechter and Calcagnetti, 1993), and a meta-analysis of data for opiate and stimulant drugs was published in 1995 (Bardo *et al*., 1995b). Other reviews on the topic of CPP can be found in Bozarth (1987b), van der Kooy (1987), White *et al*. (1987) and Calcagnetti *et al*. (1995), and a number of further reviews also make reference to place conditioning experiments (Beninger *et al*., 1989; Beninger, 1989; Beninger and Miller, 1998; Franklin, 1998; Koob *et al*., 1989; Ettenberg, 1989; Altman *et al*., 1996; White, 1996; Nader *et al*., 1997; Stolerman and Shoaib, 1991; Wise, 1989; Self and Stein, 1992; Bardo, 1998; Witt, 1994; Shaham, 1996; Phillips and Fibiger, 1990; Carney *et al*., 1991). The reader is referred to these publications for overviews of the older literature and for detailed discussions and considerations of

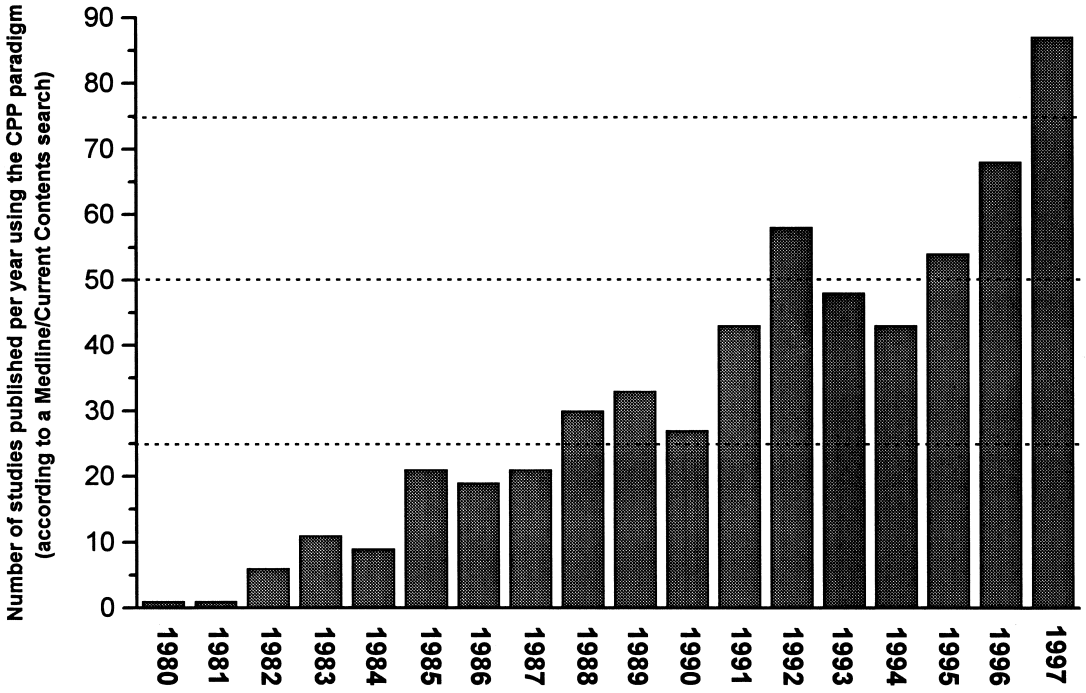

Fig. 1. This figure shows the number of published studies per year that have used the place preference conditioning paradigm to assess the motivational properties of drugs and other treatments. The figure illustrates the steady increase of the number of studies using place conditioning procedures from year to year and also demonstrates the considerable amount of data that has accumulated since the publication of the last comprehensive reviews in 1989. The numbers are based on a Medline/Current Contents search with 'place preference', 'place aversion' and 'place conditioning' as search terms.

basic methodological issues of the CPP paradigm (see in particular Carr *et al*., 1989; Bardo *et al*., 1995b) which will largely be omitted from the present review.

This review will give an overview of new methodological approaches and of new findings about anatomical and neurochemical aspects of reward- and reinforcement-related mechanisms in the brain. It will focus primarily on the studies of the last decade, but if necessary to provide the context, older studies will be included as well. No attempt will be made to provide a complete bibliography including every single study that has employed the place conditioning approach, but the intention of this article is to give a comprehensive review of those studies that have used the paradigm to explicitly test the motivational effects of drugs or non-drug treatments or the effects of lesions or genetical manipulations on brain reward mechanisms. In those instances where inconsistent results have been reported, attempts are made to resolve these discrepancies and to provide explanations for the contradicting results. A concluding chapter will provide a synthesis of those findings that have been reported consistently across different studies and tries to highlight the neurochemical and anatomical foundations of brain reward mechanisms as far as this knowledge has been derived from place preference conditioning studies reviewed in this paper.

2. METHODOLOGICAL ISSUES

2.1. The Conditioning Principle

In the place conditioning paradigm, the primary motivational properties of a drug or non-drug treatment serve as an unconditioned stimulus (UCS) that is repeatedly paired with a previously neutral set of environmental stimuli which acquire, in the course of conditioning, secondary motivational properties such that they can act as conditioned stimuli (CS) which can elicit approach (or withdrawal, if the primary motivational properties of the treatment were aversive) when the animal is subsequently exposed to these stimuli.

Although some conceptual problems do exist, the mechanisms determining place conditioning appear to follow the principles of classical (Pavlovian) conditioning. This is manifest, for example, in context-dependent blocking/unblocking effects (McKee *et al*., 1994), and in the fact that CPP can show extinction when the animals are repeatedly exposed to the CS in the absence of the UCS (Calcagnetti and Schechter, 1993a; Tzschentke and Schmidt, 1995; Hughes *et al*., 1995; Hinson *et al*., 1993; Bardo *et al*., 1986). There is also some evidence for within-session extinction during the test for CPP (Cunningham *et al*., 1995). This property might make the CPP paradigm a potentially useful tool to test drugs for anti-craving activity, since the extinction of drug-associated conditioned cues, which are presumed to be largely responsible for craving and relapse in drug-free former addicts, and the effects of drugs on this extinction, could be easily examined in place conditioning experiments.

A first-order CPP (with a place/context as the CS) can also serve as the basis of a second-order conditioning procedure to produce second-order taste-preference conditioning (with a taste as the new CS), and vice versa, a first-order conditioned taste aversion (CTA) can be the basis of a second-order CPA (Stefurak *et al*., 1990).

2.2. Design of Conditioning Apparatus

By far the most CPP studies used either two- or three-compartment conditioning boxes (in the latter design, a third, 'neutral' compartment usually serves as a connection between the two conditioning compartments and is used as a 'start box'). However, a number of studies have explored the properties and utility of novel conditioning apparatuses (Vezina and Stewart, 1987a,b; Cabib *et al*., 1996). Vezina and Stewart (1987a,b) used open fields to pair morphine or saline with different tactile cues of the open field floor. During conditioning, all four quadrants of the open field had the same texture. During the test the open field floor consisted of different proportions of quadrants with the two textures that had been paired with morphine or saline, and time was measured that the animals spent in the quadrants with the morphine-paired floor. It was demonstrated that under these circumstances the animals will exhibit a strong preference for the morphine-paired tactile cues.

A concern about CPP experiments is to what extent reaction and habituation to novelty (which might be differentially affected by different drugs) influences the outcome of the conditioning experiment (Reid *et al*., 1989). To examine the relative role of novelty, Parker (1992) employed a three-choice apparatus, with one compartment that was paired with a rewarding drug, one compartment that was paired with saline and one compartment to which the animals were never exposed until the test day. During the test, the animals preferred the compartment paired with amphetamine, morphine or apomorphine over both the novel and the saline-paired compartment. However, they also preferred the novel compartment over the saline-paired compartment. These results indicate that if a drug blocks the habituation to novelty during conditioning, this effect might contribute to the CPP observed subsequently in the drug-free test. A three-choice apparatus was also used to assess the relative strength of morphine- and cocaine-induced CPP (Parker *et al*., 1994). With this approach it was shown that short conditioning sessions yielded a relative preference for cocaine, while longer conditioning sessions produced a relative preference for morphine, an effect which is probably due to the different pharmacokinetics of both drugs (Parker *et al*., 1994). These studies show that a multi-choice apparatus can be useful to assess and compare the *relative* potency of different treatments. A multi-choice conditioning apparatus was also described by Hasenöhrl *et al*. (1989), who used a circular open field consisting of four separated uniform quadrants.

CPP experiments usually involve test-sessions with a duration of 15–20 min. The sojourn times of the animals in the different conditioning compartments are determined either by direct observation, which is very time-consuming, or by automated monitoring systems, usually based on photo-cell beam devices. Attempts have been made to improve these automated systems and to collect additional information during the experiment, primarily with respect to locomotor activity (Brockwell *et al.*, 1996).

2.3. Biased Vs Unbiased Design, Conditioning to Preferred Vs Non-Preferred Side

A conditioning apparatus can be designed such that naive animals do not show a significant preference for one of the conditioning compartments upon initial exposure ('pretest') (unbiased design), or it can be designed such that the animals show an unconditioned preference for one side over the other (biased design). In the latter case, drug administration can be paired with exposure of the animals to either the preferred or the non-preferred compartment, or the pairing can be counterbalanced, such that for half of the animals the treatment is paired with the preferred compartment, while for the other half of the animals the treatment is paired with the non-preferred compartment.

In general, a trend can be observed over the years to prefer unbiased experimental designs rather than biased designs. The biased design has often been criticized because it is susceptible to yielding false-positive results in place conditioning experiments, for example if a drug has a strong anxiolytic component that could overcome the initial aversion for the non-preferred compartment, thus increasing the preference scores for that particular compartment. However, this argument is only valid as long as a treatment only produces a relative increase in the preference for the initially non-preferred side, without producing an absolute preference (e.g. Papp and Moryl, 1994). But if, with the biased design, a genuine, absolute preference for the initially non-preferred side is obtained (e.g. Tzschentke and Schmidt, 1995), this effect cannot be explained solely by anxiolytic actions of a treatment, although such actions might contribute to the observed effects. Nevertheless, as mentioned above, researchers now seem to tend to prefer the unbiased design in order to circumvent the interpretational problems outlined in this paragraph.

Schechter (1995) demonstrated that, using a biased design, cocaethylene produces a CPP only when paired with the initially non-preferred side, but not when paired with the initially preferred side. The same was found for IP cocaine (but not IV cocaine) (Nomikos and Spyraki, 1988b), SC heroin (Schenk *et al.*, 1985) and for IP clonidine (Cervo *et al.*, 1993). For IP [Leu]enkephalin it was reported that it produced a place preference when paired with the initially non-preferred compartment, but a place aversion when paired with the initially preferred compartment (Heinrichs and Martinez, 1986). A dependence of the magnitude of CPP on the baseline preference of the animals was also reported for amphetamine (Costello *et al.*, 1989). This suggests that the biased, non-balanced design may be useful to detect motivational effects of a drug that depend on the motivational baseline or state of the animal, provided that appropriate controls are included, e.g. by pairing the drug with the preferred and the non-preferred compartment in different groups of animals, and by including appropriate saline controls (see Scoles and Siegel, 1986). Thus, use of the biased design may be useful to detect anxiolytic and anti-aversive effects of drugs independently from potential genuine rewarding effects.

2.4. Route of Drug Administration

Mayer and Parker (1993) showed that only IP cocaine, but not SC cocaine produced CPP, a finding that is in line with the results of the meta-analysis by Bardo *et al.* (1995b) who found that IP cocaine generally yields larger CPP effects than SC cocaine. In stark contrast to this, Durazzo *et al.* (1994) reported that both IP and SC cocaine produced CPP, and that the minimum IP dose necessary to elicit CPP was 10 mg/kg, while the minimum SC dose was only 0.32 mg/kg, suggesting that SC cocaine was extremely more effective in producing CPP than IP cocaine. Nomikos and Spyraki (1988b) have demonstrated that IV cocaine is more than 10 times more potent than IP cocaine in producing CPP. Differences in the effectiveness between IV cocaine and IP cocaine were also reported by O'Dell *et al.* (1996). Oral intake of cocaine (either as self-administered bolus doses or as schedule-induced drinking of cocaine solution) also produced CPP (Seidman *et al.*, 1992). It is interesting to note that the studies reporting big differences in effect size between different routes of administration have all used cocaine, a drug with extremely rapid pharmacokinetics.

2.5. Time Effects

The relative time sequence of drug administration and conditioning session can have a big effect on the outcome of the conditioning experiment. For example, it was shown that while amphetamine or nicotine injections immediately before the conditioning sessions produced CPP, amphetamine or nicotine injections just after the conditioning sessions ('delay conditioning') (Fudala and Iwamoto, 1987, 1990; Wall *et al.*, 1990), or injection of amphetamine 15 min after placing the animals into the conditioning context (Hinson *et al.*, 1991), produced CPA.

CPP experiments usually involve a number of lengthy conditioning sessions. Therefore it is of considerable practical interest to employ experimental protocols that reduce the time needed for conducting CPP experiments without reducing the value and significance of the data. An obvious way to reduce the time needed for an experiment is to reduce the number of conditioning trials. Another approach is to conduct two conditioning sessions per day, not just one as is most commonly the case. This approach has been used by some authors (e.g. Calcagnetti and Schechter, 1992a; Tzschentke and Schmidt, 1997; Bolanos *et al.*, 1996) and it has been

generally reported that this procedure generates the same results as procedures involving only one conditioning session per day, both qualitatively and quantitatively. It should be noted, however, that great care should be taken to make sure that the drug effect from the previous session does not carry over to the next session. Even with several hours between two sessions, this could easily be the case with longacting drugs such as morphine (especially since acute withdrawal effects, following the acute (positive) drug effects, also have to be taken into account), particularly when counterbalanced injection schemes are used.

2.6. State Dependency

State-dependent learning, or state-dependent retrieval, refers to the fact that a knowledge or response that has been learned or acquired while the animal was in a certain (drugged) state, can only be retrieved or reproduced when the animal is in that same state, but not when in a different state (Overton, 1978; Weingartner, 1978). The possibility that state-dependency effects might influence the outcome of place conditioning experiments is obvious, since the animals are conditioned in a certain (drugged) state, but are tested for CPP in an undrugged state in most cases.

Only relatively few studies have addressed the question of whether state-dependency effects are responsible for the expression, or rather, for the absence of expression, of CPP. Nomikos and Spyraki (1988b) have tested rats conditioned with cocaine both in the undrugged and in the drugged state and found no difference between both groups with respect to the expression of cocaine-induced CPP. Spyraki *et al.* (1985), however, reported that the picrotoxin-induced CPA was state-dependent. Tzschentke and Schmidt (1997) showed that the blockade of morphine-induced CPP by the non-competitive NMDA-antagonist MK-801 was not due to state-dependency effects, an assumption that was suggested by the fact that NMDA-antagonists can make learning and recall state-dependent (Jackson *et al.*, 1992; Carlezon *et al.*, 1995). Evidence for state-dependency effects in place conditioning was reported by Laviola and Adriani (1998). They conditioned mice with amphetamine (2 or 10 mg/kg) to one side of a shuttle box, without alternating exposure to the other side to maintain the novelty of that side. When the animals were tested after saline injection, they showed a preference for the novel side over the amphetamine-paired side. However, when tested after the injection of amphetamine (2 mg/kg) the animals that had been conditioned with the low dose of amphetamine showed a preference for the drug-paired side while the animals that had been conditioned with the high dose of amphetamine preferred the novel side. Thus, the relative preference produced by 2 mg/kg amphetamine and the relative aversion produced by 10 mg/kg amphetamine (relative with respect to novelty) was only expressed while the animals were under the influence of the conditioning drug. Olmstead and Franklin (1997a) found state-dependent morphine-induced CPP in animals bearing lesions of the periaqueductal gray (PAG) or the fornix, indicating that not only drugs but also lesions of certain brain areas can produce state-dependency effects. Tzschentke and Schmidt (1998c) showed that lesions of the infralimbic subarea of the medial prefrontal cortex (mPFC) blocked the CPP induced by morphine and the competitive NMDA receptor antagonist CGP 37849. In this case, the absence of CPP was also evident when the animals were tested after injection of the respective drug, indicating that the observed blockade was not due to state-dependency effects. But as mentioned above, in general, only few studies have controlled for state-dependency effects by testing the animals under the same treatment under which they were conditioned (e.g. Elliott, 1988; Oberling *et al.*, 1993).

2.7. Latent Inhibition

In the present context, latent inhibition refers to the fact that prior exposure to the to-be-conditioned stimulus in the absence of the unconditioned stimulus can delay or attenuate subsequent conditioning (see Lubow, 1989). In the case of place conditioning experiments, the researcher has to find a compromise between trying to avoid latent inhibition effects by reducing the preexposure time to a minimum and trying to avoid influences of anxiety or neophobia on the treatment effects by extensively habituating the animals to the conditioning environment.

Consistent with this notion, Martin-Iverson and Reimer (1996) have shown that the amount of preexposure (habituation) can indeed influence the outcome of a CPP experiment, and in their meta-analysis, Bardo *et al.* (1995b) have found that the absence or presence of a preconditioning exposure can have a significant influence on the magnitude of the observed conditioning effects, such that in studies without preexposure generally larger effects were observed.

2.8. The Operant Approach

As mentioned above, the CPP paradigm is based on Pavlovian conditioning principles. However, attempts have been made to introduce operant principles to place conditioning. Crowder and Hutto (1992a,b) reported on a procedure where animals received IV infusions of morphine or exposure to water or a conspecific upon actively entering a conditioning compartment rather than upon being placed in that compartment by the experimenter. A comparison of the magnitude of the conditioning effects obtained with this procedure and in a conventional 'classical conditioning' procedure showed that that operant method was somewhat more potent in producing place conditioning effects than the classical method.

2.9. The Relationship Between CPP, Response to Novelty, Locomotor Activity and Dopaminergic Neurotransmission in the Mesocorticolimbic System

Many studies cited hereafter have not only measured whether a drug or a drug combination produces CPP, but they have also measured treat-

ment effects on locomotor activity and/or on dopamine (DA) release or turnover. Although a detailed discussion of the interrelationships between CPP, locomotion and DA is beyond the scope of this review, it should be mentioned that from the majority of these studies the general picture emerges that there appears to be a very close correlation between the potential of a given treatment to induce CPP and to cause an increase in dopaminergic neurotransmission, whereas only a very weak or no correlation appears to exist between the potential of a treatment to induce CPP and the level of locomotor stimulation caused by this treatment. Put in other words, the establishment of a CPP seems to be dependent on dopaminergic mechanisms in most cases, but can occur independently of locomotor effects of a given treatment.

Individual differences in the behavioural response to novelty have been reported to be predictive for the vulnerability of an animal to acquire drug self-administration, for the magnitude of drug-induced locomotor responses, and for the expression of a number of cellular and biochemical features (see e.g. Piazza *et al*., 1989, 1991; Hooks *et al*., 1991, 1994). There have also been attempts to correlate individual differences in the response to novelty to the magnitude of drug-induced CPP. However, generally, no such correlation has been found. Thus, Gong *et al*. (1996a) reported no difference in the sensitivity of high and low responders to novelty to the CPP-inducing effects of cocaine, and a lack of correlation between locomotor response to novelty and the magnitude of amphetamine-induced CPP was also shown (Erb and Parker, 1994). On the other hand, rats that were more sensitive to the locomotor effects of amphetamine displayed a greater preference for a novel compartment (Bevins *et al*., 1997).

Another approach has been to try to correlate individual differences in the strength of drug-induced conditioned taste aversion (CTA) with the magnitude of CPP induced by the same drug. In this case, a correlation has been found for amphetamine, in that animals that showed the strongest CTA also showed the strongest CPP. However, no such correlation was found for morphine-induced CTA and CPP and for lithium chloride- and fenfluramine-induced CTA and CPA (Turenne *et al*., 1996). A correlation was also found between the magnitude of ethanol-induced CPP and the emotionality (in terms of defecation) and open field behaviour (in terms of rearing) of individual animals, such that strong defecation and little rearing was predictive for a big CPP effect (Nadal *et al*., 1992).

2.10. Definitions, Use of Words

Since the majority of studies has examined the influence of drug or treatment effects on the *acquisition* of CPP or CPA, this will not be explicitly indicated in the text (i.e. 'drug A had no effect on morphine-induced CPP' is intended to mean 'drug A had no effect on the acquisition of morphine-induced CPP'). If the effects of drugs or treatments on the *expression* of CPP were examined, this will be stated explicitly in the text (e.g. 'drug B blocked the expression of amphetamine-induced CPP').

3. STUDIES USING SYSTEMIC DRUG TREATMENTS

3.1. 'Single-Drug Treatments'

3.1.1. *Stimulants, Dopaminergic Drugs*

A large number of studies have confirmed the CPP-inducing effects of amphetamine and cocaine (see references in Sections 3.2.1, 4.1.1 and 4.2.1. 5., 6., 7.). While almost all of these studies have used adult rats or mice, cocaine-induced CPP was also demonstrated in 10- and 17-day-old rats (Pruitt *et al*., 1995), in 3-week-old mice (Laviola *et al*., 1992), in young chickens (Hughes *et al*., 1995) and in rhesus monkeys (Foltin and Evans, 1997), and amphetamine-induced CPP was shown in 2-week-old mice (Laviola *et al*., 1994). The induction of CPP by cocaine or amphetamine is regarded as so reliable an effect (under proper experimental conditions) that the induction of CPP by cocaine has been chosen as a positive control for the patency of an IV catheter construction in mice (Kelley *et al*., 1997a).

The induction of CPP has also been demonstrated for the psychostimulants and DA reuptake blockers (−)-amphetamine (Timar *et al*., 1996), cocaethylene (Schechter, 1995; Kushner, 1997), cathinone (Calcagnetti and Schechter, 1992a; Schechter and Meehan, 1993; Schechter and McBurney, 1991), fencamfamine (De Lucia *et al*., 1997; Planeta da Silva *et al*., 1995), methamphetamine (Cunningham and Noble, 1992b), GBR12783 (Le Pen *et al*., 1996), nomifensine (Martin-Iverson *et al*., 1985), methylphenidate (Clark and Fibiger, 1987; Gatley *et al*., 1996; Martin-Iverson *et al*., 1985), *p*-bromomethylphenidate and *p*-methoxymethylphenidate (Gatley *et al*., 1996), diethylpropion (albeit only at an intermediate, but not at a low or a high dose) (Planeta da Silva and DeLucia, 1998), bupropion (Ortmann, 1985), pipradrol (White and Hiroi, 1992) and mazindol (Gevaerd and Takahashi, 1996).

It was also shown that IP cocaine methiodide (which does not cross the blood–brain barrier) and IP procaine failed to produce CPP, suggesting that CPP induced by cocaine (HCl) is mediated centrally and that the local anaesthetic properties alone are not sufficient to produce a CPP (Hemby *et al*., 1994; Rigon and Takahashi, 1996). On the other hand, dimethocaine, another local anaesthetic, was shown to produce CPP (Rigon and Takahashi, 1996).

While the above studies unequivocally show that drugs that cause an increase in extracellular DA levels very reliably produce CPP, the attempts to determine the DA receptor subtype(s) responsible for mediating the DA effect have yielded somewhat inconsistent results. Thus, CPP was demonstrated for the the DA receptor agonists apomorphine (D1/D2) (Papp, 1988a; Parker, 1992; Funada *et al*., 1993), quinpirole (D2) (White *et al*., 1991; Hoffman and Beninger, 1988, 1989; Hoffman *et al*., 1988), bromocriptine (D2/D3) (Hoffman *et al*., 1988), PD-128,907 (D3) (Khroyan *et al*., 1997), U99194A (D3) (Kling-Petersen *et al*., 1995b), and (+)-AJ 76 (D2 autoreceptor) (Richardson *et al*., 1993). The D3 agonist 7-OH-DPAT was reported to produce CPP (Mallet and Beninger, 1994; Chaperon and Thiebot, 1996), to have no effect (Kling-Petersen *et al*.,

Table 1. This table summarizes the results of studies using systemic 'single-drug' treatments. See Section 3.1 in the text for details about drugs, experimental procedures and additional findings that could not be included in the table

Place conditioning induced by	Effect	References
Stimulants/dopaminergic drugs:		
Amphetamine	CPP	See text and Table 2
Cocaine	CPP	See text and Table 2
Cocaethylene	CPP	Schechter (1995); Kushner (1997)
Cathinone	CPP	Calcagnetti and Schechter (1992a); Schechter and Meehan (1993); Schechter and McBurney (1991)
Fencamfamine	CPP	De Lucia *et al.* (1997); Planeta da Silva *et al.* (1995)
Methamphetamine	CPP	Cunningham and Noble (1992b)
GBR 12783	CPP	Le Pen *et al.* (1996)
Nomifensine	CPP	Martin-Iverson *et al.* (1985)
Methylphenidate (and derivatives)	CPP	Martin-Iverson *et al.* (1985); Clark and Fibiger (1987); Gatley *et al.* (1996)
Diethylpropion	CPP	Planeta da Silva and DeLucia (1998)
Bupropion	CPP	Ortmann (1985)
Pipradrol	CPP	White and Hiroi (1992)
Mazindol	CPP	Gevaerd and Takahashi (1996)
Receptor-specific ligands: Agonists		
SKF38393	CPA	White *et al.* (1991); Hoffman and Beninger (1988, 1989)
SKF82958	CPP	Abrahams *et al.* (1998)
SKF81297	No effect	Abrahams *et al.* (1998)
SKF77434	No effect	Abrahams *et al.* (1998)
Apomorphine	CPP	Papp (1988a); Parker (1992); Funada *et al.* (1993)
Quinpirole	CPP	White *et al.* (1991); Hoffman and Beninger (1988, 1989); Hoffman *et al.* (1988)
Bromocriptine	CPP	Hoffman *et al.* (1988)
PD-128 907	CPP	Khroyan *et al.* (1997)
U99194A	CPP	Kling-Petersen *et al.* (1995b)
7-OH-PIPAT	No effect	Khroyan *et al.* (1997)
l-Nafadotride	No effect	Chaperon and Thiebot (1996)
7-OH-DPAT	CPP	Mallet and Beninger (1994); Chaperon and Thiebot (1996)
	No effect	Kling-Petersen *et al.* (1995b); Rodriguez de Fonseca *et al.* (1995)
	CPA	Kamei and Ohsawa (1996); Khroyan *et al.* (1995)
(+)-AJ76	CPP	Richardson *et al.* (1993)
Preclamol	No effect	Kivastik *et al.* (1996b)
Receptor-specific ligands: Antagonists		
SCH23390	CPA	Acquas and Di Chiara (1994); Funada and Shippenberg (1996); Shippenberg *et al.* (1991); Shippenberg and Herz (1987, 1988); Cervo and Samanin (1995)
SCH39166	CPA	
A-69024	CPA	
SCH23390	No effect	Acquas *et al.* (1989); Acquas and Di Chiara (1994); Hoffman and Beninger (1989); Planeta da Silva *et al.* (1995); Longoni *et al.* (1998)
Spiperone	No effect	Papp and Willner (1991); Shippenberg *et al.* (1991); Shippenberg and Herz (1988); Funada and Shippenberg (1996); Planeta da Silva *et al.* (1995); Meisel *et al.* (1996); Cervo and Samanin (1995); Bechara *et al.* (1992); Harrington and van der Kooy (1992); Spyraki and Fibiger (1988); Hoffman and Donovan (1995)
Pimozide	No effect	
α-Flupenthixol	No effect	
Spiroperidol	No effect	
Butaclamol	No effect	
Sulpiride	No effect	
Haloperidol	No effect	
Raclopride	No effect	
Haloperidol	CPA	Risinger *et al.* (1992a)
Metoclopramide	CPP	Hoffman and Beninger (1989)
xxx	No effect	Planeta da Silva *et al.* (1995)
(−)-DS121	CPP	Kling-Petersen *et al.* (1995a)
Other drugs:		
(+)-Deprenyl	CPP	Timar *et al.* (1996)
Olanzapine	CPA	Meil and Schechter (1997)
CGS 10746B	CPA	Schechter and Meehan (1994)
L-DOPA	No CPP	Katajamaki *et al.* (1998)
Entacapone	No CPP	Katajamaki *et al.* (1998)
L-DOPA + entacapone	CPP	Katajamaki *et al.* (1998)
Opiates		
Agonists:		
Morphine	CPP	see text and Table 2
Heroin	CPP	Hand *et al.* (1989); Bozarth (1987b); Tierney *et al.* (1988); Stinus *et al.* (1989); Amalric *et al.* (1987); Schenk *et al.* (1985)

Table 1 (*continued*)

Place conditioning induced by	Effect	References
Etonitazene	CPP	Sala *et al.* (1992)
Fentanyl	CPP	Mucha and Herz (1985); Koob *et al.* (1986); Finlay *et al.* (1988); Pchelintsev *et al.* (1991)
etorphine	CPP	Pchelintsev *et al.* (1991)
Sulfentanil	CPP	Mucha and Herz (1985)
Methadone	CPP	Steinpreis *et al.* (1996)
Morphine-6-glucuronide	CPP	Abbott and Franklin (1991)
Dihydroetorphine	No effect	Tokuyama *et al.* (1996a)
B-END	CPP	Koob *et al.* (1986)
TAN 67	No effect	Suzuki *et al.* (1996c)
BW373U86	CPP	Longoni *et al.* (1998)
SNC 80	CPP	Longoni *et al.* (1998)
Ketocyclazocine	CPP	Iwamoto (1986b)
Ethylketocyclazocine	CPP	Iwamoto (1986b)
U-50 488H	CPA	Shippenberg and Herz (1986, 1988); Iwamoto (1986b);
U-69 593	CPA	Funada *et al.* (1993); Suzuki *et al.* (1992d); Ableitner and
Bremazocine	CPA	Herz (1989); Shippenberg *et al.* (1993); Bechara and van der Kooy (1987); Mucha and Herz (1985)
E-2078	CPA	Funada *et al.* (1993)
TRK-820	No effect	Nagase *et al.* (1998)
Ethylketazocine	No effect	Mucha and Herz (1985)
Tifluadom	No effect	Mucha and Herz (1985)
Mr 2034	No effect	Mucha and Herz (1985)
Pentazocine	No effect	Suzuki *et al.* (1991b)
Loperamide	No effect	Agmo *et al.* (1992)
Antagonists:		
Naloxone (in naive animals)	CPA	Shippenberg and Bals-Kubik (1995); Papp *et al.* (1992); Cunningham *et al.* (1995); Parker *et al.* (1995); Shippenberg and Herz (1986, 1987, 1988, 1991); Trujillo *et al.* (1991); Acquas *et al.* (1989, 1990); Spyraki *et al.* (1985); Iwamoto (1985, 1986b); Amalric *et al.* (1987); Mucha *et al.* (1985); Mucha and Walker (1987); Vaccarino *et al.* (1992); Oberling *et al.* (1993); Bals-Kubik *et al.* (1989); Kim *et al.* (1997); Higgins *et al.* (1992b); Planeta da Silva *et al.* (1995); Bechara *et al.* (1987)
	No effect	Bardo and Neisewander (1986); Hasenöhrl *et al.* (1991); Agmo and Berenfeld (1990); Trujillo *et al.* (1991); Gerrits *et al.* (1995); Kosten (1994); Rodgers *et al.* (1984)
Naloxone (in morphine-dependent animals)	CPA	Acquas *et al.* (1990); Funada *et al.* (1996); Mucha (1987); Mucha and Walker (1987); Higgins *et al.* (1991a); Popik and Danysz (1997); Kosten (1994); Spanagel *et al.* (1994); Schulteis *et al.* (1994); Valverde *et al.* (1996b); Valverde and Roques (1998)
Naltrexone (in naive animals)	CPA	Fantino and Wieteska (1993); Suzuki *et al.* (1992d); Parker and Rennie (1992)
Naltrexone (in morphine-dependent animals)	CPA	Kelsey and Arnold (1994)
β-funaltrexamine	CPA	Suzuki *et al.* (1993a)
Naloxonazine	CPA	Suzuki *et al.* (1993a)
Methylnaltrexone	CPP	Bechara and van der Kooy (1989)
Methylnaloxone	No effect	Heinrichs and Martinez (1986)
Naltrindole (in naive animals)	No effect	De Vries *et al.* (1995); Menkens *et al.* (1992); Suzuki *et al.* (1994b); Longoni *et al.* (1998)
Naltrindole (in morphine-dependent animals)	CPA	Funada *et al.* (1996)
7-Benzylidenenaltrexone	No effect	Suzuki *et al.* (1994b)
Naltriben (in naive animals)	No effect	Suzuki *et al.* (1994b)
Naltriben (in morphine-dependent animals)	CPA	Funada *et al.* (1996)
WIN 44 441-3	CPP	Iwamoto (1986b)
Mr 2266BS	CPA	Iwamoto (1986b)
Other drugs:		
Buprenorphine	CPP	Gaiardi *et al.* (1997); Pchelintsev *et al.* (1991); Rowlett *et al.* (1994); Brown *et al.* (1991)
RB-101	CPP	Valverde *et al.* (1996a)
	No effect	Noble *et al.* (1993)
SCH34826	No effect	Agmo *et al.* (1994)
β-casomorphin	No effect	Reid and Hubbell (1994)

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Table 1 (*continued*)

Place conditioning induced by	Effect	References
Dihydrocodein	No effect	Suzuki *et al.* (1990)
Ethanol	CPP	Schechter (1992b); Risinger *et al.* (1994); Risinger and Oakes (1996a,b); Cunningham and Noble (1992a); Gevaerd and Takahashi (1996); Risinger *et al.* (1992a,b, 1996); Risinger (1997); Cunningham *et al.* (1992a, 1993, 1997); Kelley *et al.* (1997b)
	No effect	van der Kooy *et al.* (1983); Asin *et al.* (1985); Davies and Parker (1990); Suzuki *et al.* (1992b); Cunningham *et al.* (1997); Bormann and Cunningham (1998)
	CPA	van der Kooy *et al.* (1983); Bienkowski *et al.* (1997a,b); Stewart and Grupp (1986, 1989); Stewart *et al.* (1996); Cunningham *et al.* (1993, 1997); Bormann and Cunningham (1998)
Acetaldehyde	CPP	Amit and Smith (1985)
	CPA	Suzuki *et al.* (1992b)
Acute ethanol withdrawal	CPP	Gauvin *et al.* (1997)
Cholinergic drugs		
Nicotine	CPP	Risinger and Oakes (1995); Calcagnetti and Schechter (1994b); Carboni *et al.* (1989); Acquas *et al.* (1989); Fudala *et al.* (1985); Fudala and Iwamoto (1986)
	No effect	Risinger and Oakes (1995); Shoaib *et al.* (1994); Parker (1992); Clark and Fibiger (1987)
	CPA	Risinger and Oakes (1995); Jorenby *et al.* (1990); Fudala *et al.* (1985)
Cotinine	No effect	Fudala and Iwamoto (1986)
Mecamylamine	No effect	Fudala *et al.* (1985)
Lobeline	No effect	Fudala and Iwamoto (1986)
Hexamethonium	No effect	Fudala *et al.* (1985)
Scopolamine	No effect	Lynch (1991)
GABAergic drugs		
Meprobamate	CPP	Spyraki *et al.* (1985)
Hydroxypregnanone	CPP	Finn *et al.* (1997)
Picrotoxin	CPA	Acquas *et al.* (1989, 1990); Spyraki *et al.* (1985); File (1986); Papp *et al.* (1992)
GHB	CPP	Martellotta *et al.* (1997)
Progabide	No effect	Di Scala *et al.* (1985)
Sodium valproate	No effect	Spyraki *et al.* (1985)
Sodium phenobarbitone	CPA	Wilks and File (1988)
Pentobarbital	CPA	Lew and Parker (1998)
Benzodiazepine-receptor ligands:		
Diazepam	CPP	Acquas *et al.* (1989); Spyraki and Fibiger (1988); Nomikos and Spyraki (1988a); Spyraki *et al.* (1985); Borsini *et al.* (1993); File (1986)
Lorazepam	CPP	File (1986)
Alprazolam	CPP	File (1986)
Adinazolam	CPP	File (1986)
Midazolam	CPP	Pain *et al.* (1997)
Triazolam	No effect	Pettit *et al.* (1989)
Chlordiazepoxide	weak CPP	File (1986)
	CPA	Parker *et al.* (1998)
Ro 16-6028	CPP	Di Scala *et al.* (1992)
Ro 15-1788	No effect	Di Scala *et al.* (1992)
Flumazenil	No effect	Suzuki *et al.* (1995c)
CGS 8816	No effect	Spyraki *et al.* (1985)
	CPA	File (1986)
Pentylenetetrazole	CPP	Gauvin *et al.* (1991)
	CPA	Bespalov (1996)
Ro 15-4513	No effect	Risinger *et al.* (1992b)
FG 7142	CPA	Di Scala and Sandner (1989b); Oberling *et al.* (1993); Rocha *et al.* (1993a)
β-CCE	CPA	Tsuda *et al.* (1989)
Serotonergic drugs		
Agonists:		
8-OH-DPAT	CPP	Shippenberg (1991); Fletcher *et al.* (1993); Papp and Willner (1991)
Gepirone	CPP	Neisewander *et al.* (1990b)
Buspirone	CPP	Neisewander *et al.* (1990b)
mCPP	No effect	Rocha *et al.* (1993a)

Table 1 (*continued*)

Place conditioning induced by	Effect	References
mCPBG	CPA	Higgins *et al.* (1993)
PBG	CPA	Higgins *et al.* (1993)
Antagonists:		
Mianserin	No effect	Risinger and Oakes (1996a)
	CPA	Rocha *et al.* (1993a,b); Papp (1989)
Ritanserin	No effect	Nomikos and Spyraki (1988a)
Ketanserin	No effect	Rocha *et al.* (1993a)
DAU 6215	No effect	Borsini *et al.* (1993)
Ondansetron	No effect	Bisaga *et al.* (1993)
ICS 205-930	No effect	Acquas *et al.* (1990)
MDL 72222	No effect	Acquas *et al.* (1990)
DAU 6285	CPA	Bisaga *et al.* (1993)
Other drugs:		
BIMU-8	CPP	Bisaga *et al.* (1993)
Eltoprazine	CPA	Rocha *et al.* (1993a)
MDMA and derivatives	CPP	Marona-Lewicka *et al.* (1996); Bilsky *et al.* (1990b, 1991); Bilsky and Reid (1991); Schechter (1991b); Bronson *et al.* (1996)
LSD	CPP	Parker (1996); Meehan and Schechter (1998)
Fenfluramine	CPA	Marona-Lewicka *et al.* (1996); Davies and Parker (1993)
MMAI	CPA	Marona-Lewicka *et al.* (1996); Davies and Parker (1993)
Zimelidine	CPP	Kruszewska *et al.* (1986)
Citalopram	CPA	Papp (1989)
Imipramine	CPA	Papp (1989)
Amitryptiline	CPA	Papp (1989)
Fluoxetine	CPP	Collu *et al.* (1997)
	No effect	Risinger (1997)
PCPA	No effect	Papp and Willner (1991)
Glutamatergic drugs		
MK-801 (dizocilpine)	CPP	Layer *et al.* (1993a); Papp and Moryl (1994); Steinpreis *et al.* (1995); Papp *et al.* (1996); DelPozo *et al.* (1996); Kim and Jang (1997); Hoffman (1994)
	No effect	Tzschentke and Schmidt (1995, 1997, 1998b); Kim *et al.* (1996b,d); Kim and Jang (1997); Hoffman (1994)
	CPA	Sufka (1994); Cervo and Samanin (1995)
Phencyclidine (PCP)	CPP	Marglin *et al.* (1989)
	CPA	Acquas *et al.* (1989, 1990); Barr *et al.* (1985)
Memantine	No effect	Popik and Danysz (1997)
CGP 37849	CPP	Papp and Moryl (1994); Papp *et al.* (1996); Tzschentke and Schmidt (1995)
CGP 40116	CPP	Papp *et al.* (1996)
Kynurenic acid	No effect	Bespalov *et al.* (1994)
GYKI 52466	No effect	Tzschentke and Schmidt (1997)
Riluzole	CPP	Tzschentke and Schmidt (1998a)
ACPC	No effect	Papp *et al.* (1996)
Cannabinoids		
THC	CPP	Lepore *et al.* (1995)
	No effect	Sanudo-Pena *et al.* (1997)
	CPA	Sanudo-Pena *et al.* (1997); Lepore *et al.* (1995); Mallet and Beninger (1998)
Anandamide	No effect	Mallet and Beninger (1998)
CP 55 940	CPA	McGregor *et al.* (1996)
WIN 55212-2	CPA	Chaperon *et al.* (1998)
SR141716	No effect	Chaperon *et al.* (1998)
	CPP	Sanudo-Pena *et al.* (1997)
Substance P	CPP	Hasenöhrl *et al.* (1989, 1991); Huston *et al.* (1993); Gerhardt *et al.* (1993); Oitzl *et al.* (1990); Sprick *et al.* (1996); Mattioli *et al.* (1995, 1996)
C-terminal sequences of SP	CPP	Hasenöhrl *et al.* (1991); Huston *et al.* (1993); Oitzl *et al.* (1990); Mattioli *et al.* (1995, 1996)
N-terminal sequ. of SP	No effect	Hasenöhrl *et al.* (1991); Huston *et al.* (1993); Oitzl *et al.* (1990); Mattioli *et al.* (1995, 1996)
Cholecystokinin (CCK)		
CCK fragment CCK-8S	No effect	Gerhardt *et al.* (1994)
CCK fragment Boc-CCK-4	No effect	Gerhardt *et al.* (1994)
Devazepide	No effect	Higgins *et al.* (1992c)
PD-134 308	No effect	Valverde *et al.* (1996a, 1997)
L365-260	CPP	Higgins *et al.* (1992c)

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Table 1 (*continued*)

Place conditioning induced by	Effect	References
Hormones		
LHRH	CPP	De Beun *et al*. (1991a, 1992a)
Testosterone	CPP	De Beun *et al*. (1992b); Alexander *et al*. (1994)
Estradiol	CPA	De Beun *et al*. (1991b)
CRF	CPA	Cador *et al*. (1992)
Calcium channel blockers		
Isradipine	No effect	Calcagnetti and Schechter (1994a)
Nifedipine	No effect	Suzuki *et al*. (1992a)
Flunaridine	No effect	Suzuki *et al*. (1992a)
Diltiazem	No effect	Suzuki *et al*. (1992a)
Verapamil	No effect	Pucilowski *et al*. (1993)
BAY-k-8644	No effect	De Beun *et al*. (1996b)
Nimodipine	CPP	De Beun *et al*. (1996a)
	CPA	Martin-Iverson *et al*. (1997)
(Nor-)adrenergic drugs		
Clonidine	CPP	Asin and Wirtshafter (1985); Tierney *et al*. (1988)
Rilmenidine	CPP	Tierney *et al*. (1988)
Idazoxan	CPP	Cervo *et al*. (1993)
Yohimbine	CPA	File (1986)
Prazosin	No effect	Cervo *et al*. (1993)
Desipramine	No effect	Martin-Iverson *et al*. (1985)
Adenosinergic drugs		
Caffeine	CPP	Brockwell *et al*. (1991); Carey and Damianopoulos (1994)
	CPA	Brockwell *et al*. (1991); Zarrindast and Moghadamnia (1997)
Theophylline	CPP	Brockwell *et al*. (1991); Zarrindast and Moghadamnia (1997)
	CPA	Brockwell *et al*. (1991); Zarrindast and Moghadamnia (1997)
NECA	CPP	Zarrindast and Moghadamnia (1997)
8-PT	CPP	Zarrindast and Moghadamnia (1997)
R-PIA	CPA	Zarrindast and Moghadamnia (1997)
CHA	CPA	Zarrindast and Moghadamnia (1997)
CGS 15943A	CPP	Brockwell and Beninger (1996)
CPA	No effect	Brockwell and Beninger (1996)
CPX	No effect	Brockwell and Beninger (1996)
CGS 21680	No effect	Brockwell and Beninger (1996)
Diverse drugs		
Lithium chloride	CPA	Suzuki *et al*. (1992a); Parker (1992); Frisch *et al*. (1995); Cunningham and Niehus (1993); Oberling *et al*. (1993); Reilly *et al*. (1993); Shippenberg *et al*. (1988b); Bechara *et al*. (1987); Symonds and Hall (1997); Lett (1992)
Propofol	CPP	Pain *et al*. (1996, 1997)
Methohexital	No effect	Pain *et al*. (1996, 1997)
U-43 465	CPP	File (1986)
Tracazolate	CPP	File (1986)
Glue thinner vapors	CPP	Yavich *et al*. (1994)
Magnesium chloride	CPP	Lawley and Kantak (1990b)
Tripelennamine	No effect	Suzuki *et al*. (1991b)
Chlorpheniramine	CPP	Masukawa *et al*. (1993); Mattioli *et al*. (1998)
Zolantidine	CPP	Suzuki *et al*. (1995b)
L-NOArg	No effect	Kivastik *et al*. (1996a)
L-NNA	No effect	Kim and Park (1995)
NAN	CPP	Iwamoto (1986b)
des-Arg(9),(Leu(8))BK	CPA	Sufka and Roach (1996)
HOE 140	No effect	Sufka and Roach (1996)
Cyclosporine A	No effect	Suzuki *et al*. (1993b)
Ginseng extract	No effect	Tokuyama *et al*. (1996b)
Ibogaine	No effect	Parker *et al*. (1995)
Ascorbate	No effect	Pierce *et al*. (1995)
Natural reinforcers		
Rough-and-tumble play	CPP	Calcagnetti and Schechter (1992b)
Home cage odors	CPP	Hansen (1993)
Pups (for maternal rats)	CPP	Magnusson and Fleming (1995); Fleming *et al*. (1994)
Social play	CPP	Crowder and Hutto (1992a)
Successful agression	CPP	Martinez *et al*. (1995)

Table 1 (*continued*)

Place conditioning induced by	Effect	References
Male/female interaction	CPP	Meisel and Joppa (1994); Paredes and Alonso (1997); Meisel *et al.* (1996); Oldenburger *et al.* (1992); Hughes *et al.* (1990); Mehrara and Baum (1990); Miller and Baum (1987)
Ejaculation	CPP	Agmo and Berenfeld (1990); Agmo and Gomez (1993)
Water	CPP	Crowder and Hutto (1992a); Agmo *et al.* (1993); Perks and Clifton (1997)
Sucrose solution, saccharin solution	CPP	Papp *et al.* (1991); Agmo *et al.* (1995); Perks and Clifton (1997); Agmo and Marroquin (1997); Stefurak and van der Kooy (1992, 1994)
Food	CPP	Lepore *et al.* (1995); Papp (1988a, 1989); Papp *et al.* (1991); Cheeta *et al.* (1994); Willner *et al.* (1994); Guyon *et al.* (1993); Muscat *et al.* (1992); Perks and Clifton (1997); Maes and Vossen (1993); Chaperon *et al.* (1998)
Novel environment	CPP	Carr *et al.* (1988); Bardo *et al.* (1989, 1990, 1993); Parker (1992); Laviola and Adriani (1998)

1995b; Rodriguez de Fonseca *et al.*, 1995), or to produce CPA (Kamei and Ohsawa, 1996; Khroyan *et al.*, 1995; Chaperon and Thiebot, 1996), results which might be largely due to the use of different doses in the different studies. However, CPP was also reported for the preferential D3 and autoreceptor antagonist (−)-DS121 (Kling-Petersen *et al.*, 1995a) and the D2 receptor antagonist metoclopramide (Hoffman and Beninger, 1989; but see Planeta da Silva *et al.* (1995) who found no effect for metoclopramide), and also for the MAO-B inhibitor (+)-deprenyl (but not (−)-deprenyl) (Timar *et al.*, 1996). Neither the dopamine precursor L-DOPA nor the COMT-inhibitor entacapone induced CPP when given alone. However, when both drugs were administered together they produced a significant CPP (Katajamaki *et al.*, 1998).

A CPA was demonstrated for the D1 agonist SKF38393 (White *et al.*, 1991; Hoffman and Beninger, 1988, 1989), the D1 antagonists SCH 23390, SCH 39166 and A-69024 (Acquas and Di Chiara, 1994; Funada and Shippenberg, 1996; Shippenberg *et al.*, 1991; Shippenberg and Herz, 1987, 1988; Cervo and Samanin, 1995), a high dose of the atypical neuroleptic olanzapine (Meil and Schechter, 1997), the DA release inhibitor CGS 10746B (Schechter and Meehan, 1994), and for high-dose methamphetamine (Cunningham and Noble, 1992b).

No effect on place conditioning was reported for the D2 antagonists spiperone, pimozide, α-flupenthixol, spiroperidol, butaclamol and sulpiride (Papp and Willner, 1991; Shippenberg *et al.*, 1991; Shippenberg and Herz, 1988; Funada and Shippenberg, 1996; Planeta da Silva *et al.*, 1995; Meisel *et al.*, 1996; Cervo and Samanin, 1995; Bechara *et al.*, 1992; Iwamoto, 1986a; Harrington and van der Kooy, 1992) and also for haloperidol, raclopride, and the atypical antipsychotics clozapine, risperidone, sertindole and domperidone (Spyraki and Fibiger, 1988; Hoffman and Donovan, 1995; Di Scala and Sandner, 1989b; Kosten and Nestler, 1994; Suzuki and Misawa, 1995). A lack of effect has also been reported for SCH 23390 (Acquas *et al.*, 1989; Acquas and Di Chiara, 1994; Hoffman and Beninger, 1989; Planeta da Silva *et al.*, 1995; Longoni *et al.*, 1998) and a CPA has been reported for haloperidol in one study (Risinger *et al.*, 1992a). The D3 agonists 7-OH-PIPAT (Khroyan *et al.*, 1997) and l-nafadotride (Chaperon and Thiebot, 1996), the D2 autoreceptor partial agonist preclamol (Kivastik *et al.*, 1996b), and SCH 23388, the inactive enantiomer of SCH 23390, also failed to produce an effect in place conditioning.

Taken together, these results suggest that the rewarding effects of elevated extracellular DA levels are primarily mediated by the D2 receptor. On the other hand, it can also be noted that the blockade of 'baseline' DA transmission at D2 receptors is not aversive. The situation for the D1 receptor is less clear, with both D1 agonists and antagonists producing place aversions, and investigation of the role of the D3 receptor is still hampered by the lack of selective and high-affinity ligands. In a very recent report, CPP was also produced by the D1 agonist SKF 82958 (albeit only at one intermediate dose but not at lower or higher doses) but not the D1 agonists SKF 81297 and SKF 77434 (Abrahams *et al.*, 1998). From this study, it remains unclear to what extent direct stimulation of D1 receptors contributes to reward-relevant mechanisms. Thus, the paradox largely remains that D1 antagonists are very effective in blocking the rewarding effects of many drugs (generally more effective than D2 antagonists), yet at the same time it is difficult to obtain clear rewarding effects with D1 agonists (some studies even report CPA for D1 agonists, while D2 agonists commonly produce reward).

3.1.2. *Opiates*

As in the case for amphetamine and cocaine, a large number of studies have confirmed the CPP-inducing effect of morphine (see references in Sections 3.2.2, 4.1.2 and 4.2.2. 5., 6., 7.). The effect of morphine was shown to be stereospecific (Mucha and Herz, 1986) and has also been demonstrated in the hamster (Schnur and Morrell, 1990) and in newly hatched chickens (Bronson *et al.,* 1996). Morphine doses that induced CPP in adult rats were sufficient to also induce CPP in preweanling rats

which suggests that the neural substrate mediating opiate reward (and also psychostimulant reward, see Section 3.1.1) is fully functional at a very early developmental stage (Randall *et al.,* 1998).

In addition to morphine, CPP was shown for the μ-agonists heroin (Hand *et al*., 1989; Bozarth, 1987b; Tierney *et al*., 1988; Stinus *et al*., 1989; Amalric *et al*., 1987; Schenk *et al*., 1985), etonitazene (Sala *et al*., 1992), fentanyl (Mucha and Herz, 1985; Koob *et al*., 1986; Finlay *et al*., 1988; Pchelintsev *et al*., 1991), etorphine (Pchelintsev *et al*., 1991), sulfentanil (Mucha and Herz, 1985), methadone (Steinpreis *et al*., 1996; note, however, that the high dose of 10 mg/kg of methadone induced a CPA in this study), the morphine metabolite morphine-6-glucuronide (Abbott and Franklin, 1991), the mixed opiate agonist/antagonist buprenorphine (Gaiardi *et al*., 1997; Pchelintsev *et al*., 1991; Rowlett *et al*., 1994; Brown *et al*., 1991) [note, however, that a high dose of buprenorphine (3 mg/kg) did not produce CPP (Rowlett *et al*., 1994; Brown *et al*., 1991)], the μ/δ-agonist B-END (Koob *et al*., 1986), the non-peptide δ-agonists BW373U86 and SNC80 (Longoni *et al.,* 1998) the κ-agonists ketocyclazocine and ethylketocyclazocine and the κ-antagonist WIN 44 441-3 (Iwamoto, 1986b), and also for the peripheral opiate antagonist methylnaltrexone (Bechara and van der Kooy, 1989). RB-101, a complete inhibitor of enkephalin catabolism, produced a CPP in one study (Valverde *et al*., 1996a), but not in another (Noble *et al*., 1993).

CPA was demonstrated for naloxone (in opiate-naive animals; for studies using morphine-preexposed animals, see Section 8) (Shippenberg and Bals-Kubik, 1995; Papp *et al*., 1992; Cunningham *et al*., 1995; Parker *et al*., 1995; Shippenberg and Herz, 1986, 1987, 1988, 1991; Trujillo *et al*., 1991; Acquas *et al*., 1989, 1990; Spyraki *et al*., 1985; Iwamoto, 1986b; Amalric *et al*., 1987; Mucha *et al*., 1985; Mucha and Walker, 1987—for the CD1, DBA/2 and C57BL/6 mouse strains; Vaccarino *et al*., 1992; Oberling *et al*., 1993; Bals-Kubik *et al*., 1989; Kim *et al*., 1997; Higgins *et al*., 1992b; Planeta da Silva *et al*., 1995; Bechara *et al*., 1987) and for naltrexone (Fantino and Wieteska, 1993; Suzuki *et al*., 1992d; Parker and Rennie, 1992). However, no effects for naloxone have also been reported in a number of studies (Bardo and Neisewander, 1986; Hasenöhrl *et al*., 1991; Agmo and Berenfeld, 1990; Trujillo *et al*., 1991; Gerrits *et al*., 1995; Kosten, 1994; Rodgers *et al*., 1984).

CPA was also reported for the μ1/μ2-antagonist β-funaltrexamine and the μ1-antagonist naloxonazine (Suzuki *et al*., 1993a), the κ-agonists U-50 488H, U-69593 and bremazocine (Shippenberg and Herz, 1986, 1988, 1991; Shippenberg *et al*., 1993; Iwamoto, 1986b; Funada *et al*., 1993; Suzuki *et al*., 1992d; Ableitner and Herz, 1989; Bechara and van der Kooy, 1987; Mucha and Herz, 1985), the dynorphin analog E-2078 (Funada *et al*., 1993) and the κ-antagonist Mr 2266BS (Iwamoto, 1986b).

Neither CPP nor CPA was produced by the μ-agonist dihydroetorphine (Tokuyama *et al*., 1996a), the nonpeptide δ-agonist TAN 67 (Suzuki *et al*., 1996c), the δ-antagonists naltrindole (De Vries *et al*., 1995; Menkens *et al*., 1992; Suzuki *et al*., 1994b; Longoni, *et al.,* 1998), 7-benzylidenenaltrexone (δ1-specific) and naltriben (δ2-specific) (Suzuki *et al*., 1994b), the enkephalinase inhibitor SCH34826 (Agmo *et al*., 1994), the κ-agonists ethylketazocine, tifluadom, Mr 2034 (Mucha and Herz, 1985) and TRK-820 (Nagane *et al.,* 1998) the partial μ/κ-agonist pentazocine (Suzuki *et al*., 1991b), the peripheral opiate agonist loperamide (Agmo *et al*., 1992) and the peripheral opiate antagonist methylnaloxonium (Heinrichs and Martinez, 1986). Also without effect was β-casomorphin, an opioid found in milk (Reid and Hubbell, 1994) and dihydrocodein, a major active component in over-the-counter cough syrups (Suzuki *et al*., 1990).

Despite some conflicting results, these place conditioning studies have generally confirmed the putative role of the endogenous opioid system and its different receptor subtypes in reward mechanisms. Thus, activation of the μ-receptor commonly produces reliable CPP effects, while the situation is somewhat less clear for the δ-receptor. Activation of the κ-receptor appears to have predominantly aversive effects, although κ-agonists have also been shown to produce CPP and κ-antagonists to induce CPA. These results may be due to dose-dependent effects and lack of receptor specificity of the receptor ligands used. Endogenous opioids appear to excert a tonic influence on reward-relevant μ-receptors, since blockade of these receptors was found to be aversive in most cases.

3.1.3. *Ethanol*

The results of ethanol place conditioning experiments will be presented in more detail here because this case is an illustrative example for how methodological and procedural parameters can influence the outcome of a place conditioning experiment.

In an early study study examining the effects of ethanol in the CPP paradigm, it was found that while low doses (< 0.8 g/kg) were without effect, higher doses (> 0.8 g/kg) reliably produced CPA. This effect was independent of route of administration (IV or PO), rate of infusion, concentration of the administered solution, or vehicle (van der Kooy *et al*., 1983). In another early study, it was shown that ethanol produced neither CPP nor CPA in rats over a large range of doses, with either IP or IV application (Asin *et al*., 1985). A lack of effect was also found in some other studies (Davies and Parker, 1990; Suzuki *et al*., 1992b), while others have reported CPA (Bienkowski *et al*., 1997a,b). Pairing environmental cues with ethanol self-administration (drinking) paradoxically produced CPA (Stewart and Grupp, 1986), an effect that was not dependent on delayed aversively high blood alcohol levels (Stewart and Grupp, 1989). CPA produced by IP injection of ethanol was also shown in alcohol-preferring as well as in alcohol-nonpreferring rat lines (Stewart *et al*., 1996). In contrast, IP injections of ethanol have also been shown to produce CPP in both alcohol-preferring and alcohol-non-preferring rat lines (Schechter, 1992b), in two mice strains selectively bred for high and low sensitivity to ethanol-induced locomotor stimulation (Risinger *et al*., 1994), and in a number of studies using different

inbred and outbred mice strains (Risinger and Oakes, 1996a,b; Cunningham and Noble, 1992a; Gevaerd and Takahashi, 1996; Risinger, 1997; Risinger *et al*., 1992a,b, 1996; Cunningham *et al*., 1992a). CPP induced by IV ethanol has also been reported recently (Kelley *et al*., 1997b). Cunningham *et al*. (1997) presented evidence to suggest that the relative timing of ethanol injection and subsequent exposure to the CS+ can be a crucial denominator of the outcome of the conditioning experiment. Thus, it was shown that only mice injected just before or 30 min before CS+ exposure developed CPP. Mice injected right after exposure to the CS+ developed CPA. Mice injected 120 min or 60 min before, or 15 min or 60 min after exposure to the CS+ did not develop CPP or CPA. In line with these findings, it was also shown that ethanol produced the biggest CPP effects when short conditioning sessions (5 min) were used, while the effects were much smaller when the conditioning sessions were longer (30 min). Recently, qualitatively different results have been reported for the rat (Bormann and Cunningham, 1998). Rats were injected 30, 15, 10, 5 or 0 min before or 5 min after the 5 min conditioning session. None of these injections produced CPP, if anything, they tended to produce CPA.

Taken together, these results suggest that the rewarding effects of ethanol are greatest shortly after injection, at least in the mouse (Cunningham and Prather, 1992) and that, in the majority of cases, ethanol induced no effect or CPA in rats and CPP in mice when drug-naive animals were used. In an attempt to directly compare the motivational effects of ethanol in rats and mice, Cunningham *et al*. (1993) conducted a study where both species were tested under exactly the same experimental conditions. It was again found that ethanol induced CPA in rats and CPP in mice. Sensitization and tolerance effects also seem to play important roles in ethanol place conditioning (see Section 7). A review of procedural variables and how they can affect the outcome of ethanol place conditioning can be found in Stewart *et al*. (1988).

There is evidence to suggest that the positively reinforcing effects of ethanol depend at least in part on the actions of its metabolite acetaldehyde (Amit and Smith, 1985), although acetaldehyde was also reported to produce a weak CPA (Suzuki *et al*., 1992b). Gauvin *et al*. (1997) examined the delayed effects of ethanol ('hangover') and found that this form of acute ethanol withdrawal paradoxically can produce CPP.

3.1.4. *Nicotine/Cholinergic Drugs*

As in the case of ethanol, nicotine place conditioning also appears to be sensitive to procedural parameters. Therefore, the results concerning nicotine will also be presented in consideration of methodological details.

Using mice, Risinger and Oakes (1995) reported a nicotine-induced CPP at a dose of 0.5 mg/kg, no effect at 0.25 and 1.0 mg/kg and a CPA at 2.0 mg/kg nicotine IP in an unbiased design. Using rats, Calgagnetti and Schechter (1994b) showed that a dose of 0.8 mg/kg of SC nicotine produced CPP in a biased design only when nicotine was paired with the initially non-preferred compartment, but not when paired with the initially preferred compartment. Likewise, it was shown that nicotine (0.6 mg/kg SC) paired with the initially non-preferred compartment produced CPP (Carboni *et al*., 1989; Acquas *et al*., 1989; Fudala *et al*., 1985). On the other hand, Shoaib *et al*. (1994) found no CPP for 0.6 mg/kg of SC nicotine, even after increasing the number of conditioning trials from four to 12, using a counterbalanced conditioning design. A lack of nicotine-induced CPP has also been reported by Parker (1992). Likewise, Clark and Fibiger (1987) were unable to observe a CPP for SC nicotine (0.2–0.8 mg/kg) using an unbiased design, and Jorenby *et al*. (1990) even reported a CPA for 0.8 mg/kg nicotine, a dose that produced CPP in other studies (Fudala and Iwamoto, 1986; Calcagnetti and Schechter, 1994b). In the latter study, nicotine only produced CPP when it was injected immediately prior to the conditioning sessions, but not when it was administered 20, 60 or 120 min prior to conditioning. A shift from rewarding to aversive effects with increasing doses has been reported by Fudala *et al*. (1985). Thus, while nicotine can have clearly reinforcing and highly addictive properties in humans, the CPP paradigm seems not to be very well suited to examine the effects of nicotine in rodents since these effects appear to be variable and highly dependent on the experimental procedure.

Other cholinergic compounds: The muscarinic antagonist scopolamine was found to produce neither CPP nor CPA (Lynch, 1991) and the same lack of effect was found for the nicotinic antagonists mecamylamine hydrochloride, lobeline and hexamethonium bromide (peripheral) (Fudala *et al*., 1985; Fudala and Iwamoto, 1986), and also for the nicotine metabolite cotinine (Fudala and Iwamoto, 1986).

3.1.5. *GABAergic Drugs*

The direct GABA-A agonist meprobamate (Spyraki *et al*., 1985), the GABA metabolite γ-hydroxybutyric acid (GHB) (Martellotta *et al*., 1997) and the GABA-A agonist/neuroactive steroid 3-α-hydroxy-5-α-pregnan-20-one (Finn *et al*., 1997) produced CPP. The GABA mimetic progabide (SL 76002) (Di Scala *et al*., 1985) and the GABA agonist sodium valproate (Spyraki *et al*., 1985) produced neither CPP nor CPA. Sodium phenobarbitone (Wilks and File, 1988) and the GABA-A antagonist picrotoxin induced CPA (Acquas *et al*., 1989, 1990; Spyraki *et al*., 1985; File, 1986; Papp *et al*., 1992). Lew and Parker (1998) reported that repeated preexposure to pentobarbital only attenuated the CPA-inducing effects of this drug but did not result in an eventual CPP.

Diazepam (Acquas *et al*., 1989; Spyraki and Fibiger, 1988; Nomikos and Spyraki, 1988a; Spyraki *et al*., 1985; Borsini *et al*., 1993; File, 1986; but see Di Scala *et al*., 1992), lorazepam, alprazolam, adinazolam (File, 1986) and midazolam (at both subanaesthetic and anaesthetic doses) (Pain *et al*., 1997) were shown to induce CPP, while triazolam failed to

produce CPP (Pettit *et al*., 1989) and chlordiazepoxide produced only weak preference effects (File, 1986) or CPA (Parker *et al*., 1998). The benzodiazepine receptor partial agonist Ro 16-6028 produced CPP (Di Scala *et al*., 1992), whereas the benzodiazepine receptor antagonists Ro 15-1788 (Di Scala *et al*., 1992) and flumazenil (Suzuki *et al*., 1995c), and also the benzodiazepine inverse agonist Ro 15-4513 (Risinger *et al*., 1992b) produced neither CPP nor CPA. The benzodiazepine receptor antagonist CGS 8816 produced CPA in one study (File, 1986), while it had no effect in another study (Spyraki *et al*., 1985). In one study, the anxiogenic benzodiazepine receptor inverse agonist pentylenetetrazole, surprisingly, produced CPP (Gauvin *et al*., 1991), while in another study CPA was reported (Bespalov, 1996). Consistent CPA was reported for the benzodiazepine receptor inverse agonists FG 7142 (Di Scala and Sandner, 1989b; Oberling *et al*., 1993; Rocha *et al*., 1993a) and β-CCE (Tsuda *et al*., 1989).

3.1.6. *Serotonergic Drugs*

The study of the serotonergic system suffers from the large number of serotonin receptor subtypes that have been identified. Highly selective and specific ligands are not available for all subtypes, and since activation or blockade of different subtypes can have markedly different behavioural and neurochemical effects, this lack of selective ligands makes it difficult to draw a definite picture about the nature of the involvement of the serotonergic system in brain mechanisms of reward. In line with this, the picture emerging from place conditioning studies is relatively heterogenous.

The 5-HT1A agonists 8-OH-DPAT (Shippenberg, 1991; Fletcher *et al*., 1993; Papp and Willner, 1991), gepirone and buspirone (Neisewander *et al*., 1990b; but see Ali and Kelly, 1997; File, 1986), the mixed 5-HT3 antagonist/5-HT4 agonist BIMU-8 (Bisaga *et al*., 1993), the serotonin reuptake blockers zimelidine (Kruszewska *et al*., 1986), MDMA and its derivatives MBDB and MDA (Marona-Lewicka *et al*., 1996; Bilsky *et al*., 1990b, 1991; Bilsky and Reid, 1991; Schechter, 1991b; Bronson *et al*., 1996) produced CPP, while fenfluramine, the serotonin-releasing drug MMAI (Marona-Lewicka *et al*., 1996; Davies and Parker, 1993) and the serotonin (and noradrenaline) reuptake blockers citalopram, imipramine and amitryptiline (Papp, 1989) produced CPA. Nexus also produced a place preference, which, however, was probably due to non-associative processes (Bronson *et al*., 1996). The serotonin reuptake blocker fluoxetine was found to produce a CPP (Collu *et al*., 1997) or to have no effect (Risinger, 1997). For LSD, a CPP has been reported (Parker, 1996). Meehan and Schechter (1998) showed a CPP induced by LSD in male, but not in female Fawn Hooded rats.

The 5-HT2A antagonist mianserin produced no effect in one study (Risinger and Oakes, 1996a), while it induced CPA in other studies (Rocha *et al*., 1993a,b; Papp, 1989). The 5-HT2 antagonists ritanserin (Nomikos and Spyraki, 1988a) and ketanserin (Rocha *et al*., 1993a), the 5-HT1C agonist mCPP (Rocha *et al*., 1993a), the 5-HT3 antagonists DAU 6215, ondansetron (Borsini *et al*., 1993; Bisaga *et al*., 1993), ICS 205-930 and MDL 72222 (Acquas *et al*., 1990), and also the serotonin synthesis inhibitor PCPA (Papp and Willner, 1991) did not produce a place conditioning effect.

DAU 6285, a mixed 5-HT3 antagonist/5-HT4 antagonist (Bisaga *et al*., 1993), eltoprazine, a mixed 5-HT1B agonist/5-HT1C antagonist (Rocha *et al*., 1993a), and the 5-HT3 agonists *m*-chlorophenylbiguanide (mCPBG) and 1-phenylbiguanide (PBG) (Higgins *et al*., 1993) produced CPA. CPA for a high dose of 8-OH-DPAT was also reported in one study (Papp and Willner, 1991).

3.1.7. *Glutamatergic Drugs*

The most widely investigated compound in this respect is probably the non-competitive NMDA antagonist MK-801 (dizocilpine). For this substance, very inconsistent results have been reported. While a number of studies have shown CPP (Layer *et al*., 1993a; Papp and Moryl, 1994; Steinpreis *et al*., 1995; Papp *et al*., 1996; DelPozo *et al*., 1996; Kim and Jang, 1997), others have found no effect (Tzschentke and Schmidt, 1995, 1997, 1998b; Kim *et al*., 1996b,d; Kim and Jang, 1997) and even a MK-801-induced CPA has been reported (Sufka, 1994; Cervo and Samanin, 1995), and these contrasting results have been demonstrated for the same range of doses. Hoffman (1994) found MK-801-induced CPP only at one intermediate dose, but not at a low or a high dose. DelPozo *et al*. (1996) have shown that both the more active (+)-enantiomer and the less active (−)-enantiomer of MK-801 produced CPP at the same dose, which questions the receptor specificity of the CPP effect. Inconsistent place conditioning results have also been reported for phencyclide (PCP), which may be partly related to dose-dependent effects. Low to intermediate doses of PCP have been shown to produce CPP (Marglin *et al*., 1989), while higher doses have been reported to produce CPA (Acquas *et al*., 1989, 1990; Barr *et al*., 1985). Sensitization and tolerance effects also seem to contribute importantly to the outcome of place conditioning experiments using PCP (see Section 7).

The low-affinity non-competitive NMDA antagonist memantine produced neither CPP nor CPA (Popik and Danysz, 1997), while CPP has been demonstrated for the competitive NMDA antagonists CGP 37849 (Papp and Moryl, 1994; Papp *et al*., 1996; Tzschentke and Schmidt, 1995) and CGP 40116 (Papp *et al*., 1996), and for the glutamate release inhibitor riluzole (Tzschentke and Schmidt, 1998a). ACPC, a partial agonist at the strychnine-insensitive glycine binding site at the NMDA receptor complex, was without effect (Papp *et al*., 1996) and the non-selective ionotropic glutamate receptor antagonist kynurenic acid (Bespalov *et al*., 1994) and the AMPA antagonist GYKI 52466 (Tzschentke and Schmidt, 1997) also failed to produce place conditioning.

3.1.8. *Δ(9)-Tetrahydrocannabinol (THC)*

Only few studies have examined the effects of this active ingredient of marijuana and hashish, and inconsistent results have been reported. Sanudo-Pena *et al.* (1997) found no CPP at a low dose of THC (1.5 mg/kg) and a CPA at a high dose (15 mg/kg). In contrast, Mallett and Beninger (1998) found a significant CPA for the same low doses of THC (1.0 and 1.5 mg/kg), and neither CPP or CPA was found for the endogenous cannabinoid agonist anandamide. Moreover, it was reported that the cannabinoid antagonist SR141716A induced a CPP at a low and high dose (0.5 and 5 mg/kg). In contrast, Lepore *et al.* (1995) reported THC-induced CPP for 2 and 4 mg/kg, but not for 1 mg/kg, when animals received one conditioning session per day. However, when conditioning took place only every other day (to allow for a 24 hr washout period for THC), the dose of 1 mg/kg THC was sufficient to produce CPP, whereas the higher doses (2 and 4 mg/kg) produced CPA. The synthetic cannabinoid CP 55 940 was reported to produce CPA (McGregor *et al.*, 1996). The synthetic CB receptor agonist WIN 55212-2 produced a robust CPA while the CB1 receptor antagonist SR 141716 produced neither CPP nor CPA (Chaperon *et al.,* 1998).

These results suggest that cannabinoids have relatively weak rewarding as well as aversive motivational effects, which is consistent with the notion that the addictive potency of cannabis is presumably very low.

3.1.9. *Substance P (SP)*

This endogenous neurokinin has been shown to produce CPP upon systemic injection (Hasenöhrl *et al.*, 1989, 1991; Huston *et al.*, 1993; Gerhardt *et al.*, 1993; Oitzl *et al.*, 1990), an effect which seems to be due to the action of the C-terminal and not of the N-terminal of the peptide, since only the C-terminal hepta- and hexapeptide sequences of SP but not the N-terminal SP1-7 mimicked the reinforcing effects of SP (Hasenöhrl *et al.*, 1991; Huston *et al.*, 1993; Oitzl *et al.*, 1990). Similar results, i.e. CPP induced by SP, its C-terminal specific fragments but not its N-terminal specific fragments, were also found in the goldfish (Mattioli *et al.*, 1995, 1996). In the rat, SP-induced CPP has also been demonstrated after prolonged pretreatment (daily for 9 weeks) prior to conditioning (Sprick *et al.*, 1996), suggesting the absence of tolerance to the motivational effects of SP, even after extensive chronic exposure.

3.1.10. *Cholecystokinin (CCK)*

The CCK fragments CCK-8S and Boc-CCK-4 produced neither CPP nor CPA (Gerhardt *et al.*, 1994), and the CCK-A antagonist devazepide (Higgins *et al.*, 1992c) and the CCK-B antagonist PD-134 308 were also ineffective (Valverde *et al.*, 1996a, 1997). On the other hand, the CCK-B antagonist L365-260 was reported to produce a small but significant CPP (Higgins *et al.*, 1992c).

3.1.11. *Hormones*

Luteinizing hormone-releasing hormone (LHRH) has been shown to produce CPP (De Beun *et al.*, 1991a, 1992a). Testosterone produced CPP in male (De Beun *et al.*, 1992b; Alexander *et al.*, 1994; but see Caldarone *et al.*, 1996) but not in female rats (De Beun *et al.*, 1992b), while estradiol produced CPA in male as well as in female rats (De Beun *et al.*, 1991b). Corticotropin-releasing factor (CRF) produced CPA (Cador *et al.*, 1992).

3.1.12. *Calcium Channel Blockers*

Isradipine (Calcagnetti and Schechter, 1994a), nifedipine, flunaridine, diltiazem, verapamil (Pucilowski *et al.*, 1993; Suzuki *et al.*, 1992a) and BAY-k-8644 (De Beun *et al.*, 1996b) failed to produce CPP or CPA. On the other hand, nimodipine produced a CPP in one study (De Beun *et al.*, 1996a) and a CPA in another study (Martin-Iverson *et al.*, 1997).

3.1.13. *Adrenergic Drugs*

The α2-agonist clonidine produced CPP over a range of doses (Asin and Wirtshafter, 1985; Tierney *et al.*, 1988; but see Cervo *et al.*, 1993; Nader and van der Kooy, 1996), while rilmenidine, another α2-agonist, produced CPP only at one intermediate dose (Tierney *et al.*, 1988). The α2-antagonist idazoxan also produced CPP while the α1-antagonist prazosin (Cervo *et al.*, 1993) was without effect. The noradrenaline reuptake inhibitor desipramine was reported to be without effect (Martin-Iverson *et al.*, 1985) or to produce CPA (Papp, 1989). The α2-antagonist yohimbine was found to produce CPA (File, 1986).

3.1.14. *Adenosinergic Drugs*

Low to intermediate doses of caffeine (Brockwell *et al.*, 1991), low doses of theophylline, the preferential A2 agonist NECA and the adenosine antagonist 8-PT all produced CPP, whereas high doses of caffeine, theophylline and the preferential A1 agonists R-PIA and CHA produced CPA (Brockwell *et al.*, 1991; Zarrindast and Moghadamnia, 1997; but see Carey and Damianopoulos (1994) who reported a CPP for a high dose of caffeine). These latter results (using mice as subjects) differ from the findings of another study (Brockwell and Beninger, 1996) which used rats and showed that the selective A2 antagonist CGS 15943A produced CPP, whereas the A1 antagonist CPX, the A1 agonist CPA and the A2 agonist CGS 21680 were without effect.

3.1.15. *Diverse Drugs*

The anaesthetic propofol, but not the anaesthetic methohexital, produced CPP, both at subanaesthetic doses and at anaesthetic doses (in which case recovery from anaesthesia was paired with a distictive compartment) (Pain *et al.*, 1996, 1997). The non-benzodiazepine anxiolytics U-43 465 and tracazolate were found to produce CPP (File, 1986), and also glue thinner vapours (i.e. a mixture of different organic solvents) (Yavich *et al.*, 1994) and magnesium (in the form of $MgCl_2$) (Lawley and Kantak, 1990b).

The histamine H1 antagonist tripelennamine failed to produce an effect (Suzuki *et al.*, 1991b), while the H1 antagonist chlorpheniramine

(Masukawa *et al*., 1993) and the H2 antagonist zolantidine (Suzuki *et al*., 1995b) were found to produce CPP. A CPP induced by chlorpheniramine was also found in the goldfish, although only at higher doses, while a low dose produced CPA, perhaps via a H3-mediated mechanism (Mattioli *et al*., 1998).

The σ-agonists d,l-NAN and l-NAN (but not d-NAN) produced CPP (Iwamoto, 1986b), while the bradykinin BK1 antagonist des-Arg(9),(Leu(8))BK, but not the BK2 antagonist HOE 140, produced CPA (Sufka and Roach, 1996).

The immunosuppressant cyclosporine A did not produce CPP or CPA (Suzuki *et al*., 1993b), and Ginseng extract (Tokuyama *et al*., 1996b), a lipopolysaccharide purified from *Pantoea agglomerans* (Suzuki *et al*., 1994a), the putative antiaddictive drug ibogaine (Parker *et al*., 1995), the NO synthase inhibitors L-nitroarginin (L-NOARG) (Kivastik *et al*., 1996a) and L-NNA (Kim and Park, 1995), and ascorbate (Pierce *et al*., 1995) were equally ineffective.

3.1.16. *Natural Reinforcers*

One of the big advantages of the CPP paradigm is that non-drug reinforcers can be tested for their motivational properties. Thus, CPP has been shown to be produced by social interaction (rough-and-tumble play) in juvenile rats (Calcagnetti and Schechter, 1992b), home cage odours in infant rats (Hansen, 1993), interaction with pups in maternal rats (Magnusson and Fleming, 1995), social play (Crowder and Hutto, 1992a), successful intermale aggression in mice (Martinez *et al*., 1995), aggressive or sexual interaction with males in female hamsters (Meisel and Joppa, 1994; Paredes and Alonso, 1997; Meisel *et al*., 1996) and rats (Oldenburger *et al*., 1992), sexual interaction with oestrous females in male rats (Hughes *et al*., 1990; Mehrara and Baum, 1990; Miller and Baum, 1987), ejaculation (Agmo and Berenfeld, 1990; Agmo and Gomez, 1993), water (Crowder and Hutto, 1992a; Agmo *et al*., 1993; Perks and Clifton, 1997), sucrose or saccharin solution (Papp *et al*., 1991; Agmo *et al*., 1995; Perks and Clifton, 1997; Agmo and Marroquin, 1997; Stefurak and van der Kooy, 1992, 1994), and food (Lepore *et al*., 1995; Papp, 1988a, 1989; Papp *et al*., 1991; Cheeta *et al*., 1994; Willner *et al*., 1994; Guyon *et al*., 1993; Muscat *et al*., 1992; Perks and Clifton, 1997; Chapman *et al.,* 1998). Interaction with pups only produced CPP in postpartum (maternal) rats, but not in nulliparous rats, but could be induced in the latter by hormonal manipulation to mimic the state of maternity (Fleming *et al*., 1994). Food-induced CPP has been shown to depend on the actual consummatory act during the conditioning sessions, since only rats that were able to eat the food developed CPP, but not those that were exposed to food that they could see and smell but not eat in the conditioning compartment, or those that received a small meal in the home cage prior to the conditioning sessions (Maes and Vossen, 1993). A novel environment has also been shown to be able to produce CPP (Carr *et al*., 1988; Bardo *et al*., 1989, 1990, 1993; Parker, 1992; Laviola and Adriani, 1998) (see also Section 2.2).

3.2. 'Drug Combinations'

The interpretation of results from drug combination studies (Table 2) is not always straightforward. If a drug such as amphetamine or morphine is combined with another drug and this combination does not produce a place preference, this does not necessarily mean that this second drug blocked or attenuated the rewarding effects of the psychostimulant or the opiate per se. A lack of effect could also be due to fact that the additional drug made the place conditioning state-dependent, such that a test in the drug-free state would produce no effect (see Section 2.6), or it could be due to a disruption of the animals' perception of the conditioning context. If an animal is unable to perceive the distinct features of the conditioning context, it will not be able to form an association between these features and the rewarding drug effects. A lack of effect could also be due to the fact that the additional drug interfered with the process of conditioning rather than with the rewarding properties of the CPP-inducing drug. The acquisition of a CPP depends on the learning of the association between rewarding drug effect and conditioning environment. If a drug impairs learning it will also attenuate drug-induced CPP—without having any effect on drug reward. A good example for these notes of caution are NMDA receptor antagonists. These have frequently been shown to impair learning and memory (e.g. Morris *et al*., 1986; Bischoff and Tiedtke, 1992; Zajaczkowski *et al*., 1996), to impair the reaction to exteroceptive stimuli (Dai and Carey, 1994), and to produce state-dependency effects (Jackson *et al*., 1992). Yet they have also been shown to prevent the development of drug-induced CPP (see Section 3.2.1.5), an effect which could be due to all three of the aforementioned effects rather than to a blockade of the rewarding effects of the CPP-inducing drug. In fact, in self-administration (Ranaldi *et al*., 1996; Pierce *et al*., 1997) and brain-stimulation studies (Carlezon and Wise, 1993a; Ranaldi *et al*., 1997) it has been demonstrated repeatedly and convincingly that NMDA receptor antagonists enhance rather than attenuate the rewarding effects of drugs such as amphetamine, cocaine, or morphine. These issues have to be kept in mind when interpreting the results of systemic as well as local (see Section 4) drug combination studies (in principle, similar arguments also apply to the effects of lesions on drug-induced CPP, see Section 5).

3.2.1. *Place Conditioning Induced by Dopaminergic Drugs*

3.2.1.1. *Effects of dopaminergic drugs*

Place conditioning induced by cocaine: Haloperidol failed to affect cocaine-induced CPP (Mackey and van der Kooy, 1985; Kuzmin and Zvartau, 1993), methylphenidate- and nomifensine-induced CPP (Martin-Iverson *et al*., 1985). Note, however, that in the study by Martin-Iverson *et al*. (1985) a high dose of haloperidol was effective in blocking conditioning with methylphenidate. On the other hand, haloperidol attenuated the expression of cocaine-induced CPP, while amphetamine enhanced

Table 2. This table summarizes the results of studies using systemic drug-combination treatments. See Section 3.2 in the text for details about drugs, experimental procedures and additional findings that could not be included in the table. In cases where the effects of a drug on place aversion or on the expression of place conditioning were examined, this is indicated explicitely in the table by (CPA) and (expr.), respectively

Place conditioning induced by	Combined with	Result	References
Dopaminergic drugs:			
	Dopaminergic drugs:		
Cocaine	Haloperidol	CPP	Mackey and van der Kooy (1985); Kuzmin and Zvartau (1993); Spyraki *et al.* (1987)
	α-Flupenthixol	CPP	Mackey and van der Kooy (1985)
	Pimozide	CPP	Morency and Beninger (1986)
	Sulpiride	CPP	Cervo and Samanin (1995)
	SCH23390	No CPP	Pruitt *et al.* (1995); Cervo and Samanin (1995)
	Clozapine	No CPP	Kosten and Nestler (1994)
	Olanzapine	No CPP	Meil and Schechter (1997)
	Sertindole	No CPP	Suzuki and Misawa (1995)
	Preclomol	Reduced CPP	Kivastik *et al.* (1996b)
	Quinpirole	CPP	Kivastik *et al.* (1996b)
	CGS10746B	No CPP	Bilsky *et al.* (1998)
Cocaine (IV)	Haloperidol	No CPP	Spyraki *et al.* (1987)
Cocaine (expr.)	Haloperidol	Reduced CPP	Lawley and Kantak (1990a)
	Sulpiride	CPP	Cervo and Samanin (1995)
	SCH23390	CPP	Cervo and Samanin (1995)
	Amphetamine	Enhanced CPP	Lawley and Kantak (1990a)
Methylphenidate	Haloperidol	CPP	Martin-Iverson *et al.* (1985)
Nomifensine	Haloperidol	CPP	Martin-Iverson *et al.* (1985)
Amphetamine	Haloperidol	No CPP	Mackey and van der Kooy (1985); Hoffman and Donovan (1995)
	Raclopride	No CPP	
	Risperidone	No CPP	
	Clozapine	No CPP	
	α-flupenthixol	No CPP	Hoffman (1994); Mackey and van der Kooy (1985); Hoffman and Beninger (1989); Hiroi and White (1991a); Leone and Di Chiara (1987); Acquas and Di Chiara (1994)
	Metoclopramide	No CPP	
	Eticlopride	No CPP	
	Sulpiride	No CPP	
	SCH23390	No CPP	
	SCH39166	No CPP	
Amphet. (expr.)	α-flupenthixol	No CPP	Hiroi and White (1991a)
	Metoclopramide	No CPP	Hiroi and White (1991a)
	Sulpiride	No CPP	Hiroi and White (1991a)
	SCH23390	No CPP	Hiroi and White (1991a)
Methamphetamine	Sertindole	No CPP	Suzuki and Misawa (1995)
	Quinpirole	No CPP	Kamei and Ohsawa (1996)
	7-OH-DPAT	No CPP	Kamei and Ohsawa (1996)
Quinpirole	Metoclopramide	No CPP	Hoffman and Beninger (1989)
	SCH23390	No CPP	Hoffman and Beninger (1989)
SKF38393 (CPA)	Metoclopramide	No CPA	Hoffman and Beninger (1989)
	SCH23390	No CPA	Hoffman and Beninger (1989)
Bupropion	Haloperidol	CPP	Ortmann (1985)
	Sulpiride	CPP	Ortmann (1985)
Fencamfamine	Metoclopramide	CPP	Planeta da Silva *et al.* (1995)
	Pimozide	CPP	Planeta da Silva *et al.* (1995)
	SCH23390	No CPP	Planeta da Silva *et al.* (1995)
Diethylpropion	SCH23390	No CPP	Planeta da Silva *et al.* (1995)
	Haloperidol	CPP	Planeta da Silva *et al.* (1995)
pipradrol	SCH23390	No CPP	White and Hiroi (1992)
	Opioid drugs:		
Cocaine	Naloxone	No CPP	Houdi *et al.* (1989); Kuzmin and Zvartau (1993); Kim *et al.* (1997); Kuzmin *et al.* (1997); Gerrits *et al.* (1995); Biala and Langwinski (1996b)
	Naltrexone	No or reduced CPP	Sala *et al.* (1995); Bilsky *et al.* (1992); Suzuki *et al.* (1992d)
	Naltrexone (long-term)	CPP	Cramer *et al.* (1998)
	Naltrindole	No CPP	Menkens *et al.* (1992)
		CPP	De Vries *et al.* (1995); Shippenberg and Heidbreder (1995b)
	Buprenorphine	Enhanced CPP	Brown *et al.* (1991)
		No or reduced CPP	Suzuki *et al.* (1992d); Kosten *et al.* (1991)

(continued on next page)

Table 2 (*continued*)

Place conditioning induced by	Combined with	Result	References
	Morphine	Enhanced CPP	Masukawa *et al.* (1993)
	Methadone	Enhanced CPP	Bilsky *et al.* (1992)
	U-50 488H	No CPP	Crawford *et al.* (1995); Suzuki *et al.* (1992d)
Cocaine (expr.)	Naloxone	No CPP	Gerrits *et al.* (1995)
Amphetamine	Naloxone	No CPP	Trujillo *et al.* (1991); Biala and Langwinski (1996b)
Fencamfamine	Naloxone	No CPP	Planeta da Silva *et al.* (1995)
Methamphetamine	Morphine	Enhanced CPP	Masukawa *et al.* (1993)
Apomorphine	U-50 488H	CPP	Funada *et al.* (1993)
	GABAergic drugs:		
Amphetamine	Baclofen	CPP	Hoffman and Donovan (1995)
	Triazolam	Reduced CPP	Pettit *et al.* (1989)
	Progabide	CPP	Di Scala *et al.* (1985)
Amphet. (expr.)	Pentobarbital	CPP	Hiroi and White (1991b)
Cocaine (expr.)	Pentobarbital	Reduced CPP	Lawley and Kantak (1990a)
	Serotonergic drugs:		
Cocaine	MDL 72222	CPP	Cervo *et al.* (1996)
	Tropisetron	CPP	Cervo *et al.* (1996)
	Ondansetron	CPP	Cervo *et al.* (1996)
	MDL 72222	No CPP	Suzuki *et al.* (1992c)
	ICS 205-930	No CPP	Suzuki *et al.* (1992c)
	Buspirone	CPP	Ali and Kelly (1997)
Cocaine (expr.)	Buspirone	CPP	Ali and Kelly (1997)
	Ondansetron	CPP	Cervo *et al.* (1996)
Amphetamine	ICS 205-930	CPP	Acquas *et al.* (1988); Carboni *et al.* (1989)
	MDL 72222	CPP	Acquas *et al.* (1988); Carboni *et al.* (1989)
	Ritanserine	No CPP	Nomikos and Spyraki (1988a)
	Zimelidine	No CPP	Kruszewska *et al.* (1986)
Methamphetamine	ICS 205-930	No CPP	Suzuki *et al.* (1992c)
	MDL 72222	No CPP	Suzuki *et al.* (1992c)
	Glutamatergic drugs:		
Cocaine	MK-801	No CPP	Cervo and Samanin (1995); Kim *et al.* (1996b)
Cocaine (expr.)	MK-801	CPP	Cervo and Samanin (1995)
Amphetamine	MK-801	CPP	Hoffman (1994)
	Riluzole	No CPP	Tzschentke and Schmidt (1998a)
Amphet. (expr.)	MK-801	No CPP	Tzschentke and Schmidt (1997)
	GYKI 52466	No CPP	Tzschentke and Schmidt (1997)
	(±)CPP	No CPP	Bespalov (1996)
Methamphetamine	MK-801	No CPP	Kim and Jang (1997)
	Calcium channel blockers:		
Cocaine	Nifedipine	No CPP	Biala and Langwinski (1996a); Suzuki *et al.* (1992a)
	PN 200-110	No CPP	Pani *et al.* (1991)
	Flunarizine	No CPP	Suzuki *et al.* (1992a)
	Diltiazem	No CPP	Suzuki *et al.* (1992a)
	Verapamil	No CPP	Pucilowski *et al.* (1993)
	Nimodipine	No CPP	Martin-Iverson *et al.* (1997)
	Isradipine (long-term)	CPP	Cramer *et al.* (1998)
	Isradipine (long-term) + naltrexone (long-term)	No CPP	Cramer *et al.* (1998)
Amphetamine	Isradipine	No CPP	Pucilowski *et al.* (1995)
Methamphetamine	Nifedipine	Reduced CPP	Suzuki *et al.* (1992a)
	Diltiazem	Reduced CPP	Suzuki *et al.* (1992a)
	Flunarizine	CPP	Suzuki *et al.* (1992a)
	Other drugs and treatments:		
Cocaine	Ginseng extract	No CPP	Kim *et al.* (1996a,c); Tokuyama *et al.* (1996b); Takahashi and Tokuyama (1998)
	Pantoea agglom. lipopolysaccaride	No CPP	Suzuki *et al.* (1994a)
	Ibogaine	No CPP	Moroz *et al.* (1997)
	L-NNA	No CPP	Kim and Park (1995)
	Caffeine	Enhanced CPP	Tuazon *et al.* (1992)

Table 2 (*continued*)

Place conditioning induced by	Combined with	Result	References
	Theophylline	Enhanced CPP	Tuazon *et al.* (1992)
	SR141716	No CPP	Chaperon *et al.* (1998)
	Chlorpheniramine	Enhanced CPP	Masukawa *et al.* (1993)
	Lithium chloride	CPP	Suzuki *et al.* (1992a)
	Exp. inflammat.	Reduced CPP	Suzuki *et al.* (1996b)
Cocaine (expr.)	$MgCl_2$	Enhanced CPP	Lawley and Kantak (1990a)
	SR141716	CPP	Chaperon *et al.* (1998)
Amphetamine	Ascorbate	Enhanced CPP	Pierce *et al.* (1995)
	Chronic lithium	CPP	Shippenberg and Herz (1991)
	Cysteamine	CPP	Martin-Iverson *et al.* (1986)
	Perinatal ozone	CPP	Dell'Omo *et al.* (1995)
	Prazosin	CPP	Hoffman and Donovan (1995)
Amphet. (expr.)	Scopolamine	Enhanced CPP	Lynch (1991)
Methamphetamine	Ginseng extract	No CPP	Tokuyama *et al.* (1996b); Takahashi and Tokuyama (1998)
	Ginsenosides Rb-1 and Rg(1)	No CPP	Kim *et al.* (1998a)
	Caffeine	No CPP	Tuazon *et al.* (1992)
	Theophylline	No CPP	Tuazon *et al.* (1992)
	Chlorpheniramine	Enhanced CPP	Masukawa *et al.* (1993)
	Exp. inflammation	Reduced CPP	Suzuki *et al.* (1996b)
	Exp. diabetes	Enhanced CPP	Kamei and Ohsawa (1996)
	Environmental factors:		
Cocaine	Isolation rearing	No CPP	Schenk *et al.* (1986)
	Precocious Weaning	Enhanced CPP	Laviola and Dell'Omo (1997)
	Food deprivation	Enhanced CPP	Bell *et al.* (1997)
Amphetamine	Isolation rearing	No CPP	Wongwitdecha and Marsden (1995)
	Isolation rearing	CPP	Schenk *et al.* (1986); Bowling and Bardo (1994)
	Rear. in enriched environment	Enhanced CPP	Bowling and Bardo (1994)
	Chron. mild stress	No CPP	Papp *et al.* (1991, 1993a,b)
	Acute restr. stress	No CPP	Zurita *et al.* (1996)
Cathinone	Prior discrimin. learning	Enhanced CPP	Schechter (1991a)
Quinpirole	Chron. mild stress	No CPP	Papp *et al.* (1991, 1993a,b)
Opioid drugs:			
	Dopaminergic drugs:		
Morphine	Amphetamine	Enhanced CPP	Gaiardi *et al.* (1998)
	SCH23390	No CPP	Suzuki *et al.* (1995a,b); Acquas *et al.* (1989); Leone and Di Chiara (1987)
	Sulpiride	CPP	Shippenberg and Herz (1988)
	Spiperone	CPP	Shippenberg and Herz (1988)
	Haloperidol	CPP	Mackey and van der Kooy (1985)
	α-Flupenthixol	CPP	Mackey and van der Kooy (1985)
	Haloperidol	No CPP	Leone and Di Chiara (1987)
	Sertindole	No CPP	Suzuki and Misawa (1995)
	Preclamol	CPP	Kivastik *et al.* (1996b)
	Quinpirole	CPP	Kivastik *et al.* (1996b)
	7-OH-DPAT	No CPP	Rodriguez de Fonseca *et al.* (1995)
Morphine (expr.)	7-OH-DPAT	No CPP	Rodriguez de Fonseca *et al.* (1995)
Heroin	Pimozide	Reduced CPP	Hand *et al.* (1989)
Heroin (expr.)	Pimozide	Reduced CPP	Hand *et al.* (1989)
BW373U86	SCH23390	No CPP	Longoni *et al.* (1998)
SNC 80	SCH23390	No CPP	Longoni *et al.* (1998)
U-69593 (CPA)	SCH23390	No CPA	Shippenberg and Herz (1987, 1988); Acquas *et al.* (1989)
	Sulpiride	CPA	Shippenberg and Herz (1988)
	Spiperone	CPA	Shippenberg and Herz (1988)
Naloxone (CPA)	Sulpiride	CPA	Shippenberg and Herz (1988)
	Spiperone	CPA	Shippenberg and Herz (1988)
	Opioid drugs:		
Morphine	Naloxone	No CPP	Shippenberg and Herz (1986); Bardo and Neisewander (1986); Neisewander *et al.* (1990a); Bilsky *et al.* (1990a); Biala and Langwinski (1996b)

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Table 2 (*continued*)

Place conditioning induced by	Combined with	Result	References
	Naltrexone	No CPP	Piepponen *et al.* (1997); Bilsky *et al.* (1990a); Bardo and Neisewander (1987)
	β-funaltrexamine	No CPP	Suzuki *et al.* (1993a)
	Naloxonazine	No CPP	Piepponen *et al.* (1997)
	Naloxonazine	CPP	Suzuki *et al.* (1993a)
	Naltrindole	CPP	Piepponen *et al.* (1997)
	Naltrindole	No CPP	Suzuki *et al.* (1994b)
	7-Benzylidene-naltrexone	No CPP	Suzuki *et al.* (1994b)
	Naltriben	No CPP	Suzuki *et al.* (1994b)
	TAN 67	Enhanced CPP	Suzuki *et al.* (1996c)
	Methylnaloxone	CPP	Agmo *et al.* (1992)
	U-50 488H	No CPP	Bolanos *et al.* (1996); Funada *et al.* (1993)
	E-2078	No CPP	Funada *et al.* (1993)
Morphine (expr.)	Naloxone	Enhanced CPP	Neisewander *et al.* (1990a); Noble *et al.* (1993)
	RB-101	CPP	Noble *et al.* (1993)
Heroin	Naloxone	No CPP	Hand *et al.* (1989)
[Leu]enkephalin	Methylnaloxone	Reduced CPP	Heinrichs and Martinez (1986)
BW373U86	Naltrindole	No CPP	Longoni *et al.* (1998)
SNC 80	Naltrindole	No CPP	Longoni *et al.* (1998)
U-50 488H (CPA)	Naloxone	CPA	Shippenberg and Herz (1986)
	Mr 2266	Reduced CPA	Bechara and van der Kooy (1987)
Naloxone (CPA)	Dexamethasone	CPA	Mucha *et al.* (1985)
	GABAergic drugs:		
Morphine	Triazolam	CPP	Pettit *et al.* (1989)
	Ro 15-1788	CPP	Bilsky *et al.* (1990a)
	Diazepam	No CPP	Suzuki *et al.* (1995c)
	Serotonergic drugs:		
Morphine	ICS 205-930	No CPP	Acquas *et al.* (1988); Carboni *et al.* (1988, 1989); Higgins *et al.* (1992a); Bisaga *et al.* (1993)
	MDL 72222	No CPP	
	Ondansetron	No CPP	
	Ritanserin	Reduced CPP	Nomikos and Spyraki (1988a)
	DAU 6285	No CPP	Bisaga *et al.* (1993)
	BIMU-8	CPP	Bisaga *et al.* (1993)
	Zimelidine	CPP	Kruszewska *et al.* (1986)
	Glutamatergic drugs:		
Morphine	MK-801	No CPP	Kim *et al.* (1996b); DelPozo *et al.* (1996); Tzschentke and Schmidt (1995, 1997)
	Memantine	No CPP	Popik and Danysz (1997)
	Kynurenic acid	No CPP	Bespalov *et al.* (1994)
	CGP37849	Reduced CPP	Tzschentke and Schmidt (1995)
	Riluzole	No CPP	Tzschentke and Schmidt (1998a)
Morphine (expr.)	MK-801	No CPP	Tzschentke and Schmidt (1997)
	Memantine	No CPP	Popik and Danysz (1997)
	Kynurenic acid	No CPP	Bespalov *et al.* (1994)
	CCKergic drugs:		
Morphine	PD 142898	No CPP	Higgins *et al.* (1991b); Singh *et al.* (1996a,b)
	PD 140548	No CPP	Higgins *et al.* (1991b); Singh *et al.* (1996a,b)
	CI 988	CPP	Higgins *et al.* (1991b); Singh *et al.* (1996a,b)
	Devazepide	Reduced CPP	Higgins *et al.* (1992c)
	L365-260	Enhanced CPP	Higgins *et al.* (1992c)
	PD 134308	Enhanced CPP	Valverde *et al.* (1996a)
RB-101	PD 134308	Enhanced CPP	Valverde *et al.* (1996a)
	Other drugs and treatments:		
Morphine	Antipain	No CPP	Lyupina *et al.* (1996)
	Leupeptin	No CPP	Lyupina *et al.* (1996)
	Ibogaine	No CPP	Luxton *et al.* (1996); Parker *et al.* (1995)
	Ginseng total saponin	No CPP	Kim *et al.* (1998b)
	SR141716	No CPP	Chaperon *et al.* (1998)
	L-NOArg	No CPP	Kivastik *et al.* (1996a)
	Nifedipine	No CPP	Biala and Langwinski (1996a)
	Isradipine	No CPP	Kuzmin *et al.* (1992)
	Nitroprusside	No CPP	Biala and Langwinski (1996b)
	Chronic lithium	No CPP	Shippenberg and Herz (1991)
	L-histidine	Reduced CPP	Suzuki *et al.* (1995b)

Table 2 (*continued*)

Place conditioning induced by	Combined with	Result	References
	α-Fluoromethyl-histidine	Enhanced CPP	Suzuki *et al.* (1995b)
	Zolantidine	Enhanced CPP	Suzuki *et al.* (1995b)
	Ethanol	Enhanced CPP	Marglin *et al.* (1988)
	Cyclosporine	No CPP	Suzuki *et al.* (1993b)
	Chronic cadmium	Reduced CPP	Miller and Nation (1997)
	Exp. inflammation	Reduced CPP	Suzuki *et al.* (1996b)
Morphine (expr.)	Molsidomine	CPP	Biala and Langwinski (1996b)
Heroin	Clonidine	No CPP	Hand *et al.* (1989)
Dihydrocodeine	Chlorpheniramine	Enhanced CPP	Suzuki *et al.* (1990)
Naloxone (CPA)	Chronic lithium	no CPA	Shippenberg and Herz (1991)
U-69593 (CPA)	Chronic lithium	CPA	Shippenberg and Herz (1991)
	Environmental factors:		
Morphine	Chron. mild stress	No CPP	Papp *et al.* (1992)
	Acute restr. stress	No CPP	Kiyatkin and Belyi (1991)
	Social isolation	No CPP	Coudereau *et al.* (1997); Wongwitdecha and Marsden (1996)
		Reduced CPP	Schenk *et al.* (1985)
	Rear. in enriched environment	Enhanced CPP	Bardo *et al.* (1997)
	Social defeat	Reduced CPP	Coventry *et al.* (1997)
	Food deprivation	Enhanced CPP	Gaiardi *et al.* (1987)
	Sucrose solution	Enhanced CPP	Lett (1989b)
Naloxone (CPA)	Chron. mild stress	CPA	Papp *et al.* (1992)
Naloxone (CPA) (in morphine-depend. animals)	Memantine	No CPA	Popik and Danysz (1997)
	MK-801	No CPA	Higgins *et al.* (1992b)
	Propylnorapom.	No CPA	Harris and Aston-Jones (1994)
	α-Flupenthixol	No CPA	Bechara *et al.* (1995)
	DAU 6215	No CPA	Borsini *et al.* (1993)
	Ondansetron	No CPA	Higgins *et al.* (1991a)
	ICS 205-930	No CPA	Acquas *et al.* (1990)
	MDL 72222	No CPA	Acquas *et al.* (1990); Higgins *et al.* (1991a)
	Chlordiazepoxide	No CPA	Higgins *et al.* (1991a)
	Gepirone	CPA	Higgins *et al.* (1991a)
	Clonidine	No CPA	Kosten (1994)
	Propranolol	No CPA	Harris and Aston-Jones (1993)
	Atenolol	No CPA	Harris and Aston-Jones (1993)
	Fluvoxamine	No CPA	Rafieian-Kopaei *et al.* (1995)
	Paroxetine	No CPA	Rafieian-Kopaei *et al.* (1995)
	Binaltorphimine	Enhanced CPA	Spanagel *et al.* (1994)
	PD-134 308 (long-term)	Reduced CPA	Valverde and Roques (1998)
	L-365-260 (long-term)	No CPA	Valverde and Roques (1998)
	Devazepide (long-term)	CPA	Valverde and Roques (1998)
	BC 264 (long-term)	CPA	Valverde and Roques (1998)
Ethanol	Mianserin	Enhanced CPP	Risinger and Oakes (1996a)
	Fluoxetine	CPP	Risinger (1997)
	Naloxone	No CPP	Biala and Langwinski (1996b)
		CPP	Cunningham *et al.* (1995)
	Nitroprusside	Reduced CPP	Biala and Langwinski (1996b)
	Mazindol	CPP	Gevaerd and Takahashi (1996)
	Haloperidol	CPP	Risinger *et al.* (1992a); Cunningham *et al.* (1992a)
	Ro 15-4513	CPP	Risinger *et al.* (1992b)
	Nifedipine	CPP	Biala and Langwinski (1996a)
	Aminoglutethim.	CPP	Chester and Cunningham (1998)
	Pyrazole	Enhanced CPP	Suzuki *et al.* (1992b)
	Cond. fear stress	Enhanced CPP	Matsuzawa *et al.* (1998)
Ethanol (expr.)	Naloxone	CPP	Cunningham *et al.* (1995)
	Molsidomine	Reduced CPP	Biala and Langwinski (1996b)
Ethanol (CPA)	Tropisetron	CPA	Bienkowski *et al.* (1997a)
	Social interaction	Reduced CPA	Gauvin *et al.* (1994)
	Increased ambient temperature	Reduced CPA	Cunningham and Niehus (1993)
Nicotine	ICS 205-930	No CPP	Acquas *et al.* (1988); Carboni *et al.* (1988, 1989)
	MDL 72222	No CPP	Acquas *et al.* (1988); Carboni *et al.* (1988, 1989)

(continued on next page)

Table 2 (*continued*)

Place conditioning induced by	Combined with	Result	References
	SCH23390	No CPP	Acquas *et al*. (1989)
	Mecamylamine	No CPP	Fudala *et al*. (1985)
	Hexamethonium	CPP	Fudala *et al*. (1985)
GABAergic drugs:			
Diazepam	SCH23390	No CPP	Acquas *et al*. (1989)
	Haloperidol	No CPP	Spyraki and Fibiger (1988)
	Domperidon	CPP	Spyraki and Fibiger (1988)
	Ritanserin	No CPP	Nomikos and Spyraki (1988a)
	CGS 8216	No CPP	Spyraki *et al*. (1985)
	Picrotoxin	No CPP	Spyraki *et al*. (1985)
	Naloxone	No CPP	Spyraki *et al*. (1985)
	Sodium valproate	CPP	Spyraki *et al*. (1985)
FG7142 (CPA)	Haloperidol	No CPA	Di Scala and Sandner (1989b)
Picrotoxin (CPA)	SCH23390	No CPA	Acquas *et al*. (1989)
	ICS 205-930	No CPA	Acquas *et al*. (1990)
	MDL 72222	No CPA	Acquas *et al*. (1990)
	Chron. mild stress	CPA	Papp *et al*. (1992)
Pentylenetetra-zole(expr.) (CPA)	(±)CPP	No CPA	Bespalov (1996)
Serotonergic drugs:			
8-OH-DPAT	PCPA	No CPP	Papp and Willner (1991)
	Pimozide	No CPP	Papp and Willner (1991)
	Sulpiride	No CPP	Papp and Willner (1991)
	Spiperone	No CPP	Shippenberg (1991)
	SCH23390	No CPP	Shippenberg (1991)
	Sulpiride	CPP	Shippenberg (1991)
8-OH-DPAT (CPA)	PCPA	CPA	Papp and Willner (1991)
	Pimozide	CPA	Papp and Willner (1991)
MDMA	MDL 72222	No CPP	Bilsky and Reid (1991)
	CGS 10746	No CPP	Bilsky *et al*. (1998)
	Naltrexone	Reduced CPP	Bilsky *et al*. (1991)
Mianserin (CPA)	mCPP	No CPA	Rocha *et al*. (1993a)
Eltoprazine (CPA)	mCPP	No CPA	Rocha *et al*. (1993a)
mCPBG (CPA)	Ondansetron	No CPA	Higgins *et al*. (1993)
PBG (CPA)	ICS 205-930	No CPA	Higgins *et al*. (1993)
Various drug combinations:			
Zolantidine	SCH23390	No CPP	Suzuki *et al*. (1995b)
Pentazocine + tripelennamine	SCH23390	No CPP	Suzuki *et al*. (1991b)
Propofol	Midazolam	No CPP	Pain *et al*. (1997)
Clonidine	Idazoxan	No CPP	Cervo *et al*. (1993)
	Prazosin	CPP	Cervo *et al*. (1993)
Substance P	Naloxone	No CPP	Hasenöhrl *et al*. (1991)
	Haloperidol	No CPP	Mattioli *et al*. (1995)
WIN 55212-2 (CPA)	SR141716	No CPA	Chaperon *et al*. (1998)
PCP (CPA)	SCH23390	No CPA	Acquas *et al*. (1989); Nabeshima *et al*. (1996)
	Butaclamol	No CPA	Iwamoto (1986a)
	Spiroperidol	No CPA	Iwamoto (1986a)
	ICS 205-930	No CPA	Acquas *et al*. (1990)
	MDL 72222	No CPA	Acquas *et al*. (1990)
Lithium chloride (CPA)	Metoclopramide	No CPA	Frisch *et al*. (1995)
	Ginkgo biloba + Zingiber offic. extracts	No CPA	Frisch *et al*. (1995)
	Dexamethasone	CPA	Shippenberg *et al*. (1998)
	Ibogaine	CPA	Parker *et al*. (1995)
	Naloxone	No CPA	Acquas and Di Chiara (1994)
	SCH23390	No CPA	Acquas and Di Chiara (1994)
	SCH39166	No CPA	Acquas and Di Chiara (1994)
	High ambient temperature	Reduced CPA	Cunningham and Niehus (1993)
Natural reinforcers:			
Sex. interaction in females	Raclopride	No CPP	Meisel *et al*. (1996)
Sex. interaction in males	Pimozide	CPP	Agmo and Berenfeld (1990)
	Naloxone	CPA	Agmo and Berenfeld (1990)

Table 2 (*continued*)

Place conditioning induced by	Combined with	Result	References
Sex. interaction in males (expr.)	Naloxone	Reduced CPP	Miller and Baum (1987); Mehrara and Baum (1990)
Home cage odors in infant rats	Clonidine	No CPP	Hansen (1993)
	Raclopride	CPP	Hansen (1993)
	Naltrexone	CPP	Hansen (1993)
	Propranolol	CPP	Hansen (1993)
Food	Sulpiride (low d.)	Enhanced CPP	Guyon *et al*. (1993)
	Amisulpiride (low dose)	Enhanced CPP	Guyon *et al*. (1993)
	Pimozide (low d.)	Enhanced CPP	Guyon *et al*. (1993)
	Sulpiride (high d.)	Reduced CPP	Guyon *et al*. (1993)
	Amisulpiride (high dose)	Reduced CPP	Guyon *et al*. (1993)
	Pimozide (hi. d.)	Reduced CPP	Guyon *et al*. (1993)
	Haloperidol	Reduced CPP	Guyon *et al*. (1993)
	Metoclopramide	Reduced CPP	Guyon *et al*. (1993)
	Chlorpromazine	Reduced CPP	Guyon *et al*. (1993)
	Naloxone	No CPP	Agmo *et al*. (1993)
	Pimozide	No CPP	Agmo *et al*. (1993)
	Raclopride	No CPP	Agmo *et al*. (1993)
	SCH23390	No CPP	Agmo *et al*. (1993)
	α-flupenthixol	CPP	Bechara *et al*. (1992); Harrington and van der Kooy (1992)
	Memantine	CPP	Popik and Danysz (1997)
	SR141716	No CPP	Chaperon *et al*. (1998)
	Chron. mild stress	No CPP	Papp *et al*. (1991); Muscat *et al*. (1992); Cheeta *et al*. (1994); D'Aquila *et al*. (1997)
Food (expr.)	Memantine	CPP	Popik and Danysz (1997)
Sucrose solution	α-Flupenthixol	No CPP	Agmo *et al*. (1995)
	Naloxone	No CPP	Agmo *et al*. (1995)
	Chron. mild stress	No CPP	Papp *et al*. (1991); Muscat *et al*. (1992); Cheeta *et al*. (1994); D'Aquila *et al*. (1997)
Food shocks (CPA)	Diazepam	No CPA	Papp (1988a)
	ICS 205-930	No CPA	Papp (1988a)
Novel environment (expr.)	Haloperidol	No CPP	Bardo *et al*. (1989)
	Apomorphine (low dose)	No CPP	Bardo *et al*. (1990)
	SKF 38393	No CPP	Bardo *et al*. (1993)
	Quinpirole	No CPP	Bardo *et al*. (1993)
	SCH23390	No CPP	Bardo *et al*. (1993)
	Morphine	CPP	Bardo *et al*. (1989)
	Naltrexone	CPP	Bardo *et al*. (1989)
	Amphetamine	CPP	Bardo *et al*. (1989)
	Apomorphine (high dose)	CPP	Bardo *et al*. (1990)
	Eticlopride	CPP	Bardo *et al*. (1993)

the expression of cocaine-induced CPP (Lawley and Kantak, 1990a). A similar lack of effect as for haloperidol on the acquisition of cocaine-induced CPP was also reported for α-flupenthixol (Mackey and van der Kooy, 1985) and pimozide (Morency and Beninger, 1986). Note, however, that although haloperidol did not affect IP cocaine-induced CPP, it did disrupt CPP induced by IV cocaine (Spyraki *et al*., 1987). Note also that the D2 antagonists sulpiride and eticlopride prevented cocaine-induced CPP in 10-day-old but not in 17-day-old rats, while SCH 23390 was effective at both ages (Pruitt *et al*., 1995) and in adult rats (Cervo and Samanin, 1995). In the latter study, SCH 23390 did not affect the expression of cocaine-induced CPP and sulpiride had no effect on either acquisition or expression of cocaine-induced CPP. On the other hand, a blockade of cocaine-induced CPP by clozapine (Kosten and Nestler, 1994), olanzapine (Meil and Schechter, 1997) and sertindole (Suzuki and Misawa, 1995) was reported. The partial DA autoreceptor agonist preclomol, but not autoreceptor-specific doses of quinpirole, attenuated cocaine-induced CPP (Kivastik *et al*., 1996b). CGS10746B, which reduces presynaptic DA release, blocked cocaine-induced CPP (Bilsky *et al*., 1998).

Place conditioning induced by amphetamine: Amphetamine-induced CPP was reported to be blocked by haloperidol, raclopride, risperidone and clozapine (Mackey and van der Kooy, 1985;

Hoffman and Donovan, 1995), and methamphetamine-induced CPP was blocked by sertindole (Suzuki and Misawa, 1995), quinpirole and the D3 agonist 7-OH-DPAT (Kamei and Ohsawa, 1996). Amphetamine-induced CPP was also prevented by the D1 antagonists SCH 23390 and SCH 39166, and the D2 antagonists α-flupenthixol, metoclopramide, eticlopride, and sulpiride (Hoffman, 1994; Mackey and van der Kooy, 1985; Hoffman and Beninger, 1989; Hiroi and White, 1991a; Leone and Di Chiara, 1987; Acquas and Di Chiara, 1994). Expression of amphetamine-induced CPP was also blocked by SCH 23390 and the D2 antagonists, although high doses of the D2 antagonists that might have lost specificity for the D2 receptors had to be used to obtain this effect (Hiroi and White, 1991a).

Place conditioning induced by other dopaminergic drugs: Quinpirole-induced CPP and SKF 38393-induced CPA was prevented by SCH 23390 and metoclopramide (Hoffman and Beninger, 1989), while bupropion-induced CPP was not affected by haloperidol or sulpiride (Ortmann, 1985). Fencamfamine-induced CPP was blocked by SCH 23390, but not by metoclopramide and pimozide (Planeta da Silva *et al*., 1995). Likewise, diethylpropion-induced CPP was blocked by SCH23390 but not by haloperidol (Planeta da Silva and DeLucia, 1998). Pipradrol-induced CPP was also blocked by SCH 23390 (White and Hiroi, 1992). The CPA induced by the D1 antagonist SCH 23390 was found to be prevented by pairing another D1 antagonist, SCH 39166, with both compartments during conditioning (Acquas and Di Chiara, 1994).

Taken together, these results suggest that the rewarding properties of cocaine and related DA reuptake blockers appear to be dependent on D1 receptor-mediated mechanisms, while they seem to be largely independent of D2 receptor-mediated mechanisms. In contrast to this, while also dependent on dopaminergic transmission at the D1 receptor, the rewarding properties of amphetamine appear to be highly dependent on dopaminergic activity at D2 receptors as well. Thus, the rewarding effects of cocaine and amphetamine not only seem to depend to a differential degree on different anatomical substrates (see Section 4.1.1) but also appear to be mediated (at least partly) by different receptor mechanisms.

3.2.1.2. *Effects of opioidergic drugs*

Naloxone blocked cocaine-induced CPP (Houdi *et al*., 1989; Kuzmin and Zvartau, 1993; Kim *et al*., 1997; Kuzmin *et al*., 1997; Gerrits *et al*., 1995; Biala and Langwinski, 1996b), amphetamine-induced CPP (Trujillo *et al*., 1991; Biala and Langwinski, 1996b) and fencamfamine-induced CPP (Planeta da Silva *et al*., 1995), while naloxone methyl-iodide, a methylated naloxone analogon that does not cross the blood–brain barrier, had no effect (Kuzmin *et al*., 1997), suggesting that peripheral opioid receptors are not involved in the mediation of psychostimulant-induced reward. Naloxone was also reported to block the expression of cocaine-induced CPP (Gerrits *et al*., 1995). Naltrexone also blocked or attenuated cocaine-induced CPP (Sala *et al*., 1995; Bilsky *et al*., 1992; Suzuki *et al*., 1992d). However, it was also reported that long-term pretreatment with naltrexone did not affect cocaine-induced CPP (Cramer *et al.,* 1998). The δ-antagonist naltrindole also prevented cocaine-induced CPP in one study (Menkens *et al*., 1992), but not in others (De Vries *et al*., 1995; Shippenberg and Heidbreder, 1995b).

Combined subthreshold doses of cocaine and buprenorphine were able to produce a CPP, and a combination of larger doses of both drugs also produced potentiated effects (Brown *et al*., 1991). In contrast to this, it has also been reported that acute pretreatment with buprenorphine blocked cocaine-induced CPP (Suzuki *et al*., 1992d), and that chronic pretreatment with buprenorphine (2 times/day for 2 weeks) significantly attenuated cocaine-induced CPP (Kosten *et al*., 1991). Morphine had an additive effect on methamphetamine-induced CPP and a potentiating effect on cocaine-induced CPP (Masukawa *et al*., 1993). Methadone was also shown to enhance the CPP-inducing effects of cocaine (Bilsky *et al*., 1992). On the other hand, it was reported that U-50 488H blocked cocaine-induced CPP (Crawford *et al*., 1995; Suzuki *et al*., 1992d) but did not affect apomorphine-induced CPP (Funada *et al*., 1993).

3.2.1.3. *Effects of GABAergic drugs*

The GABA-B agonist baclofen failed to disrupt amphetamine-induced CPP (Hoffman and Donovan, 1995), while triazolam attenuated amphetamine-induced CPP (Pettit *et al*., 1989). Sodium pentobarbital failed to affect the expression of amphetamine-induced CPP (Hiroi and White, 1991b), while it attenuated the expression of cocaine-induced CPP (Lawley and Kantak, 1990a). The GABA mimetic progabide (SL 76002) did not affect amphetamine-induced CPP (Di Scala *et al*., 1985).

3.2.1.4. *Effects of serotonergic drugs*

Cocaine-induced CPP was not affected by the 5-HT3 antagonists MDL 72222, tropisetron and ondansetron, and ondansetron had also no effect on the expression of the cocaine-induced CPP (Cervo *et al*., 1996). A similar lack of effect of the 5-HT3 antagonists ICS 205-930 and MDL 72222 on amphetamine-induced CPP was also shown (Carboni *et al*., 1989; Acquas *et al*., 1988). No effect on acquisition and expression of cocaine-induced CPP was also reported for the 5-HT1A agonist buspirone (Ali and Kelly, 1997). In contrast to these results, it was also reported that MDL 72222 and ICS 205-930 blocked cocaine-induced and (at high doses) methamphetamine-induced CPP (Suzuki *et al*., 1992c). Amphetamine-induced CPP was prevented by the 5-HT2 antagonist ritanserine (Nomikos and Spyraki, 1988a; see also Spyraki and Nomikos, 1991) and the serotonin reuptake inhibitor zimelidine (Kruszewska *et al*., 1986).

3.2.1.5. *Effects of glutamatergic drugs*

It has been shown that the NMDA antagonist MK-801 can block cocaine-induced CPP (Kim *et al*., 1996b; Cervo and Samanin, 1995) and meth-

amphetamine-induced CPP (Kim and Jang, 1997), while no effect of MK-801 was found on amphetamine-induced CPP (Hoffman, 1994). On the other hand, the competitive NMDA antagonist (±) CPP was shown to prevent the expression of a previously established amphetamine-induced CPP (Bespalov, 1996), MK-801 did not affect the expression of cocaine-induced CPP (Cervo and Samanin, 1995) but blocked the expression of amphetamine-induced CPP (Tzschentke and Schmidt, 1997), an effect that has also been reported for the AMPA antagonist GYKI 52466 (Tzschentke and Schmidt, 1997). The glutamate release inhibitor riluzole blocked amphetamine-induced CPP (Tzschentke and Schmidt, 1998a).

3.2.1.6. *Effects of calcium channel blockers*

Cocaine-induced CPP was blocked or attenuated by nifedipine (Biala and Langwinski, 1996a; Suzuki *et al*., 1992a), PN 200-110 (Pani *et al*., 1991), flunarizine, diltiazem (Suzuki *et al*., 1992a), verapamil (Pucilowski *et al*., 1993) and nimodipine (Martin-Iverson *et al*., 1997). No effect on cocaine-induced CPP was obtained by long-term pretreatment with isradipine. However, if isradipine was combined with naltrexone during the pretreatment phase, this drug combination blocked cocaine-induced CPP (Cramer *et al.,* 1998). Amphetamine-induced CPP was prevented by isradipine (Pucilowski *et al*., 1995) and methamphetamine-induced CPP was attenuated by nifedipine and diltiazem, but not by flunarizine (Suzuki *et al*., 1992a).

3.2.1.7. *Effects of other substances and treatments*

It has been shown that methamphetamine- and cocaine-induced CPP could be blocked by Ginseng extract (Kim *et al*., 1996a,c; Tokuyama *et al*., 1996b; Takahashi and Tokuyama, 1998) and methamphetamine-induced CPP was also prevented by the ginsenosides Rb-1 and Rg(1), the major components of Ginseng saponin (Kim *et al.,* 1998a). Cocaine-induced CPP was also blocked by a lipopolysaccharide purified from *Pantoea agglomerans* (Suzuki *et al*., 1994a), by the putative anti-addictive drug ibogaine (Moroz *et al*., 1997), and also by the nitric oxide synthase inhibitor L-NNA (Kim and Park, 1995). Caffeine and theophylline prevented methamphetamine-induced CPP, but enhanced the CPP induced by cocaine (Tuazon *et al*., 1992), while the H1 antagonist chlorpheniramine had an additive effect on cocaine-induced CPP and a potentiating effect on methamphetamine-induced CPP (Masukawa *et al*., 1993). The development but not the expression of cocaine-induced CPP was blocked by the CB1 receptor antagonist SR 141716 (Chaperon *et al.,* 1998). The magnitude of amphetamine-induced CPP was enhanced by blockade of the association between place and amphetamine-induced sickness (Lett, 1988), a low dose of ascorbate potentiated the CPP-inducing effect of a low dose of amphetamine (Pierce *et al*., 1995), the expression of amphetamine-induced CPP was enhanced by scopolamine (Lynch, 1991) and the expression of cocaine-induced CPP was enhanced by magnesium chloride (Lawley and Kantak, 1990a).

Chronic administration of a lithium-containing diet before and during conditioning did not affect amphetamine-induced CPP (Shippenberg and Herz, 1991) and coadministration of lithium chloride did also not affect cocaine-induced CPP (Suzuki *et al*., 1992a). Amphetamine-induced CPP was not affected significantly by cysteamine, a presumed selective depletor of somatostatin (Martin-Iverson *et al*., 1986), by combined gestational and postnatal exposure to ozone (Dell'Omo *et al*., 1995) and by the peripheral α1-antagonist prazosin (Hoffman and Donovan, 1995).

Inflammation induced by formalin or carrageenan attenuated the ability of methamphetamine and cocaine to induce CPP (Suzuki *et al*., 1996b), while methamphetamine-induced CPP was found to be much stronger in diabetic than in non-diabetic mice (Kamei and Ohsawa, 1996).

3.2.1.8. *Effects of environmental factors*

Isolation rearing abolished the ability of cocaine (Schenk *et al*., 1986) and amphetamine (Wongwitdecha and Marsden, 1995) to produce CPP. However, isolation rearing had no effect on amphetamine-induced CPP in the study of Schenk *et al*. (1986), and Bowling and Bardo (1994) also reported no difference in the potential of amphetamine to induce CPP between single- and group-housed rats. However, when the rats were group-housed in an 'enriched' environment, these animals showed a greater magnitude of amphetamine-induced CPP (see also Bardo *et al*., 1995a). Precocious weaning enhanced the CPP-inducing effect of cocaine in adult mice, while sexual segregation during development (rearing in the absence of members of the respective other sex) prevented cocaine-induced CPP (Laviola and Dell'Omo, 1997).

Chronic unpredictable mild stress blocked the ability of amphetamine and quinpirole to induce CPP (Papp *et al*., 1991, 1993a,b), and amphetamine-induced CPP was blocked by acute restraint stress, an effect that was antagonized by naloxone (Zurita *et al*., 1996). On the other hand, food deprivation was shown to increase the magnitude of cocaine-induced CPP (Bell *et al*., 1997).

Cathinone-induced CPP was potentiated by prior drug discrimination learning (cathinone vs saline). This effect was not due to sensitization of the rewarding effects of cathinone with repeated administration (see Section 7), because yoked controls receiving the same amount of the drug independently of discrimination training did not show this effect (Schechter, 1991a). This suggests that the potential of a drug to be perceived as a distinct stimulus (i.e. distinct from saline or any other control treatment) significantly contributes to the drug's ability to produce CPP.

3.2.2. *Place Conditioning Induced by Opioids*

3.2.2.1. *Effects of dopaminergic drugs*

Amphetamine enhanced the ability of morphine to induce CPP (Gaiardi *et al*., 1998). SCH 23390 prevented morphine-induced CPP and naloxone- and U-69593-induced CPA (Suzuki *et al*., 1995a,b; Acquas *et al*., 1989; Shippenberg and Herz, 1987,

1988; Leone and Di Chiara, 1987). SCH23390 also blocked CPP induced by the non-peptide δ-agonists BW373U86 and SNC 80 (Longoni *et al.,* 1998), while the D2 antagonists sulpiride and spiperone did not affect morphine-induced CPP and naloxone- and U-69593-induced CPA (Shippenberg and Herz, 1988). A similar lack of effect on morphine-induced CPP was reported for haloperidol and α-flupenthixol (Mackey and van der Kooy, 1985). In an extension of this work, Bechara *et al.* (1992) showed that α-flupenthixol and pimozide blocked CPP induced by morphine or heroin in morphine-dependent, but not in morphine-naive rats. On the other hand, Leone and Di Chiara (1987) reported that haloperidol was able to block morphine-induced CPP in non-dependent animals, and sertindole also blocked morphine-induced CPP (Suzuki and Misawa, 1995). Pimozide was shown to attenuate the acquisition and the expression of heroin-induced CPP (Hand *et al.*, 1989), while the partial DA autoreceptor agonist preclamol and autoreceptor-specific doses of quinpirole failed to affect morphine-induced CPP (Kivastik *et al.*, 1996b). An intermediate and a high dose of the D3 agonist 7-OH-DPAT prevented the development of a morphine-induced CPP, while a low, but not an intermediate or a high dose of 7-OH-DPAT blocked the expression of morphine-induced CPP, suggesting the importance of postsynaptic D3 receptors for the acquisition of and presynaptic D3 autoreceptors for the expression of morphine-induced CPP (Rodriguez de Fonseca *et al.*, 1995).

3.2.2.2. *Effects of opioidergic drugs*

The development, but not the expression, of heroin-induced CPP was blocked by naloxone (Hand *et al.*, 1989). Likewise, naloxone blocked the development (Shippenberg and Herz, 1986; Bardo and Neisewander, 1986; Neisewander *et al.*, 1990a; Bilsky *et al.*, 1990a; Biala and Langwinski, 1996b), but enhanced the expression of morphine-induced CPP (Neisewander *et al.*, 1990a; Noble *et al.*, 1993). Morphine-induced CPP was also antagonized by naltrexone (Piepponen *et al.*, 1997; Bilsky *et al.*, 1990a), the μ1/μ2 antagonist β-funaltrexamine (Suzuki *et al.*, 1993a) and the selective μ1 antagonist naloxonazine, but not by the δ-antagonist naltrindole (Piepponen *et al.*, 1997; but see Suzuki *et al.*, 1994b). On the other hand, a lack of effect on morphine-induced CPP was also reported for naloxonazine (Suzuki *et al.*, 1993a), and for methylnaloxone, which does not readily cross the blood–brain barrier (Agmo *et al.*, 1992), indicating that central opiate receptors are responsible for the reinforcing actions of morphine and heroin. Bardo and Neisewander (1987) reported that chronic treatment with naltrexone during the conditioning experiment (by means of an SC implanted slow-release pellet) blocked morphine-induced CPP, and the κ-agonists U-50 488H and E-2078 also inhibited morphine-induced CPP (Bolanos *et al.*, 1996; Funada *et al.*, 1993), an effect that was antagonized by concurrent treatment with the κ-antagonist nor-binaltorphimine (Funada *et al.*, 1993). Morphine-induced CPP was prevented by naltrindole, 7-benzylidenenaltrexone (δ1-selective) and naltriben (δ2-selective) in ddY mice, but not in μ1-receptor-deficient CXBK mice (Suzuki *et al.*, 1994b).

On the other hand, morphine-induced CPP was enhanced by coadministration of the δ-agonist TAN 67, an effect that was abolished by naltrindole, 7-benzylidenenaltrexone and naltriben (Suzuki *et al.*, 1996c) and CPP induced by the non-peptide δ-agonists BW373U86 and SNC 80 was blocked by naltrindole (Longoni *et al.,* 1998). A low dose of morphine (presumably acting primarily on peripheral μ-receptors) produced CPA which was blocked by coadministration of the peripherally acting opiate antagonist methylnaltrexone (Bechara *et al.*, 1987). [Leu]enkephalin-induced CPP was attenuated by methylnaloxonium (Heinrichs and Martinez, 1986). Unlike naloxone, RB-101, a complete inhibitor of enkephalin catabolism, did not affect the expression of morphine-induced CPP (Noble *et al.*, 1993). U69593-induced CPA was not affected by naloxone (Shippenberg and Herz, 1986), but U-50 488H-induced CPA was attenuated by the κ-antagonist Mr2266 (Bechara and van der Kooy, 1987). Suppression of circulating β-endorphin by dexamethasone had no effect on naloxone-induced CPA (Mucha *et al.*, 1985).

3.2.2.3. *Effects of GABAergic drugs*

Morphine-induced CPP was not affected by triazolam (Pettit *et al.*, 1989) or the benzodiazepine antagonist Ro 15-1788 (Bilsky *et al.*, 1990a). On the other hand, morphine-induced CPP was blocked by diazepam, an effect that was antagonized by flumazenil (Suzuki *et al.*, 1995c).

3.2.2.4. *Effects of serotonergic drugs*

Morphine-induced CPP was blocked or attenuated by the 5-HT3 antagonists ICS 205-930, MDL 72222 and ondansetron (Acquas *et al.*, 1988; Carboni *et al.*, 1988, 1989; Higgins *et al.*, 1992a; Bisaga *et al.*, 1993) and attenuated by the 5-HT2 antagonist ritanserin (Nomikos and Spyraki, 1988a; see also Spyraki and Nomikos, 1991). DAU 6285, a mixed 5-HT3 antagonist/5-HT4 antagonist, prevented morphine-induced CPP, while BIMU-8, a mixed 5-HT3 antagonist/5-HT4 agonist (Bisaga *et al.*, 1993) and the serotonin reuptake inhibitor zimelidine (Kruszewska *et al.*, 1986) were without effect. When compared to the results from other sections, the effects of serotonergic drugs on morphine-induced CPP are remarkably consistent and implicate the activation of 5-HT2 and 5-HT3 receptors as important for the mediation of the rewarding effects of morphine.

3.2.2.5. *Effects of glutamatergic drugs*

As in the case of cocaine, it has consistently been shown that the NMDA antagonist MK-801 blocks morphine-induced CPP (Kim *et al.*, 1996b; DelPozo *et al.*, 1996; Tzschentke and Schmidt, 1995, 1997). DelPozo *et al.* (1996) showed that this blockade is only obtained with the more active (+)-enantiomer, but not with the less active (−)-enantiomer of MK-801. It was also shown that MK-801 prevents the expression of morphine-induced CPP (Tzschentke

and Schmidt, 1997). Likewise, it was shown that memantine (Popik and Danysz, 1997) and kynurenic acid (Bespalov *et al*., 1994) blocked acquisition and expression of morphine-induced CPP. The competitive NMDA antagonist CGP 37849 (Tzschentke and Schmidt, 1995) and the glutamate release inhibitor riluzole (Tzschentke and Schmidt, 1998a) were also shown to attenuate or block, respectively, morphine-induced CPP. As in the case of the effects of serotonergic drugs on morphine-induced CPP, the results obtained for NMDA antagonists are very consistent and implicate an important role of NMDA receptors for the acquisition as well as for the expression of morphine-induced CPP.

3.2.2.6. *Effects of CCKergic drugs*

The mixed CCK-A/B antagonist PD 142898 and the selective CCK-A antagonist PD 140548, but not the selective CCK-B antagonist CI 988, blocked morphine-induced CPP (Higgins *et al*., 1991b; Singh *et al*., 1996a,b). In another study, the CCK-A antagonist devazepide attenuated morphine-induced CPP, while a combination of subthreshold doses of morphine and the CCK-B antagonist L365-260 produced a significant CPP (Higgins *et al*., 1992c). The CCK-B antagonist PD-134 308, at a dose that was itself ineffective, enhanced the CPP-inducing effects of subthreshold doses of morphine and of the enkephalin catabolism inhibitor RB-101 (Valverde *et al*., 1996a). Taken together, these results for CCKergic drugs suggest that, generally speaking, CCK-A receptor activation has a facilitating effect while CCK-B receptor activation has an inhibiting effect on opiate reward.

3.2.2.7. *Effects other drugs and treatments*

Morphine-induced CPP has been found to be blocked or attenuated by a variety of drugs and treatments, such as antipain and leupeptin, inhibitors of calcium-dependent endopeptidases (Lyupina *et al*., 1996), ibogaine (Luxton *et al*., 1996; Parker *et al*., 1995), ginseng total saponin (Kim *et al*., 1998b), the CB1 antagonist SR 141716 (Chaperon *et al*., 1998) the NO synthase inhibitor L-NOARG (Kivastik *et al*., 1996a), the calcium channel blockers nifedipine and isradipine (Biala and Langwinski, 1996a; Kuzmin *et al*., 1992) and the NO-donor sodium nitroprusside (Biala and Langwinski, 1996b). In the latter study, the NO-donor molsidomine did not affect the expression of morphine-induced CPP. Chronic administration of lithium-containing diet prior to and during conditioning blocked morphine-induced CPP and naloxone-induced, but not U-69593-induced, CPA (Shippenberg and Herz, 1991).

The histamine precursor L-histidine attenuated morphine-induced CPP, while the histidine decarboxylase inhibitor α-fluoromethylhistidine and the H2 antagonist zolantidine potentiated morphine-induced CPP (an effect that was antagonized by SCH 23390) (Suzuki *et al*., 1995b). A potentiating effect on morphine-induced CPP was also observed for ethanol (Marglin *et al*., 1988). Dihydrocodein, a major active component in over-the-counter cough syrups, produced a small, non-significant CPP. This effect was strongly enhanced by coadministration of a combination of other ingredients of cough syrups (methylephedrine, caffeine, chlorpheniramine). When those constituents were administered seperately in combination with dihydrocodein, only chlorpheniramine was able to enhance dihydrocodein effect. CPP induced by these two constituents was prevented by SCH 23390 (Suzuki *et al*., 1990).

Clonidine disrupted the acquisition of heroin-induced CPP (Hand *et al*., 1989). In the same study, clonidine also disrupted the expression of heroin-induced CPP, albeit only at very high, debilitating doses. In another study, clonidine blocked the rewarding effects of morphine (and also the aversive effects of withdrawal) only in rats withdrawn from morphine, but was without effect on morphine-induced CPP in drug-naive animals (Nader and van der Kooy, 1996). The immunosuppressant cyclosporine A blocked morphine-induced CPP in ddY mice, but not in μ1-receptor deficient CXBK mice (Suzuki *et al*., 1993b). Chronic exposure to cadmium Miller and Nation, 1997) and inflammation induced by formalin or carrageenan (Suzuki *et al*., 1996b) attenuated the ability of morphine and fentanyl to induce CPP.

3.2.2.8. *Effects of environmental factors*

Chronic mild stress abolished morphine-induced CPP (Papp *et al*., 1992), an effect that could be reversed by the CCK-B antagonist PD-134 308 (Valverde *et al*., 1997), but did not affect naloxone-induced CPA (Papp *et al*., 1992). When morphine administration and conditioning occurred under restraint stress conditions, morphine was unable to induce CPP (Kiyatkin and Belyi, 1991). Social isolation over several weeks also prevented morphine-induced CPP (Coudereau *et al*., 1997; Wongwitdecha and Marsden, 1996). Schenk *et al*. (1985) showed that social isolation also attenuated the CPP-inducing effects of heroin, and that the isolation effect was stronger in animals isolated during adolescence than in animals isolated for the same duration after reaching maturity. Different rearing environments have been shown to affect the magnitude of morphine-induced CPP. Thus, rats raised in a stimulus-enriched environment together with conspecifics showed a bigger morphine-induced CPP than rats raised individually in an impoverished environment (Bardo *et al*., 1997). Morphine-induced CPP was also attenuated by low social status and the experience of defeat against conspecifics (Coventry *et al*., 1997). Food-deprived rats showed stronger morphine-induced CPP (Gaiardi *et al*., 1987) and sucrose solution also enhanced morphine-induced CPP (Lett, 1989b).

3.2.3. *Place Conditioning Induced by Ethanol*

3.2.3.1. *Effects of serotonergic drugs*

The 5-HT2 antagonist mianserin enhanced ethanol-induced CPP (Risinger and Oakes, 1996a), while the serotonin reuptake blocker fluoxetine did not affect ethanol-induced CPP (Risinger, 1997). The 5-HT3 antagonist tropisetron did not affect ethanol-induced CPA (Bienkowski *et al*., 1997a).

3.2.3.2. *Effects of other drugs or treatments*

Ethanol-induced CPP was found to be blocked by naloxone and to be reduced by sodium nitroprusside (Biala and Langwinski, 1996b). Note, however, that Cunningham *et al.* (1995) reported no effect of naloxone on the acquisition and expression of ethanol-induced CPP. No effect was also reported for mazindol (Gevaerd and Takahashi, 1996), haloperidol (Risinger *et al.*, 1992a; Cunningham *et al.*, 1992a), the benzodiazepine receptor inverse agonist Ro 15-4513 (Risinger *et al.*, 1992b), the calcium channel blocker nifedipine (Biala and Langwinski, 1996a) and the steroid synthesis inhibitor aminoglutethimide (Chester and Cunningham, 1998). On the other hand, pyrazole (an alcohol dehydrogenase inhibitor) potentiated the CPP-inducing effect of ethanol, an effect that could be antagonized by the 5-HT3 antagonists MDL 72222 and ICS 205-930 (Suzuki *et al.*, 1992b). The expression of ethanol-induced CPP was attenuated by molsidomine (Biala and Langwinski, 1996b).

In one study it was found that ethanol-induced CPA could be attenuated by interaction with a conspecific (either sober or intoxicated) during the conditioning sessions (Gauvin *et al.*, 1994), and in another study it was shown that ethanol-induced CPA could be attenuated by counteracting the drug-induced hypothermia by increasing the ambient temperature to 32°C during conditioning, suggesting that the aversive effects of ethanol in rats might be, at least partly, due to the experience of drug-induced hypothermia (Cunningham and Niehus, 1993). A dose of ethanol (300 mg/kg, i.p.) that did not produce CPP under standard conditions, was able to produce a substantial CPP when it was paired with an environment in which the animals had previously received electric foot shock and in which they therefore experienced conditioned fear stress during ethanol conditioning. Additional exposure to conditioned fear stress immediately before the test for conditioning further enhanced the expression of ethanol-induced CPP (Matsuzawa *et al.,* 1998). These results suggest that psychological stress can be an important determinant of ethanol reward and ethanol-induced place conditioning.

3.2.4. *Place Conditioning Induced by Nicotine*

Nicotine-induced CPP was prevented by the 5-HT3 antagonists ICS 205-930 and MDL 72222 (Acquas *et al.*, 1988; Carboni *et al.*, 1988, 1989), and also by SCH 23390 (Acquas *et al.*, 1989), and mecamylamine but not hexamethonium (Fudala *et al.*, 1985). In rats chronically treated with nicotine (but not in nicotine-naive rats), the nicotinic receptor antagonist mecamylamine produced CPA. This effect was antagonized by coadministration of the 5-HT3 antagonist ondansetron (Suzuki *et al.*, 1996a, 1997b).

3.2.5. *Place Conditioning Induced by GABAergic Drugs*

Diazepam-induced CPP and picrotoxin-induced CPA was blocked by SCH 23390 (Acquas *et al.*, 1989), and diazepam-induced CPP was also blocked by haloperidol (but not domperidone) (Spyraki and Fibiger, 1988), ritanserin (Nomikos and Spyraki, 1988a), CGS 8216, picrotoxin and naloxone, but not by sodium valproate (Spyraki *et al.*, 1985). FG 7142-induced CPA was prevented by haloperidol (Di Scala and Sandner, 1989b) and the expression of a previously established pentylenetetrazole-induced CPA was blocked by the competitive NMDA antagonist (±) CPP (Bespalov, 1996). CPA induced by picrotoxin was blocked by the 5-HT3 antagonists ICS 205-930 and MDL 72222 (Acquas *et al.*, 1990) but was not affected by chronic mild stress (Papp *et al.*, 1992).

3.2.6. *Place Conditioning Induced by Serotonergic Drugs*

Low-dose 8-OH-DPAT-induced CPP was prevented by the 5-HT synthesis inhibitor PCPA, pimozide and sulpiride, while neither PCPA nor pimozide affected high-dose 8-OH-DPAT-induced CPA (Papp and Willner, 1991). 8-OH-DPAT-induced CPP was also blocked by the 5-HT1A/D2 antagonist spiperone and SCH 23390, but not by sulpiride (Shippenberg, 1991). MDMA-induced CPP was blocked by the 5-HT3 antagonist MDL 72222 (Bilsky and Reid, 1991) and the DA release inhibitor CGS 10746B (Bilsky *et al.*, 1998) and attenuated by naltrexone (Bilsky *et al.*, 1991). CPA induced by the 5-HT3 agonists mCPBG and PBG was prevented by the 5-HT3 antagonists ondansetron, ICS 205-930 and quarternized ICS 205-930 (Higgins *et al.*, 1993), and CPA induced by mianserin and eltoprazine was blocked by the 5-HT1C agonist mCPP (Rocha *et al.*, 1993a).

3.2.7. *Various Combinations*

SCH23390 was able to block CPP induced by the histamine H2 antagonist zolantidine (Suzuki *et al.*, 1995b), the CPP produced by concurrent application of pentazocine and tripelennamine (at doses that were ineffective when given alone) (Suzuki *et al.*, 1991b), and the CPA induced by PCP (Acquas *et al.*, 1989; Nabeshima *et al.*, 1996). PCP-induced CPA was also blocked or attenuated by butaclamol and spiroperidol (Iwamoto, 1986a) and by the 5-HT3 antagonists ICS 205-930 and MDL 72222 (Acquas *et al.*, 1990).

Propofol-induced CPP was prevented by midazolam (Pain *et al.*, 1997), clonidine-induced CPP was blocked by the α2-antagonist idazoxan but not by the α1-antagonist prazosin (Cervo *et al.*, 1993), and CPP induced by SP or its C-terminal hexapeptide analog [pGlu6]-SP(6-11) was blocked by naloxone (Hasenöhrl *et al.*, 1991) and haloperidol (Mattioli *et al.*, 1995). The CPA produced by the synthetic CB receptor agonist WIN 55212-2 was blocked by the CB1 receptor antagonist SR 141716 (Chaperon *et al.,* 1998).

3.2.8. *Place Conditioning Induced by Natural Reinforcers*

CPP induced by sexual behaviour in female hamsters was blocked by raclopride (Meisel *et al.*, 1996), while pimozide failed to prevent CPP induced by ejaculation in rats (Agmo and Berenfeld, 1990). On the other hand, ejaculation-induced CPP was

blocked by naloxone (in fact, naloxone converted the CPP into a CPA) (Agmo and Berenfeld, 1990). It was also shown that while naloxone did not affect the acquisition it significantly attenuated the expression of a CPP induced by exposure to and copulation with an oestrous female (Miller and Baum, 1987; Mehrara and Baum, 1990). The CPP produced by home cage odours in infant rats was blocked by clonidine, but not by raclopride, naltrexone or propranolol (Hansen, 1993) and the CPP induced in maternal rats by interaction with their pups could be disrupted by chemically blocking olfactory or oral sensory perception in the maternal rats (Magnusson and Fleming, 1995).

Food-induced CPP was enhanced by low doses of sulpiride, amisulpiride and pimozide. Higher doses of these compounds as well as low and high doses of haloperidol, metoclopramide and chlorpromazine attenuated the CPP-inducing effect of food (Guyon *et al*., 1993). The CPP-enhancing effect of low-dose amisulpiride was blocked by SCH 23390 (Guyon *et al*., 1993; see Scatton *et al*., 1997). α-Flupenthixol prevented the CPA induced by lack of food in food-deprived rats but not the CPP induced by food in non-food-deprived rats (Bechara *et al*., 1992; Harrington and van der Kooy, 1992). It was also reported that food-induced CPP was blocked by naloxone, pimozide, raclopride and SCH 23390 (Agmo *et al*., 1993) and the CB1 antagonist SR 141716 (Chaperon *et al.,* 1998). CPP induced by sucrose solution was blocked by α-flupenthixol and high-dose but not low-dose naloxone (note that low doses of naloxone that were not sufficient to block sucrose-induced CPP were behaviourally active in that they were sufficient to reduce the amount of sucrose consumption) (Agmo *et al*., 1995). The acquisition and expression of food-induced CPP was not affected by memantine (Popik and Danysz, 1997), while chronic unpredictable mild stress blocked the ability of food and sucrose solution to induce CPP (Papp *et al*., 1991; Muscat *et al*., 1992; Cheeta *et al*., 1994; D'Aquila *et al*., 1997). Inescapable footshock produced CPA, an effect which was prevented by diazepam and the 5-HT3 antagonist ICS 205-930 (Papp, 1988b).

The expression of novelty-induced CPP was disrupted by haloperidol, but not by morphine, naltrexone or amphetamine (Bardo *et al*., 1989), also by low-dose (presumably autoreceptor-specific) but not high-dose apomorphine (Bardo *et al*., 1990), and by the D1 agonist SKF 38393, the D2 agonist quinpirole, the D1 antagonist SCH 23390, but not the D2 antagonist eticlopride (Bardo *et al*., 1993).

4. STUDIES USING INTRACRANIAL DRUG INJECTIONS

4.1. 'Single Drug Treatments'

4.1.1. *Dopaminergic Drugs*

Amphetamine produced a CPP only when injected into the nucleus accumbens (NAS), but not when injected into the mPFC, the striatum, the amygdala or the area postrema region (Carr and White, 1986; Josselyn and Beninger, 1993; Schildein *et al.,* 1998). SKF 38393 and quinpirole both produced CPP when injected into the NAS (Papp *et al*., 1993a; White *et al*., 1991) (note that in the latter study SKF 38393 produced place aversions when injected systemically). On the other hand, the evidence that cocaine injections into the NAS produce CPP is very sparse (Aulisi and Hoebel, 1983; see Hemby *et al*., 1992a). α-Flupenthixol was without effect when injected into the NAS (Josselyn and Beninger, 1993), while SCH 23390 produced CPA when injected into the NAS, but not when injected into the ventral tegmental area (VTA), striatum or mPFC (Shippenberg *et al*., 1991). Sulpiride produced CPP when injected into the perifornical region of the lateral hypothalamus (Morutto and Phillips, 1997, 1998), but was without effect when injected into the NAS or striatum (Baker *et al*., 1996). Gong *et al*. (1996b) reported that cocaine and amphetamine (but not procaine) produced a CPP when injected into the ventral pallidum (VP).

ICV injections of cocaine, cocaine-methiodide (Hemby *et al*., 1994; Morency and Beninger, 1986), cathinone (Calcagnetti and Schechter, 1993b) and bromocriptine (Morency and Beninger, 1986) produced CPP, while ICV injections of procaine failed to produce CPP (Morency and Beninger, 1986) and ICV injections of SCH23390 (Shippenberg *et al*., 1991) and the DA release inhibitor CGS 10746B (Calcagnetti and Schechter, 1991) produced CPA.

Taken together, these results confirm the central role of the NAS for amphetamine-induced reward. Unfortunately, the anatomical substrate of cocaine-induced reward (which probably does not include the NAS) has received very little attention in place conditioning studies. Only recently has the VP been added to those stuctures which are presumed to mediate cocaine- (and amphetamine-) induced reward (Table 3).

4.1.2. *Opioidergic Drugs*

Intra-VTA injections of morphine (Abbott and Franklin, 1991; Bozarth, 1987a; Zvartau *et al*., 1986; Mamoon *et al*., 1995; Jaeger and van der Kooy, 1996; Nader and van der Kooy, 1997; Olmstead and Franklin, 1997b), morphine-6-glucuronide (Abbott and Franklin, 1991) and the μ/κ-partial agonist butorphanol (Mamoon *et al*., 1995) produced CPP. Intra-VTA injections of morphine elicited CPP even in neonatal (4-day-old) rats (Barr and Rossi, 1992). Intranigral injections of a high dose of morphine, but not of lower doses of the morphine metabolite morphine-6-glucuronide, the μ-agonist DAGO, the δ-agonist DPDPE or the κ-agonist U-50 488H, also produced CPP (Baumeister *et al*., 1993). Injections of the μ-agonist DAMGO into the VTA, but not into the NAS, the mPFC or the lateral hypothalamus, produced CPP, whereas injections of the κ-agonists U-50 488H or E-2078 into each of these four regions produced CPA (Bals-Kubik *et al*., 1993). In the same study, injections of either the μ- or the κ-agonists into the substantia nigra (SN) or the striatum were without effect. Likewise, morphine injections into the parabrachial nucleus failed to induce a CPP (Jaeger and van der Kooy, 1996). On the other hand, intrathecal (Advokat, 1985) and

intra-hippocampal (Corrigall and Linseman, 1988) injections of morphine and injections of DALA into the medial preoptic area (Agmo and Gomez, 1991) were shown to produce CPP. Morphine also produced CPP when injected into the periaqueductal gray (PAG), but not when injected into sites just dorsal to the PAG or the VTA, or into the striatum, mPFC, hippocampus, lateral nucleus of the amygdala, pedunculopontine tegmental nucleus (PPTg), posterior hypothalamus, VP or NAS (core or shell) (Olmstead and Franklin, 1997b; Schildein *et al.,* 1998). Intra-VTA and intra-NAS infusions, but not intra-striatal or intra-mPFC infusions of naloxone produced CPA. A CPA was also obtained by intra-VTA and intra-NAS infusions of the selective μ-antagonist CTOP (Shippenberg and Bals-Kubik, 1995).

After ICV injection, a CPP has been demonstrated for morphine (Shippenberg *et al*., 1987; Olmstead and Franklin, 1997b), dynorphin A [1-17] (Iwamoto, 1988, 1989), β-endorphin (Bals-Kubik *et al*., 1988, 1990; Amalric *et al*., 1987; Spanagel *et al*., 1991), but not its naturally occurring fragment β-endorphin-(1-27) (Bals-Kubik *et al*., 1988), also the μ-agonist DAGO (Bals-Kubik *et al*., 1988, 1990), the δ1-agonist DPDPE (Suzuki *et al*., 1996d, 1997d; Shippenberg *et al*., 1987; Bals-Kubik *et al*., 1988, 1990) and the δ2-agonist deltorphin II (Suzuki *et al*., 1996d, 1997d), whereas the δ-antagonist ICI 174 864, the κ-antagonist nor-binaltorphimine (Bals-Kubik *et al*., 1989; Shippenberg *et al*., 1987), dynorphin A [2-17], Leu-enkephalin (Iwamoto, 1988, 1989) and the enkephalinase inhibitor phospho-leuphe (Agmo *et al*., 1994) were without effect. ICV injections of U-50488H, E-2078, naloxone, CTOP (Bals-Kubik *et al*., 1988, 1989) and methylnalaxonium (Hand *et al*., 1988) were found to produce CPA.

In general, the results of the above studies have confirmed the central role of the VTA for the mediation of the rewarding effects of opioid drugs (at least for those that exert their effects predominantly by activating μ-receptors). Nevertheless, opioid reward has been elicited from a number of other forebrain and hindbrain structures, a fact which may not be particularly surprising considering that the endogenous opioid system, together with its receptors, has a much wider distribution in the brain than, for example, the dopaminergic system.

4.1.3. *Cholinergic Drugs*

Museo and Wise (1994) reported that intra-VTA injections of the nicotinic agonist cytisine produced CPP, and Iwamoto (1990) showed CPP with ICV and intra-PPTg injections of nicotine. Intra-VTA injection of carbachol, a cholinergic agonist, also produced CPP (Yeomans *et al*., 1985).

4.1.4. *GABAergic Drugs*

Blockade of GABAergic neurotransmission in the PAG by injection of the glutamate decarboxylase inhibitor semicarbazide produced CPA, while injection of the GABA-A agonist muscimol into the same region was without effect (Aguiar and Brandao, 1994; Di Scala and Sandner, 1989a). Injection of the GABA-A antagonist picrotoxin into the VP was without effect on place conditioning (Gong *et al*., 1997a) and injection of the GABA-B agonist baclofen into the VTA was equally ineffective (Tsuji *et al*., 1996).

4.1.5. *Serotonergic Drugs*

The 5-HT1 agonist 8-OH-DPAT produced CPP when injected into the median and dorsal raphe nuclei (Fletcher *et al*., 1993). ICV injection of the 5-HT3 antagonist PBG failed to produce CPP or CPA (Higgins *et al*., 1993).

4.1.6. *Glutamatergic Drugs*

Injection of AMPA into the VP was without effect on place conditioning (Gong *et al*., 1997a) and ICV (Cervo and Samanin, 1995) or intra-NAS (Layer *et al*., 1993b) injection of DNQX was equally ineffective.

4.1.7. *Substance P*

SP injected into the medial forebrain bundle, the lateral hypothalamus, or the medial septal nucleus, but not into the amygdala, SN, the rostral VP or the NAS shell produced CPP (Holzhauer-Oitzl *et al*., 1987; Staubli and Huston, 1985; Hasenöhrl *et al*., 1998; Schildein *et al.,* 1998). SP also produced CPP when injected into the nucleus basalis magnocellularis, an effect mediated by the C-terminus sequence and not the N-terminus sequence of the peptide (Huston *et al*., 1993; Hasenöhrl *et al*., 1992, 1998; Boix *et al*., 1995; Holzhauer-Oitzl *et al*., 1988). On the other hand, intra-PAG injection of SP (Aguiar and Brandao, 1994) and ICV injection of the stable SP analogue DiMethyl-C7 (Elliott, 1988) was reported to produce CPA.

4.1.8. *Hormones*

Injections of testosterone into the NAS produced CPP (Packard *et al*., 1997) and ICV infusion of CRF was shown to produce CPA (Cador *et al*., 1992).

4.1.9. *Diverse Drugs*

Intra-NAS infusion of neuropeptide Y produced CPP (Josselyn and Beninger, 1993), while ICV injections of the neuropeptide bombesin produced strong CPA (Meisenberg *et al*., 1990). ICV injections of the neuropeptide orphanin FQ (Devine *et al*., 1996), pertussis toxin (Suzuki *et al*., 1991a), the CCK-fragments Boc-CCK-4 or CCK-8s (Huston *et al*., 1998), and tumour necrosis factor-a (Fantino and Wieteska, 1993), and also CCK infusions into the VTA (Pettit and Mueller, 1989) produced neither CPP nor CPA.

4.1.10. *Non-Drug Treatments*

Corcoran *et al.* (1992) have examined the motivational effects of amygdala kindling and found that stimulation that triggered afterdischarges associated with nonconvulsive seizures produced small CPA or CPP depending on whether kindling was paired with the initially preferred or non-preferred compartment, respectively. Kindling that triggered generalized seizures produced only a small and non-

Table 3. This table summarizes the results of studies using intracranial single-drug treatments. See Section 4.1 in the text for details about drugs, experimental procedures and additional findings that could not be included in the table

Place conditioning induced by	Injected into	Result	References
Dopaminergic drugs:			
Amphetamine	NAS	CPP	Carr and White (1986); Josselyn and Beninger (1993);
	mPFC	No effect	Schildein *et al.* (1998)
	Striatum	No effect	
	Amygdala	No effect	
	Area postrema	No effect	
	VP	CPP	Gong *et al.* (1996b)
Cocaine	NAS	CPP	Aulisi and Hoebel (1983)
	NAS	No effect	Hemby *et al.* (1992a)
	VP	CPP	Gong *et al.* (1996b)
	ICV	CPP	Morency and Beninger (1986); Hemby *et al.* (1994)
Cocaine-methiodide	ICV	CPP	Morency and Beninger (1986)
Cathinone	ICV	CPP	Calcagnetti and Schechter (1993b)
Bromocriptine	ICV	CPP	Morency and Beninger (1986)
SKF 38393	NAS	CPP	White *et al.* (1991)
Quinpirole	NAS	CPP	Papp *et al.* (1993a); White *et al.* (1991)
α-Flupenthixol	NAS	No effect	Josselyn and Beninger (1993)
Sulpiride	Perifornical LH	CPP	Morutto and Phillips (1997, 1998)
	NAS	No effect	Baker *et al.* (1996)
	Striatum	No effect	Baker *et al.* (1996)
SCH23390	NAS	CPA	Shippenberg *et al.* (1991)
	VTA	No effect	Shippenberg *et al.* (1991)
	Striatum	No effect	Shippenberg *et al.* (1991)
	mPFC	No effect	Shippenberg *et al.* (1991)
	ICV	CPA	Shippenberg *et al.* (1991)
Procaine	VP	No effect	Gong *et al.* (1996b)
	ICV	No effect	Morency and Beninger (1986)
CGS10746B	ICV	CPA	Calcagnetti and Schechter (1991)
Opioid drugs:			
Morphine	VTA	CPP	Abbott and Franklin (1991); Bozarth (1987a); Zvartau *et al.* (1986); Mamoon *et al.* (1995); Jaeger and van der Kooy (1996); Nader and van der Kooy (1997); Olmstead and Franklin (1997b); Barr and Rossi (1992)
	PAG	CPP	Olmstead and Franklin (1997b)
	Dorsal of PAG	No effect	Olmstead and Franklin (1997b)
	Dorsal of VTA	No effect	Olmstead and Franklin (1997b)
	Striatum	No effect	Olmstead and Franklin (1997b)
	mPFC	No effect	Olmstead and Franklin (1997b)
	Hippocampus	No effect	Olmstead and Franklin (1997b)
	Amygdala lateral nucl.	No effect	Olmstead and Franklin (1997b)
	PPTg	No effect	Olmstead and Franklin (1997b)
	Post. hypothal.	No effect	Olmstead and Franklin (1997b)
	VP	No effect	Olmstead and Franklin (1997b)
	NAS core	No effect	Olmstead and Franklin (1997b)
	NAS shell	No effect	Schildein *et al.* (1998); Olmstead and Franklin (1997b)
	Parabrachial nucl.	No effect	Jaeger and van der Kooy (1996)
	Intrathecal	CPP	Advokat (1985)
	Hippocampus	CPP	Corrigall and Linseman (1988)
	Medial preoptic area	CPP	Agmo and Gomez (1991)
	ICV	CPP	Shippenberg *et al.* (1987); Olmstead and Franklin (1997b)
Morphine (high dose)	SN	CPP	Baumeister *et al.* (1993)
Morphine-6-glucuronide	VTA	CPP	Abbott and Franklin (1991)
	SN	No effect	Baumeister *et al.* (1993)
Butorphanol	VTA	CPP	Mamoon *et al.* (1995)
DAMGO	VTA	CPP	Bals-Kubik *et al.* (1993)
	SN	No effect	Bals-Kubik *et al.* (1993)
	NAS	No effect	Bals-Kubik *et al.* (1993)
	Striatum	No effect	Bals-Kubik *et al.* (1993)
	mPFC	No effect	Bals-Kubik *et al.* (1993)
	LH	No effect	Bals-Kubik *et al.* (1993)

(continued on next page)

U-50 488H	VTA	CPA	Bals-Kubik *et al.* (1993)
	NAS	CPA	Bals-Kubik *et al.* (1993)
	mPFC	CPA	Bals-Kubik *et al.* (1993)
	LH	CPA	Bals-Kubik *et al.* (1993)
	SN	No effect	Bals-Kubik *et al.* (1993); Baumeister *et al.* (1993)
	Striatum	No effect	Bals-Kubik *et al.* (1993)
	ICV	CPA	Bals-Kubik *et al.* (1988, 1989)
Naloxone	VTA	CPA	Shippenberg and Bals-Kubik (1995)
	NAS	CPA	Shippenberg and Bals-Kubik (1995)
	Striatum	No effect	Shippenberg and Bals-Kubik (1995)
	mPFC	No effect	Shippenberg and Bals-Kubik (1995)
	ICV	CPA	Bals-Kubik *et al.* (1988, 1989)
Methylnaloxone	ICV	CPA	Hand *et al.* (1988)
	NAS	CPA	Stinus *et al.* (1990)
Methylnaltrexone	ICV	CPA	Mucha *et al.* (1985)
CTOP	VTA	CPA	Shippenberg and Bals-Kubik (1995)
	NAS	CPA	Shippenberg and Bals-Kubik (1995)
	ICV	CPA	Bals-Kubik *et al.* (1988, 1989)
DALA	Medial preoptic area	CPP	Agmo and Gomez (1991)
DAGO	SN	No effect	Baumeister *et al.* (1993)
	ICV	CPP	Bals-Kubik *et al.* (1988, 1990)
DPDPE	SN	No effect	Baumeister *et al.* (1993)
	ICV	CPP	Suzuki *et al.* (1996d, 1997d); Shippenberg *et al.* (1987); Bals-Kubik *et al.* (1988, 1990)
Deltorphin II	ICV	CPP	Suzuki *et al.* (1996d, 1997d)
Dynorphin A [1-17]	ICV	CPP	Iwamoto (1988, 1989)
Dynorphin A [2-17]	ICV	No effect	Iwamoto (1988)
E-2078	ICV	CPA	Bals-Kubik *et al.* (1988, 1989)
β-Endorphin	ICV	CPP	Bals-Kubik *et al.* (1988, 1990); Amalric *et al.* (1987); Spanagel *et al.* (1991)
β-Endorphin (1-27)	ICV	No effect	Bals-Kubik *et al.* (1988)
Leu-enkephalin	ICV	No effect	Iwamoto (1988, 1989)
ICI 174 864	ICV	No effect	Bals-Kubik *et al.* (1989); Shippenberg *et al.* (1987)
Nor-binaltorphimine	ICV	No effect	Bals-Kubik *et al.* (1989)
Phospho-leu-phe	ICV	No effect	Agmo *et al.* (1994)
Cholinergic drugs:			
Nicotine	PPTg	CPP	Iwamoto (1990)
	ICV	CPP	Iwamoto (1990)
Cytisine	VTA	CPP	Museo and Wise (1994)
Carbachol	VTA	CPP	Yeomans *et al.* (1985)
GABAergic drugs:			
Muscimol	PAG	No effect	Aguiar and Brandao (1994)
Semicarbazide	PAG	CPA	Di Scala and Sandner (1989a)
Picrotoxin	VP	No effect	Gong *et al.* (1997a)
Baclofen	VTA	No effect	Tsuji *et al.* (1996)
Serotonergic drugs:			
8-OH-DPAT	Medial raphe	CPP	Fletcher *et al.* (1993)
	Dorsal raphe	CPP	Fletcher *et al.* (1993)
PBG	ICV	No effect	Higgins *et al.* (1993)
Glutamatergic drugs:			
AMPA	VP	No effect	Gong *et al.* (1997a)
DNQX	NAS	No effect	Layer *et al.* (1993b)
DNQX	ICV	No effect	Cervo and Samanin (1995)
Substance P	MFB	CPP	Holzhauer-Oitzl *et al.* (1987); Staubli and Huston (1985); Hasenöhrl *et al.* (1998)
	LH	CPP	
	Medial septal n.	CPP	
	Amygdala	No effect	
	SN	No effect	
	Rostral VP	No effect	
	PAG	CPA	Aguiar and Brandao (1994)
	NAS shell	No effect	Schildein *et al.* (1998)
Substance P (C-terminus fragm.)	Nucl. basalis magnocellularis	CPP	Huston *et al.* (1993); Hasenöhrl *et al.* (1992)
Substance P (N-terminus fragm.)	Nucl. basalis magnocellularis	No effect	Huston *et al.* (1993); Hasenöhrl *et al.* (1992)
Dimethyl-C7	ICV	CPA	Elliott (1988)
Hormones:			
Testosterone	NAS	CPP	Packard *et al.* (1997)
CRF	ICV	CPA	Cador *et al.* (1992)
Diverse drugs:			
CCK	VTA	No effect	Pettit and Mueller (1989)

Neuropeptide Y	NAS	CPP	Josselyn and Beninger (1993)
Bombesin	ICV	CPA	Meisenberg *et al.* (1990)
Orphanin FQ	ICV	No effect	Devine *et al.* (1996)
Pertussis toxin	ICV	No effect	Suzuki *et al.* (1991a)
CCK-8s and Boc-CCK-4	ICV	No effect	Huston *et al.* (1998)
TNF	ICV	No effect	Fantino and Wieteska (1993)
Electrical stimulation:	MFB/LH	CPP	De Witte and Gewiss (1987); Duvauchelle and Ettenberg (1991); Ettenberg and Duvauchelle (1988); Healey *et al.* (1989)
	Dorsomedial tegmentum	CPA	De Witte and Gewiss (1987)
	mPFC	CPP	Duvauchelle and Ettenberg (1991)
	VTA	CPP	Duvauchelle *et al.* (1992a)
	Locus coeruleus	CPP	Duvauchelle *et al.* (1992b)

significant CPA. From these results the authors concluded that amygdaloid afterdischarges produce weak positively or negatively reinforcing effects, depending on the behavioural baseline, and that generalized amygdaloid seizures are, at most, mildly aversive.

Electrical stimulation of the medial forebrain bundle at the level of the hypothalamus (at parameters that sustained self-stimulation behaviour) produced CPP, while electrical stimulation of the mesencephalic dorsomedial tegmentum (at parameters that elicited switch-off behaviour) produced CPA (De Witte and Gewiss, 1987; Duvauchelle and Ettenberg, 1991). Interestingly, it was also reported that even animals that did not show self-stimulation or switch-off behaviour at the parameters used developed CPP or CPA, respectively, and it was concluded that this might suggest that the CPP paradigm is more sensitive than the operant bar pressing procedures to detect mild rewarding or aversive effects of electrical brain stimulation (De Witte and Gewiss, 1987). A CPP induced by electrical stimulation of the lateral hypothalamus was also reported in other studies (Healey *et al.*, 1989; Ettenberg and Duvauchelle, 1988). CPP was also induced by electrical stimulation of the mPFC (Duvauchelle and Ettenberg, 1991), the VTA (Duvauchelle *et al.*, 1992a) and the locus coeruleus (Duvauchelle *et al.*, 1992b).

4.2. 'Drug Combinations'

4.2.1. *Place Conditioning Induced by Dopaminergic Drugs*

The expression of IP amphetamine-induced CPP was blocked by intra-NAS α-flupenthixol and reserpine, but not α-methyl-para-thyrosine (Hiroi and White, 1990), and also by intra-NAS SCH 23390 and sulpiride, while similar injections into the striatum were without effect (Hiroi and White, 1991a). IV cocaine-induced CPP was not affected by intra-NAS or intra-striatal infusion of sulpiride (Baker *et al.*, 1996), while IP cocaine-induced CPP was attenuated by intra-NAS DNQX, but not by intra-NAS fluphenazine. The expression of IP cocaine-induced CPP was blocked by intra-NAS infusion of both DNQX and fluphenazine (Kaddis *et al.*, 1995). However, it was also reported that ICV DNQX prevented only the expression but not the acquisition of IP cocaine-induced CPP (Cervo and Samanin, 1995), while intra-NAS DNQX blocked both the acquisition and expression of IP amphetamine-induced CPP (Layer *et al.*, 1993b).

IP amphetamine-induced CPP was potentiated by intra-VTA CCK (Pettit and Mueller, 1989), while ICV cocaine-induced CPP was attenuated by ICV pimozide (Morency and Beninger, 1986). CPP induced by ICV cathinone was blocked by ICV CGS 10746B, a DA release inhibitor (Calcagnetti and Schechter, 1993b). SC cocaine-induced CPP was prevented by ICV administration of antisense oligodeoxynucleotide to δ-receptor mRNA (Suzuki *et al.*, 1997c), CPP induced by intra-NAS quinpirole was blocked by prior exposure to chronic mild unpredictable stress (Papp *et al.*, 1993a), and isolation rearing attenuated the ability of intra-perifornical sulpiride to produce CPP (Morutto and Phillips, 1997). CPP induced by intra-perifornical sulpiride was also blocked by intra-VTA AP5 (Morutto and Phillips, 1998).

CPP induced by systemic cocaine was blocked by ICV injection of the non-selective protein kinase inhibitor H7, by the selective PKA inhibitor H89, and by the selective PKC inhibitor chelerythrine (Cervo *et al.*, 1997). In this latter study, the blocking effect was only observed when the kinase inhibitors were administered immediately after each conditioning session (consolidation), but not when they were administered before cocaine during the training phase (acquisition) or before testing for place preference (expression), indicating a selective role of these protein kinases in the consolidation of stimulus-reward associations (Table 4).

4.2.2. *Place Conditioning Induced by Opioids*

CPP induced by systemic morphine was prevented by ICV application of the antisense oligodeoxynucleotide to δ-receptor mRNA (Suzuki *et al.*, 1997a), by intra-VTA and intra-PAG (at higher doses) injections of naloxone methiodide (Olmstead and Franklin, 1997b), by intra-NAS SCH 23390, but not by intra-NAS sulpiride (Shippenberg *et al.*, 1993), and by intra-VTA baclofen, an effect that was reversed by concurrent intra-VTA injection of the

GABA-B antagonist 2-hydroxysaclofen, but not the GABA-A antagonist bicuculline (Tsuji *et al*., 1996). The expression, but not the acquisition, of systemic morphine-induced CPP was blocked by intra-NAS DNQX (Layer *et al*., 1993b). CPP induced by intra-VTA morphine was prevented by systemic α-flupenthixol in opiate-dependent and withdrawn rats, but not in previously drug-naive rats (Nader and van der Kooy, 1997).

ICV application of the μ-antagonist CTOP blocked CPP induced by ICV β-endorphin and the μ-agonist DAGO, but not the δ1-agonist DPDPE, whereas ICV infusion of the δ-antagonist ICI 174 864 blocked CPP induced by β-endorphin and DPDPE, but not that induced by DAGO (Bals-Kubik *et al*., 1990; Shippenberg *et al*., 1987). CPP induced by ICV DPDPE was blocked by systemic 7-benzylidenenaltrexone (BNTX, δ1-antagonist) but not naltriben (δ2-antagonist), and CPP induced by ICV deltorphin II (δ2-agonist) was prevented by naltriben, but not by BNTX (Suzuki *et al*., 1996d, 1997d). ICI 174 864 had no effect on ICV morphine-induced CPP (Shippenberg *et al*., 1987), while CPP induced by ICV β-endorphin was blocked by SC naloxone (Amalric *et al*., 1987).

SC SCH 23390 blocked ICV DPDPE-induced CPP, but did not affect deltorphin II-induced CPP, whereas SC sulpiride did not affect either DPDPE- or deltorphin II-induced CPP (Suzuki *et al*., 1996d). IVC injection of β-endorphin-(1-27), a naturally occurring fragment of β-endorphin, prevented CPP induced by ICV β-endorphin, DAGO and DPDPE, but not the CPA induced by ICV U-50488H (Bals-Kubik *et al*., 1988). CPA induced by systemic U-69593 was blocked by intra-NAS SCH 23390 (Shippenberg *et al*., 1993), and CPP induced by ICV morphine, DAGO and DPDPE was blocked by ICV pertussis toxin (Suzuki *et al*., 1991a).

4.2.3. *Various Combinations*

CPP induced by intra-NAS neuropeptide Y was blocked by intra-NAS α-flupenthixol (Josselyn and Beninger, 1993). SC nicotine-induced CPA was prevented by an ICV injection of the peripheral nicotinic antagonist chlorisondamine 2 weeks prior to the conditioning experiment (Fudala and Iwamoto, 1987). ICV CRF-induced CPA was blocked by ICV injection of the CRF antagonist α-helical-CRF(9-41) (Cador *et al*., 1992).

4.2.4. *Place Conditioning Induced by Electrical Stimulation*

CPP induced by stimulation of the LH and the mPFC was blocked by IP haloperidol (Ettenberg and Duvauchelle, 1988; Duvauchelle and Ettenberg, 1991) and CPP induced by stimulation of the locus coeruleus was prevented by IP pimozide (Duvauchelle *et al*., 1992b), whereas CPA induced by stimulation of the dorsomedial tegmentum was unaffected by haloperidol (Duvauchelle and Ettenberg, 1991). CPP induced by stimulation of the VTA was attenuated or blocked by IP haloperidol and by intra-NAS α-flupenthixol, while it was unaffected or even slightly increased by intra-mPFC α-flupenthixol (Duvauchelle *et al*., 1992a).

4.2.5. *Place Conditioning Induced by Natural Reinforcers*

CPP induced by ejaculation in male rats was blocked by the infusion of methylnaloxonium into the medial preoptic area, but not into the NAS (Agmo and Gomez, 1993).

5. STUDIES EXAMINING THE EFFECTS OF LESIONS

5.1. 6-Hydroxy-Dopamine (6-OHDA) Lesions

Lesions of NAS blocked novelty-induced CPP (Pierce *et al*., 1990), diazepam-induced CPP (Spyraki and Fibiger, 1988), morphine-induced CPP and U-69593-induced CPA (Shippenberg *et al*., 1993), and the CPA induced by intra-VTA CTOP, but not the CPA induced by intra-NAS CTOP or systemic naloxone (Shippenberg and Bals-Kubik, 1995). Lesions of the VP prevented cocaine-induced CPP (Gong *et al*., 1997b), while lesions of the olfactory tubercle did not affect amphetamine-induced CPP (Clark *et al*., 1990) and lesions of the striatum and the mPFC had no effect on morphine-induced CPP and U-69593-induced CPA (Shippenberg *et al*., 1993). Lesions of the mPFC had also no effect on cocaine-induced CPP (Hemby *et al*., 1992b), a finding which is somewhat surprising in light of the fact that cocaine is self-administered into the mPFC (Goeders and Smith, 1983, 1986). This may suggest that non-dopaminergic mechanisms within the mPFC play an important role in mediating the rewarding effects of cocaine. This is in line with the finding that excitotoxic lesions of the prelimbic mPFC can disrupt cocaine-induced CPP (see below). Lesions of the visceral (agranular insular) cortex did not affect morphine-induced CPP, but blocked morphine-induced CPA (induced by IP injection of a low dose of morphine acting primarily on peripheral m-receptors) (Zito *et al*., 1988). Intraventricular 6-OHDA infusion did not affect methylphenidate-induced CPP (Martin-Iverson *et al*., 1985).

5.2. Excitotoxic Lesions (By Ibotenic Acid, Kainic Acid or Quinolinic Acid)

Lesions of the NAS blocked amphetamine-induced but not morphine-induced CPP (Olmstead and Franklin, 1996, Olmstead and Franklin, 1997a). Lesions of the VP and the mediodorsal thalamus significantly attenuated sucrose-induced CPP in hungry rats (McAlonan *et al*., 1993). Lesions of the VP also prevented the acquisition but not the expression of amphetamine-induced CPP (Hiroi and White, 1993), while lesions of the lateral nucleus, but not of the basolateral nucleus of the amygdala, the endopiriform nucleus or the ventral hippocampus, blocked the acquisition as well as the expression of amphetamine-induced CPP (Hiroi and White, 1991b). Lesions of the lateral nucleus of the amygdala, but not of the striatum, also blocked a food-induced CPP, while fornix lesions facilitated this CPP (White and McDonald, 1993). Destruction of the whole amygdala was reported to prevent cocaine-induced CPP (Brown and Fibiger, 1993)

Table 4. This table summarizes the results of studies using intracranial drug-combination treatments. See Section 4.2 in the text for details about drugs, experimental procedures and additional findings that could not be included in the table. In cases where the effects of a drug on place aversion or on the expression of place conditioning were examined, this is indicated explicitely in the table by (CPA) and (expr.), respectively. The injection routes/sites are given in parentheses

Place conditioning induced by	Combined with:	Result	References
Dopaminergic drugs:			
Cocaine (IP)	Fluphenazine (NAS)	CPP	Kaddis *et al.* (1995)
	DNQX (NAS)	Reduced CPP	Kaddis *et al.* (1995)
	DNQX (ICV)	CPP	Cervo and Samanin (1995)
Cocaine (IP) (expr.)	Fluphenazine (NAS)	No CPP	Kaddis *et al.* (1995)
	DNQX (NAS)	No CPP	Kaddis *et al.* (1995)
	DNQX (ICV)	No CPP	Cervo and Samanin (1995)
Cocaine (IV)	Sulpiride (NAS)	CPP	Baker *et al.* (1996)
	Sulpiride (striatum)	CPP	Baker *et al.* (1996)
Cocaine (SC)	δ-Antisense (ICV)	No CPP	Suzuki *et al.* (1997c)
Cocaine (IP)	H7 (ICV)	No CPP	Cervo *et al.* (1997)
	H89 (ICV)	No CPP	Cervo *et al.* (1997)
	Chelerythrine (ICV)	No CPP	Cervo *et al.* (1997)
Cocaine (ICV)	Pimozide (ICV)	Reduced CPP	Morency and Beninger (1986)
Amphetamine (IP)	DNQX (NAS)	No CPP	Layer *et al.* (1993b)
	CCK (VTA)	Enhanced CPP	Pettit and Mueller (1989)
Amphet. (IP) (expr.)	DNQX (NAS)	No CPP	Layer *et al.* (1993b)
	SCH23390 (NAS)	No CPP	Hiroi and White (1991a)
	SCH23390 (striat.)	CPP	Hiroi and White (1991a)
	Sulpiride (NAS)	No CPP	Hiroi and White (1991a)
	Sulpiride (striatum)	CPP	Hiroi and White (1991a)
	α-flupenth. (NAS)	No CPP	Hiroi and White (1990)
	Reserpine (NAS)	No CPP	Hiroi and White (1990)
	AMPT (NAS)	CPP	Hiroi and White (1990)
Cathinone (ICV)	CGS 10746B (ICV)	No CPP	Calcagnetti and Schechter (1993b)
Quinpirole (NAS)	Mild chronic stress	No CPP	Papp *et al.* (1993a)
Sulpiride (perif. LH)	Isolation rearing	Reduced CPP	Morutto and Phillips (1997)
	AP5 (VTA)	No CPP	Morutto and Phillips (1998)
Opioid drugs:			
Morphine (IP)	SCH23390 (NAS)	No CPP	Shippenberg *et al.* (1993)
	Sulpiride (NAS)	CPP	Shippenberg *et al.* (1993)
	Naloxone methiodide (VTA or PAG)	No CPP	Olmstead and Franklin (1997b)
	Baclofen (VTA)	No CPP	Tsuji *et al.* (1996)
	δ-Antisense (ICV)	No CPP	Suzuki *et al.* (1997a)
	DNQX (NAS)	CPP	Layer *et al.* (1993b)
Morphin (IP) (expr.)	DNQX (NAS)	No CPP	Layer *et al.* (1993b)
Morphine (ICV)	ICI 174 864 (ICV)	CPP	Shippenberg *et al.* (1987)
	Pertussis toxin (ICV)	No CPP	Suzuki *et al.* (1991a)
β-endorphin (ICV)	CTOP (ICV)	No CPP	Bals-Kubik *et al.* (1990)
	ICI 174 864 (ICV)	No CPP	Bals-Kubik *et al.* (1990)
	Naloxone (SC)	No CPP	Amalric *et al.* (1987)
	β-Endorphin (1-27) (ICV)	No CPP	Bals-Kubik *et al.* (1988)
DAGO (ICV)	CTOP (ICV)	No CPP	Bals-Kubik *et al.* (1990)
	ICI 174 864 (ICV)	CPP	Bals-Kubik *et al.* (1990)
	β-Endorphin (1-27) (ICV)	No CPP	Bals-Kubik *et al.* (1988)
	Pertussis toxin (ICV)	No CPP	Suzuki *et al.* (1991a)
DPDPE (ICV)	CTOP (ICV)	CPP	Bals-Kubik *et al.* (1990);
	ICI 174 864 (ICV)	No CPP	Shippenberg *et al.* (1987)
	BNTX (SC)	No CPP	Suzuki *et al.* (1996d, 1997d)
	Naltriben (SC)	CPP	Suzuki *et al.* (1996d, 1997d)
	SCH23390 (SC)	No CPP	Suzuki *et al.* (1996d)
	Sulpiride (SC)	CPP	Suzuki *et al.* (1996d)
	β-Endorphin (1-27) (ICV)	No CPP	Bals-Kubik *et al.* (1988)
	Pertussis toxin (ICV)	No CPP	Suzuki *et al.* (1991a)
Deltorphin II (ICV)	BNTX (SC)	CPP	Suzuki *et al.* (1996d, 1997d)
	Naltriben (SC)	No CPP	Suzuki *et al.* (1996d, 1997d)
	SCH23390 (SC)	CPP	Suzuki *et al.* (1996d)
	Sulpiride (SC)	CPP	Suzuki *et al.* (1996d)
U-69593 (IP) (CPA)	SCH23390 (NAS)	No CPA	Shippenberg *et al.* (1993)
U-50 488H (ICV) (CPA)	β-Endorphin (1-27) (ICV)	CPA	Bals-Kubik *et al.* (1988)
Naloxone (IP) (CPA)	H7 (NAS)	Reduced CPA	Valverde *et al.* (1996b)
	H8 (NAS)	Reduced CPA	Valverde *et al.* (1996b)

(continued on next page)

Table 4 (*continued*)

Place conditioning induced by	Combined with:	Result	References
Methylnaloxone (amygdala) (CPA)	α-Helical CRF (9-41) (in amygdala)	no CPA	Heinrichs *et al.* (1995)
Various drug combinations:			
Neuropeptide Y (NAS)	α-Flupenthixol (NAS)	No CPP	Josselyn and Beninger (1993)
Nicotine (SC) (CPA)	Chlorisondamine (ICV)	no CPA	Fudala and Iwamoto (1987)
CRF (ICV) (CPA)	α-Helical-CRF(9-41) (ICV)	no CPA	Cador *et al.* (1992)
Lithium chloride (IP) (CPA)	SCH23390 (NAS)	CPA	Shippenberg *et al.* (1993)
	6-OHDA (NAS)	CPA	Shippenberg *et al.* (1993)
Electrical stimulation:			
Of the LH	Haloperidol (IP)	No CPP	Ettenberg and Duvauchelle (1988)
Of the mPFC	Haloperidol (IP)	No CPP	Duvauchelle and Ettenberg (1991)
Of locus coeruleus	Pimozide (IP)	No CPP	Duvauchelle *et al.* (1992b)
Of the VTA	Haloperidol (IP)	No CPP	Duvauchelle *et al.* (1992a)
	α-Flupenth. (NAS)	No CPP	Duvauchelle *et al.* (1992a)
	α-Flupenth. (mPFC)	Enhanced CPP	Duvauchelle *et al.* (1992a)
Of dorsomedial tegmentum (CPA)	Haloperidol (IP)	CPA	Duvauchelle and Ettenberg (1991)
Natural reinforcers:			
Ejaculation	Methylnaloxone (med. preoptic area)	No CPP	Agmo and Gomez (1993)
	Methylnaloxone (NAS)	CPP	Agmo and Gomez (1993)

and lesions of the basolateral nucleus of the amygdala blocked the expression of sucrose-induced CPP in hungry rats (Everitt *et al.*, 1991). In this latter study, lesions of the nucleus accumbens also blocked and lesions of the ventromedial striatum attenuated sucrose-induced CPP, while lesions of the dorsolateral striatum were without effect.

Small lesions restricted to the prelimbic subarea of the mPFC were found to block cocaine-induced CPP, but to have no effect on amphetamine- and morphine-induced CPP (Tzschentke and Schmidt, 1998b), while similar small lesions restricted to the infralimbic subarea of the mPFC were found to block morphine- and CGP 37849-induced CPP but not CPP induced by amphetamine or cocaine (Tzschentke and Schmidt, 1998c). Lesions of the visceral cortex failed to affect morphine-induced CPP or lithium chloride-induced CPA (Mackey *et al.*, 1986).

Lesions of the PPTg, but not of the PAG, prevented the acquisition but not the expression of morphine- and amphetamine-induced CPP, while having no effect on cocaine-induced CPP (Bechara and van der Kooy, 1989; Olmstead and Franklin, 1993, 1994; Parker and van der Kooy, 1995). Lesions of the PPTg also blocked heroin-induced CPP, albeit only when a low dose of heroin was used (0.05 mg/kg), while the CPP induced by a high dose (0.5 mg/kg) was not affected (Nader *et al.*, 1994). PPTg lesions also blocked CPP induced by systemic or intra-VTA morphine or by food only in previously drug-naive or food-sated rats, but not in opiate-dependent and withdrawn or food-deprived rats (Bechara and van der Kooy, 1992a,b; Nader and van der Kooy, 1994, 1997). Likewise, PPTg lesions failed to affect CPA induced by morphine withdrawal in morphine-dependent rats or induced by hunger in food-deprived rats (Bechara and van der Kooy, 1992a). On the other hand, PPTg lesions prevented saccharin-induced CPP in both water-deprived and non-deprived rats (Stefurak and van der Kooy, 1994). Olmstead and Franklin (1997a) found that lesions of the PPTg, the PAG or the fornix reduced morphine-induced CPP, while lesions of the mesolimbic DA system, the VP, the lateral nucleus of the amygdala or the striatum had no effect on morphine-induced CPP. In the case of the PAG and fornix lesions it appeared that the absence of CPP in the drug-free test was due to state-dependency effects, because when the animals were retested after morphine injection they did show CPP. PPTg-lesioned animals failed to show CPP even when tested under morphine (Olmstead and Franklin, 1997a). Lesions of the lateral or medial parabrachial nucleus did not affect morphine-induced CPP (Bechara *et al.*, 1993), but blocked CPA induced by withdrawal in morphine-dependent rats (Nader *et al.*, 1996).

5.3. Other Types of Lesions

Electrolytic lesions of the dorsal striatum potentiated amphetamine-induced CPP (Hiroi and White, 1991a) and similar lesions of the medial septum enhanced cocaine-induced CPP (Gong *et al.*, 1995). On the other hand, electrolytic lesions of the NAS have been reported to block morphine-induced CPP (Kelsey *et al.*, 1989).

Radiofrequency lesions of the medio-basal arcuate hypothalamus were without effect on morphine-induced CPP or U-50 488H-induced CPA, but attenuated naloxone-induced CPA (Mucha *et al.*, 1985).

Rats bearing knife-cut lesions of the connection between the medial and the sulcal PFC, but not intact rats, developed CPP induced by mPFC self-stimulation (Robertson and Laferriere, 1989). Knife cuts of this same connection also facilitated the induction of CPA by low-dose lithium chloride

(Schalomon *et al*., 1994). On the other hand, aspiration lesion of the mPFC led to the development of a cocaine-induced CPA, while lesions of the orbital or precentral PFC blocked cocaine-induced CPP, but did not lead to a CPA (Isaac *et al*., 1989).

Depletion of central noradrenaline by systemic DSP4 did not affect diazepam-induced CPP (Spyraki and Fibiger, 1988), while 5,7-dihydroxytryptamine lesions of the NAS prevented diazepam-induced CPP and attenuated morphine-induced CPP, but failed to affect amphetamine-induced CPP (Spyraki *et al*., 1988). On the other hand, central depletion of serotonin by ICV 5,7-dihydroxytryptamine potentiated mianserin-induced CPA, but suppressed FG 7142-induced CPA (Rocha *et al*., 1993b), while it had no effect on ethanol-induced CPA (Bienkowski *et al*., 1997b).

Adrenalectomy potentiated morphine-induced but not cocaine-induced CPP (Suzuki *et al*., 1995a), while olfactory bulbectomy has been shown to block the expression of cocaine-induced CPP, an effect which was not related to anosmia (Calcagnetti *et al*., 1996). Vagotomy blocked the CPA induced by a low dose of morphine and shifted the U-50 488H-induced CPA into place preferences (Bechara and van der Kooy, 1987) (Table 5).

6. GENETIC MODELS

6.1. Different Strains of Rats

Fischer 344 rats showed no nicotine CPP after five pairings and a nicotine CPA after 10 pairings, whereas Lewis rats showed a CPP for nicotine after five as well as after 10 pairings (Horan *et al*., 1997). A greater sensitivitity of Lewis rats as compared to Fischer 344 rats was also reported for the CPP-inducing effects of cocaine (Kosten *et al*., 1994). In one study, Fischer 344 were found to show a more pronounced amphetamine-induced CPP than Lewis rats (Stohr *et al.,* 1998). This finding is at odds with other experimental evidence that suggests that Lewis rats show greater behavioral responses to psychoactive drugs than Fischer rats (Horan *et al.,* 1997 (see above); Kosten *et al.,* 1994 (see above); Kosten *et al.,* 1997; Suzuki *et al.,* 1988, 1992e). Sprague-Dawley rats were found to be more sensitive to the CPP-inducing effects of morphine than Wistar rats. Shoaib *et al*. (1995) showed that the threshold dose of morphine for the induction of a significant CPP was 3 mg/kg for Sprague-Dawley rats and 5 mg/kg for Wistar rats. Fenfluramine failed to produce CPP or CPA in Sprague-Dawley rats, but produced a CPA in Fawn Hooded rats (a strain that has a genetic platelet storage pool deficiency causing a reduced capacity for platelets to store and release serotonin) (Meehan and Schechter, 1994), and ICV application of thyrotropin releasing hormone (TRH) attenuated the development of morphine-induced CPP in Fischer 344 rats, but not in Wistar Albino Glaxo rats (Borisova and Sudakov, 1995).

The LC2-Hi and LC2-Lo strains (selected for high and low self-stimulation rates, respectively) were shown to differ in their sensitivity to the rewarding effects of morphine and heroin and to the aversive effects of naloxone. Thus, Dymshitz and Lieblich (1987) found that intermediate doses of morphine or heroin produced a CPP in LC2-Hi rats, but not in LC2-Lo rats and that naloxone produced a significantly greater CPA in LC2-Hi rats than in LC2-Lo rats. Rats selectively bred for high alcohol sleep times showed a smaller ethanol-induced CPA than rats selectively bred for low alcohol sleep times, indicating a possible independence of motivational (aversive) and physically intoxicating effects of ethanol (Schechter and Krimmer, 1992).

The CPP paradigm has not only been used to test but also to generate different lines of rats. Thus, selectively pairing rats that showed strong or weak cocaine-induced CPP over three generations produced lines of rats that either strongly preferred cocaine and showed strong cocaine-induced locomotor activation or that found cocaine aversive and showed only a small locomotor response to cocaine, respectively (Schechter, 1992a). Another example for the generation of distinct rat lines using the CPP method was reported by Kushner (1997) who selectively mated cocaethylene-preferring males and females or cocaethylene-nonpreferring males and females.

6.2. Different Strains of Mice

Differences in the reinforcing actions of morphine or cocaine were shown for the C57BL/6J, BALB/c, 129/SvJ, DBA, CBA and other strains (Seale and Carney, 1991; Semenova *et al*., 1995; Miner, 1997). The DBA/2J strain was found to be hyporesponsive to the CPP-inducing effects of amphetamine, etonitazene, PCP, caffeine and procaine (Seale and Carney, 1991), whereas morphine-induced CPP was greater in DBA/2J mice than in C57BL/6J mice and ethanol produced a CPP only in DBA/2J mice, but not in C57BL/6J mice (Cunningham *et al*., 1992b). The δ1-agonist DPDPE and the δ2-agonist deltorphin II produced CPP in ddY mice, but not in μ1-receptor-deficient CXBK mice (Suzuki *et al*., 1994b). On the other hand, morphine produced a CPP in both ddY and CXBK mice, an effect that could be antagonized by SCH 23390 (Suzuki *et al*., 1993a).

Mice selectively bred to show locomotor activation produced by nicotine showed a significantly greater nicotine-induced CPP than mice selectively bred to show locomotor depression produced by nicotine (Schechter *et al*., 1995). A mouse line selectively bred for the occurrence of severe ethanol withdrawal symptoms (Withdrawal Seizure Prone mice) showed significantly larger ethanol-induced CPP than a mouse line selectively bred for the occurrence of attenuated ethanol withdrawal symptoms (Withdrawal Seizure Resistant mice) (Crabbe *et al.,* 1992). Mice selectively bred for insensitivity to ethanol-induced hypothermia (Hot mice) also developed a significantly larger ethanol-induced CPP than mice selected for ethanol hypothermic sensitivity (Cold mice) (Cunningham *et al*., 1991), suggesting that ethanol-induced hypothermia counteracts or attenuates the rewarding effects of ethanol, which is in line with the finding of Cunningham and Niehus (1993) who showed that an increased ambient temperature

Table 5. This table summarizes the results of studies examining the effects of lesions on place conditioning. See Section 5 in the text for details about drugs, experimental procedures and additional findings that could not be included in the table. In cases where lesion effects on place aversion or on the expression of place conditioning were examined this is explicitely indicated by (CPA) and (expr.)

Lesioned area	Place conditioning produced by	Result	References
6-OHDA lesions:			
NAS	Morphine	No CPP	Shippenberg *et al.* (1993)
	U-69593 (CPA)	No CPA	Shippenberg *et al.* (1993)
	Diazepam	No CPP	Spyraki and Fibiger (1988)
	Novel environment	No CPP	Pierce *et al.* (1990)
	CTOP (VTA) (CPA)	No CPA	Shippenberg and Bals-Kubik (1995)
	CTOP (NAS) (CPA)	CPA	Shippenberg and Bals-Kubik (1995)
	Naloxone (IP) (CPA)	CPA	Shippenberg and Bals-Kubik (1995)
VP	Cocaine	No CPP	Gong *et al.* (1997b)
Olfactory tubercle	Amphetamine	CPP	Clark *et al.* (1990)
Striatum	Morphine	CPP	Shippenberg *et al.* (1993)
	U-69593 (CPA)	CPA	Shippenberg *et al.* (1993)
mPFC	Morphine	CPP	Shippenberg *et al.* (1993)
	U-69593 (CPA)	CPA	Shippenberg *et al.* (1993)
	Cocaine	CPP	Hemby *et al.* (1992b)
Visceral cortex	Morphine	CPP	Zito *et al.* (1988)
	Morphine (CPA)	No CPA	Zito *et al.* (1988)
ICV	Methylphenidate	CPP	Martin-Iverson *et al.* (1985)
Excitotoxic lesions:			
NAS	Amphetamine	No CPP	Olmstead and Franklin (1996)
	Morphine	CPP	Olmstead and Franklin (1997a)
	Sucrose	No CPP	Everitt *et al.* (1991)
	Naltrexone (CPA)	CPA	Kelsey and Arnold (1994)
Striatum	Morphine	CPP	Olmstead and Franklin (1997a)
	Food	CPP	White and McDonald (1993)
Striatum (ventromed.)	Sucrose	Reduced CPP	Everitt *et al.* (1991)
Striatum (dorsolateral)	Sucrose	CPP	Everitt *et al.* (1991)
VP	Sucrose	Reduced CPP	McAlonan *et al.* (1993)
	Amphetamine	No CPP	Hiroi and White (1993)
	Amphetamine (expr.)	CPP	Hiroi and White (1993)
	Morphine	CPP	Olmstead and Franklin (1997a)
Amygdala (whole)	Cocaine	No CPP	Brown and Fibiger (1993)
Amygdala (lat. nucl.)	Morphine	CPP	Olmstead and Franklin (1997a)
	Amphetamine	No CPP	Hiroi and White (1991b)
	amphetamine (expr.)	No CPP	Hiroi and White (1991b)
	Food	No CPP	White and McDonald (1993)
Amygdala (basolat. nucleus)	Amphetamine	CPP	Hiroi and White (1991b)
	Amphetamine (expr.)	CPP	Hiroi and White (1991b)
	Sucrose (expr.)	No CPP	Everitt *et al.* (1991)
Amygdala (mediodors. nucleus)	Naltrexone (CPA)	Reduced CPA	Kelsey and Arnold (1994)
Endopiriform nucl.	Amphetamine	CPP	Hiroi and White (1991b)
	Amphetamine (expr.)	CPP	Hiroi and White (1991b)
Ventral hippocampus	Amphetamine	CPP	Hiroi and White (1991b)
	Amphetamine (expr.)	CPP	Hiroi and White (1991b)
Fornix	Morphine	Reduced CPP	Olmstead and Franklin (1997a)
	Food	Enhanced CPP	White and McDonald (1993)
MD thalamus	Sucrose	Reduced CPP	McAlonan *et al.* (1993)
mPFC (prelimbic)	Cocaine	No CPP	Tzschentke and Schmidt (1998b)
	Amphetamine	CPP	Tzschentke and Schmidt (1998b)
	Morphine	CPP	Tzschentke and Schmidt (1998b)
mPFC (infralimbic)	Cocaine	CPP	Tzschentke and Schmidt (1998c)
	Amphetamine	CPP	Tzschentke and Schmidt (1998c)
	Morphine	No CPP	Tzschentke and Schmidt (1998c)
	CGP37849	No CPP	Tzschentke and Schmidt (1998c)
Visceral cortex	Morphine	CPP	Mackey *et al.* (1986)
	Lithium chloride (CPA)	CPA	Mackey *et al.* (1986)

Table 5 (*continued*)

Lesioned area	Place conditioning produced by	Result	References
PPTg	Cocaine	CPP	Olmstead and Franklin (1993, 1994, 1997a); Parker and van der Kooy (1995); Bechara and van der Kooy (1989)
	Cocaine (expr.)	CPP	
	Amphetamine	No CPP	
	Amphetamine (expr.)	CPP	
	Morphine	No CPP	
	Morphine (expr.)	CPP	
	Heroin (low dose)	No CPP	Nader *et al.* (1994)
	Heroin (high dose)	CPP	Nader *et al.* (1994)
	Morphine (IP) (in naive animals)	No CPP	Bechara and van der Kooy (1992a,b); Nader and van der Kooy (1994, 1997)
	Morphine (VTA) (in naive animals)	No CPP	
	Morphine (IP) (in dependent animals)	CPP	
	Morphine (VTA) (in dependent animals)	CPP	
	Food (satiated animals)	No CPP	
	Food (deprived animals)	CPP	
	Morphine withdr. in depend. animals (CPA)	CPA	Bechara and van der Kooy (1992a)
	Hunger in food-depr. animals (CPA)	CPA	Bechara and van der Kooy (1992a)
	Saccharin solution	No CPP	Stefurak and van der Kooy (1994)
PAG	Cocaine	CPP	Bechara and van der Kooy (1989);
	Cocaine (expr.)	CPP	Olmstead and Franklin (1993, 1994);
	Amphetamine	CPP	Parker and van der Kooy (1995)
	Amphetamine (expr.)	CPP	
	Morphine	CPP	
	Morphine (expr.)	CPP	
	Morphine	Reduced CPP	Olmstead and Franklin (1997a)
Med. parabrach. nucl.	Morphine	CPP	Bechara *et al.* (1993)
	Morphine withdr. in depend. animals (CPA)	No CPA	Nader *et al.* (1996)
Other lesions:			
NAS (electrolytic)	Morphine	No CPP	Kelsey *et al.* (1989)
Striatum (electrolytic)	Amphetamine	Enhanced CPP	Hiroi and White (1991a)
Medial septum (electrolytic)	Cocaine	Enhanced CPP	Gong *et al.* (1995)
Mediobasal arcuate hypothalamus (radiofrequency)	Morphine	CPP	Mucha *et al.* (1985)
	U-50 488H (CPA)	CPA	Mucha *et al.* (1985)
	Naloxone (CPA)	reduced CPA	Mucha *et al.* (1985)
	Lithium chloride (CPA)	No CPA	Shippenberg *et al.* (1988b)
Connection of sulcal and mPFC (knife cut)	mPFC self-stimulation	Enhanced CPP	Robertson and Laferriere (1989)
	Lithium chloride (CPA)	Enhanced CPA	Schalomon *et al.* (1994)
mPFC (aspiration)	Cocaine	CPA	Isaac *et al.* (1989)
Orbital PFC (aspirat.)	Cocaine	No CPP	Isaac *et al.* (1989)
Precentral PFC (asp.)	Cocaine	No CPP	Isaac *et al.* (1989)
Central NA depletion (IP DSP4)	Diazepam	CPP	Spyraki and Fibiger (1988)
Central 5-HT depl. (ICV 5,7-DHT)	Mianserin (CPA)	Enhanced CPA	Rocha *et al.* (1993b)
	FG 7142 (CPA)	No CPA	Rocha *et al.* (1993b)
	Ethanol (CPA)	CPA	Bienkowski *et al.* (1997b)
NAS 5-HT depl. (5,7-DHT)	Diazepam	No CPP	Spyraki *et al.* (1988)
	Morphine	Reduced CPP	Spyraki *et al.* (1988)
	Amphetamine	CPP	Spyraki *et al.* (1988)
Adrenalectomy	Morphine	Enhanced CPP	Suzuki *et al.* (1995a)
	Cocaine	CPP	Suzuki *et al.* (1995a)
Olfact. bulbectomy	Cocaine (expr.)	No CPP	Calcagnetti *et al.* (1996)
Vagotomy	Morphine (low dose) (CPA)	No CPA	Bechara and van der Kooy (1987)
	U-50 488H (CPA)	CPP	Bechara and van der Kooy (1987)

can attenuate ethanol-induced CPA (see Section 3.2.3.2). In a further examination of this phenomenon, Dickinson and Cunningham (1998) showed, using genetically heterogeneous mice, that animals conditioned and tested under normal ambient temperature, showed an ethanol-induced CPP, while animals that were conditioned or tested under low or high ambient temperatures failed to show ethanol-induced CPP. These results suggest that abnormal ambient temperatures during conditioning or during testing may have a rather general and non-specific disruptive effects on the development and/or expression of ethanol-induced CPP in outbred mice.

Only mice selectively bred to show strong alcohol withdrawal signs (High Alcohol Withdrawal mice) showed ethanol-induced CPP while mice selectively bred for weak alcohol withdrawal signs (Low Alcohol Withdrawal mice) failed to develop ethanol-induced CPP (Chester *et al.,* 1998). These findings, together with the above-mentioned results of Crabbe *et al.* (1992), may indicate that the subjective rewarding effects of ethanol are closely correlated with the overall physiological effects which are responsible for the development of somatic ethanol dependence (manifest in withdrawal symptoms).

6.3. Genetically Engineered Animals

Cunningham (1995) compared 20 BXD recombinant inbred mouse strains in place preference conditioning to ethanol and found that while some strains did not show any preference for the ethanol-paired compartment, other strains showed strong ethanol-induced CPP. Quantitative trait loci analysis showed strong associations between the magnitude of the CPP effect and certain marker loci on several chromosomes. Thus, the CPP paradigm was used to localize genes influencing the rewarding effects of ethanol.

FosB mutant mice showed a stronger cocaine-induced CPP than wild-type littermates (Hiroi *et al.*, 1997). VMAT2 (vesicular monoamine transporter) knockout mice showed reduced amphetamine-induced CPP (Takahashi *et al.*, 1997), while D1 receptor deficient mice (either hetero- or homozygous) showed normal cocaine-induced CPP (Miner *et al.*, 1995). Mice lacking the μ-receptor gene (Matthes *et al.*, 1996) and mice lacking D2 receptors (Maldonado *et al.*, 1997) did not develop morphine-induced CPP, but displayed intact food-induced CPP. Knockout mice lacking the 5-HT1B receptor did not develop ethanol-induced CPP (Risinger *et al.*, 1996).

7. THE ISSUE OF TOLERANCE AND SENSITIZATION TO THE REWARDING EFFECTS OF DRUGS

Sensitization and tolerance to the behavioural effects of drugs of abuse are well known and extensively studied phenomena (for reviews see Wise and Leeb, 1993; Trujillo and Akil, 1995; Kalivas *et al.*, 1993; Kalivas and Stewart, 1991; Robinson and Berridge, 1993; Robinson and Becker, 1986; Stewart and Badiani, 1993). Especially in the case of sensitization, long-term behavioural changes with repeated drug administration are usually measured in terms of locomotor behaviour. Interestingly, evidence exists that sensitization can develop not only to the locomotor-activating effects of drugs, but also to their rewarding effects. Evidence for this comes from self-administration studies (e.g. Horger *et al.*, 1990) and, in particular, from CPP studies.

Prominent sensitization of rewarding effects have been reported for ethanol (see also Section 3.1.3). For example, it has been shown that in naive rats ethanol produces either a CPA (Holloway *et al.*, 1992) or no effect (Reid *et al.*, 1985; Bienkowski *et al.*, 1996), while in rats preexposed to ethanol prior to the conditioning sessions or in rats receiving extended conditioning training, ethanol commonly produced CPP (Holloway *et al.*, 1992; Reid *et al.*, 1985; Bozarth, 1990; Bienkowski *et al.*, 1996), an effect which may be due to both sensitization of the rewarding and tolerance to the aversive effects of ethanol.

Bienkowski *et al.* (1995) found that rats preexposed to a low dose of ethanol (20 daily IP injections of 0.5 g/kg) subsequently developed ethanol-induced CPP, while rats pretreated with a higher dose of ethanol (20 daily injections of 1.0 g/kg) developed ethanol-induced CPA. The same group (Bienkowski *et al.*, 1996) also showed that five or 15 conditioning sessions (with 0.5 or 1.0 g/kg ethanol) were not sufficient to produce a significant CPP. Only when the rats were pretreated with 20 injections of ethanol (0.5 g/kg IP) prior to the conditioning experiment did this procedure produce a CPP (note, however, that the same 'sensitization' effect was obtained with 20 daily injections of saline!). In contrast, Bozarth (1990) reported that a conditioning regimen with 15 daily conditioning trials with 1.0 g/kg IP ethanol produced CPP, while conditioning with 0.5 g/kg ethanol IP failed to produce an effect, and Davies and Parker (1990) showed that neither naive nor ethanol-preexposed rats showed ethanol-induced CPP (or CPA) in their study. In one study, rats that had been trained to self-administer ethanol prior to the ethanol conditioning experiment developed a CPP, rats that had received ethanol/saline drug-discrimination training developed neither CPP nor CPA, and rats that went into the conditioning experiments without prior training or exposure to ethanol, developed a CPA (Gauvin and Holloway, 1992), suggesting that the reward-enhancing effect of preexposure may not only depend on the mere quantitative exposure to the drug but also on the context in which this preexposure occurs (in particular contingent vs non-contingent administration).

Sensitizing effects of preexposure or of extended conditioning training have also been shown for morphine (Contarino *et al.*, 1997; Shippenberg *et al.*, 1996a; Lett, 1989a; Gaiardi *et al.*, 1991; but see Martin *et al.*, 1988). In two studies, however, non-contingent pretreatment prior to conditioning resulted in tolerance to the rewarding effects of morphine and in tolerance to the aversive effects of the κ-agonist U-69593 (Shippenberg *et al.*, 1988a, 1989). Although the exact reasons for these discrepancies are not known, it should be considered that tem-

poral factors of drug application play an important role in determining whether tolerance or sensitization develops. Thus, it has been shown that continuous administration or the frequent administration of lower doses of drugs generally produce tolerance, while intermittent administration of higher doses generally produce sensitization (see e.g. Kuribara, 1996; Vanderschuren *et al*., 1997; Post, 1980). Evidence for a possible context dependence of the effects of morphine preexposure on subsequent place conditioning has been presented by McKee *et al*. (1994), who showed that morphine injections prior to conditioning in a context different from the conditioning context were without effect on subsequent place conditioning, whereas morphine-induced CPP was reduced when the preexposures occurred in the same context as the subsequent conditioning.

Reward-sensitizing effects of preexposure have also been shown for nicotine (Shoaib *et al*., 1994; but see Fudala and Iwamoto, 1986), amphetamine and cocaine (Lett, 1989a; Shippenberg *et al*., 1996b; Shippenberg and Heidbreder, 1995a) and fencamfamine (De Lucia *et al*., 1997). Cross-sensitization of the rewarding effects of morphine, amphetamine and cocaine in CPP was also reported (Lett, 1989a; Shippenberg and Heidbreder, 1995b). The reward-sensitizing effect of cocaine-preexposure could be blocked by concurrent preexposure to the δ-antagonist naltrindole, but not lithium chloride (Shippenberg and Heidbreder, 1995a). Note that in this latter study coadministration of naltrindole with cocaine during the conditioning sessions did not affect the development of cocaine-induced CPP itself. The reward-sensitizing effect of cocaine-preexposure was also blocked by the κ-agonists U50 488H and U69593 administered either SC or ICV (Shippenberg *et al*., 1996b) and SCH 23390, but not raclopride (Shippenberg and Heidbreder, 1995b). The blockade of cocaine reward sensitzation by the κ-agonists was prevented by concurrent treatment with the κ-antagonist nor-binaltorphimine. Administration of U69593, SCH 23390 or raclopride alone prior to cocaine place conditioning did not affect the CPP-inducing effects of cocaine (Shippenberg *et al*., 1996b; Shippenberg and Heidbreder, 1995b). In a further examination of this issue, Shippenberg *et al*. (1998) showed sensitization of the conditioned rewarding effects of morphine and cocaine and also cross-sensitization between the rewarding effects of both drugs, such that pretreatment with morphine or cocaine produced enhanced CPP induced by cocaine or morphine, respectively. These authors also showed that the enhancing effect of morphine pretreatment on morphine- and cocaine-induced CPP was not affected by coadministration of the κ-agonist U69593 during the pretreatment phase. On the other hand, when U69593 was coadministered during cocaine pretreatment, the enhancing effect of cocaine pretreatment on morphine-induced CPP was abolished. These results show that a κ-agonist prevents sensitization and cross-sensitization induced by cocaine but, rather surprisingly, does not affect morphine-induced sensitization or cross-sensitization of reward.

Acute haloperidol injections during the conditioning experiment attenuated cocaine-induced CPP, while long-term pretreatment with haloperidol for 30 days prior to and during the conditioning experiment significantly enhanced the CPP-inducing effects of low doses of cocaine, presumably by up-regulation or supersensitization of DA receptors (Kosten *et al*., 1996). Similarly, the potential of heroin to produce CPP was enhanced by chronic pretreatment with the D2 antagonist flupenthixol decanoate (every 10 days for 6 weeks) (Stinus *et al*., 1989), and Bardo and Neisewander (1987) reported that chronic pretreatment with naltrexone over 10 days (by means of an SC implanted slow-release pellet) sensitized rats to the CPP-inducing effects of IV morphine (see also Suzuki *et al*., 1991c).

The putative anti-addictive drug ibogaine prevented the establishment of amphetamine-induced CPP when one or two conditioning trials were used, but only to a much lesser extent when four conditioning trials were used (Moroz *et al*., 1997). The authors argued that the diminished effects of ibogaine after four conditioning trials may be due to the development of tolerance to ibogaine. While this is a valid interpretation, in light of the phenomena described above, the observed diminished effect of ibogaine might also be due to sensitization of the rewarding effects of amphetamine during prolonged conditioning or simply by a stronger conditioning effect (produced by more drug-context pairings) that could not be overcome by ibogaine.

Cross-sensitization of rewarding effects has also been reported for the antidepressants fluoxetine and imipramine, and cocaine. Collu *et al*. (1994, 1996) reported that only animals that received chronic pretreatment with either of these two serotonin reuptake blockers prior to the conditioning experiment developed CPP after a single administration of cocaine. Pretreatment with imipramine had differential effects on apomorphine- and food-induced CPP, also depending on the duration of the pretreatment (compare with haloperidol above). Thus, short-term administration of imipramine prevented the development of CPP, while long-term administration enhanced the CPP-inducing effects of apomorphine and food (Papp, 1988a). In line with these results, it was also reported that short term treatment (during conditioning sessions) with the antidepressants imipramine, desipramine, amitryptiline, mianserin and citalopram attenuated food-induced CPP in food-deprived rats, while long-term pretreatment (for 16 days prior to conditioning) significantly enhanced food-induced CPP (Papp, 1989). This sensitizing effect could be mimicked by nine applications of electroconvulsive shock prior to conditioning (Papp, 1989).

Animals subjected to chronic mild unpredictable stress showed disrupted development of amphetamine- and quinpirole-induced CPP (see Section 3.2.1.8). When these chronically stressed animals were subjected to repeated quinpirole treatment that also produced locomotor sensitization prior to quinpirole place conditioning they showed normal, unimpaired quinpirole-induced CPP (Papp *et al*., 1993b). A similar reversal of stress-induced anhedonia was also produced by chronic treatment with the

D2-agonist pramipexole (Willner *et al*., 1994), the 5-HT1A agonist/5-HT2 antagonist flibaserin (D'Aquila *et al*., 1997) and the atypical antidepressants mianserin (Cheeta *et al*., 1994), fluoxetine and maprotiline, while the benzodiazepine chlordiazepoxide was ineffective (Muscat *et al*., 1992; D'Aquila *et al*., 1997).

Prenatal morphine exposure (Gagin *et al*., 1997) and perinatal exposure to low doses of THC sensitized the adult offspring to the CPP-inducing effects of morphine (Rubio *et al*., 1995; see Navarro *et al*., 1995) and prenatal exposure to oxazepam transiently sensitized the offspring to the CPP-inducing effects of cocaine (a sensitized response was seen only when conditioning took place between the age of 14 and 24 days, but not after the age of 28 days) (Dell'Omo *et al*., 1993). On the other hand, prenatal cocaine exposure using an aggressive treatment schedule (dams were injected with 40 mg/kg daily during gestational days 8–20) produced offspring that failed to develop cocaine-induced CPP (Heyser *et al*., 1992).

The relatively inconsistent place conditioning results that have been reported for PCP may be largely related to tolerance and sensitization effects. Thus, Kitaichi *et al*. (1996) found that acute administration of PCP produced CPA, repeated treatment over 14 days resulted in no effect, and repeated treatment over 28 days finally led to a PCP-induced CPP (see also Section 3.1.7). Iwamoto (1986a) also found that repeated exposure to PCP reduced its potential to produce CPA (as it did after initial exposures, even at relatively low doses).

Interestingly, intracranial self-stimulation paradigms, which appear to be very sensitive to detect relatively subtle rewarding or reward-enhancing effects of drugs (see Wise, 1996) seem to be less well suited than the CPP paradigm to detect changes in the rewarding potential of a drug during repeated treatment (Wise and Munn, 1993; Carlezon and Wise, 1993b; Bauco and Wise, 1994; but see Corbett, 1991).

8. STUDIES EXPLICITLY EXAMINING CPA

One of the big advantages of the place preference conditioning paradigm is that it can also be used to study aversive aspects and components of motivational effects of drugs and treatments, which is possible only to a limited extent with the (otherwise very powerful) self-administration and self-stimulation paradigms.

8.1. CPA Produced by Opiate Antagonist-Precipitated Withdrawal

CPA is reliably produced by a number of opiate receptor antagonists in chronically morphine-preexposed (i.e. morphine-dependent) rats. In morphine-dependent rats usually significantly lower doses of an antagonist are needed to produce CPA than in non-dependent rats) (see Section 3.2.1.2). A precipitated withdrawal-induced CPA has been shown for naloxone (Acquas *et al*., 1990; Funada *et al*., 1996; Mucha, 1987; Mucha and Walker, 1987; Higgins *et al*., 1991a; Popik and Danysz, 1997; Kosten, 1994; Spanagel *et al*., 1994; Schulteis *et al*., 1994; Valverde *et al*., 1996b; Valverde and Roques, 1998), naltrexone (Kelsey and Arnold, 1994), naltrindole (Funada *et al*., 1996), naltriben (Funada *et al*., 1996), methylnaltrexone (ICV) (Mucha *et al*., 1985) and methylnaloxone (ICV) (Hand *et al*., 1988; Stinus *et al*., 1990).

CPA induced by naloxone-precipitated withdrawal in morphine-dependent rats is frequently used to assess the effects of drugs on the negative motivational aspects of withdrawal. Drugs which block or attenuate the development of naloxone-precipitated withdrawal-induced CPA might have the potential to alleviate withdrawal distress in human opiate addicts. Thus, naloxone-precipitated withdrawal-induced CPA was blocked or attenuated by memantine (Popik and Danysz, 1997), MK-801 (Higgins *et al*., 1992b), the D2 agonist propylnorapomorphine (Harris and Aston-Jones, 1994), the D2 antagonist α-flupenthixol (Bechara *et al*., 1995), the 5-HT3 antagonists DAU 6215 (Borsini *et al*., 1993), ondansetron, ICS 205-930 and MDL 72 222, also by chlordiazepoxide, but not by gepirone (Acquas *et al*., 1990; Higgins *et al*., 1991a), and also by the α2-agonist clonidine (Kosten, 1994), the non-selective β-antagonist propranolol, the β1-antagonist atenolol (Harris and Aston-Jones, 1993), acute coadministration of, but not chronic preexposure to, the 5-HT reuptake blocker fluvoxamine, and chronic preexposure to, but not acute coadministration of, the 5-HT reuptake blocker paroxetine (Rafieian-Kopaei *et al*., 1995). Chronic administration of the CCK-B antagonists PD-134,308 and L-365,260 during the development of morphine dependence reduced or blocked, respectively, the CPA induced by naloxone, while the CCK-A antagonist devazepide and the CCK-B agonist BC 264 were without effect (Valverde and Roques, 1998). On the other hand, naloxone-precipitated withdrawal-induced CPA was potentiated by the κ-antagonist nor-binaltorphimine (Spanagel *et al*., 1994).

When during chronic morphine-pretreatment the animals were co-treated with intra-NAS injections of the kinase inhibitors H7 or H8 the magnitude of naloxone-precipitated withdrawal-induced CPA was significantly reduced (Valverde *et al*., 1996b). In morphine-dependent rats, ICV methylnaloxonium produced CPA (Hand *et al*., 1988). CPA was also induced when low doses of methylnaloxonium were injected into the NAS, while much higher doses where needed to produce CPA when injected into the mediodorsal thalamus, PAG, VTA or amygdala (Stinus *et al*., 1990). This finding is in apparent contrast to the results of Kelsey and Arnold (1994) who report that lesions of the mediodorsal amygdala, but not of the NAS, reduced the aversiveness of naltrexone-precipited morphine-withdrawal. Heinrichs *et al*. (1995) reported that the CPA induced by intra-amygdala injection of methylnaloxonium could be prevented by injection of the CRF antagonist α-helical CRF (9-41) into the same site. Taken together, these latter studies demonstrate that exclusively central mechanisms are sufficient to induce full opiate withdrawal aversion.

8.2. CPA Produced by Lithium Chloride

Besides naloxone-precipitated withdrawal, one of the most reliable and most frequently used treatments to induce CPA is the injection of lithium chloride (Suzuki *et al*., 1992a; Parker, 1992; Frisch *et al*., 1995; Cunningham and Niehus, 1993; Oberling *et al*., 1993; Reilly *et al*., 1993; Shippenberg *et al*., 1988b; Bechara *et al*., 1987; Symonds and Hall, 1997; Lett, 1992). CPA induced by lithium chloride was shown to be blocked by the antiemetic metoclopramide and a combination of extracts from *Ginkgo biloba* and *Zingiber officinale* (Frisch *et al*., 1995), while ibogaine was ineffective (Parker *et al*., 1995). Lithium chloride-induced CPA could also be prevented by naloxone, high doses of SCH 23390 and SCH 39166 (Acquas and Di Chiara, 1994), and radiofrequency lesions of the mediobasal arcuate hypothalamus, a precedure which markedly reduced the levels of β-endorphin in the hypothalamus. On the other hand, chronic dexamethasone treatment, which reduces circulating β-endorphin levels (Shippenberg *et al*., 1988b), intra-NAS injection of SCH 23390 or 6-OHDA lesions of the NAS (Shippenberg *et al*., 1993) were without effect. CPA induced by lithium chloride was also shown to be attenuated by counteracting the drug-induced hypothermia by increasing the ambient temperature to 32°C during conditioning, suggesting that the aversive effects of lithium chloride might be, at least partly, due to the experience of drug-induced hypothermia (Cunningham and Niehus, 1993).

9. CONCLUDING REMARKS

An overview of the literature reviewed in the present paper shows that the largest number of studies have examined the interaction of two (or more) drugs after systemic administration. Thus, a number of studies have tested novel drugs such as the atypical neuroleptics or the new and atypical antidepressants. A large number of studies have examined new receptor subtype-selective agonists and antagonists as they became available over the years, most notably a number of D2- and D3-selective ligands, agonists and antagonists specific for μ- and δ-receptor subtypes, benzodiazepine receptor agonists and antagonists, antagonists of the glutamatergic NMDA- and AMPA receptors, and a whole range of new serotonin receptor subtype-specific compounds. Natural reinforcers such as food, water or sucrose solution have also been used frequently.

From the studies examining drug interactions, several issues are evident. For example, a number of studies confirmed that amphetamine-induced CPP appears to be highly dependent on D1, as well as on D2 receptor-mediated mechanisms, whereas cocaine-induced CPP is hardly affected by D2 antagonists, but only by D1 antagonism and atypical neuroleptics. A number of studies also confirmed that endogenous opioid systems play an important role in the mediation of the rewarding effects of psychostimulants since naloxone was consistently shown to block cocaine- and amphetamine-induced CPP. On the other hand, inconsistent results have been reported for the importance of serotonin receptors for psychostimulant-induced CPP, but the majority of results suggest a minor role for serotonin, at least for its action at 5-HT1 and 5-HT3 receptors. The picture for glutamate receptors also appears to be somewhat inconsistent with respect to the role of different subtypes in the expression of previously established psychostimulant-induced CPP; nevertheless, glutamate receptors appear to be importantly involved in the acquisition of CPP. The importance of rearing conditions for the ability of psychostimulants to produce CPP was also demonstrated in several studies. In general, animals that were reared in 'enriched' conditions showed a larger drug-induced CPP than animals that were reared in 'impoverished' conditions, and food deprivation generally enhanced the rewarding potential of the drugs tested.

With respect to CPP induced by morphine and other opiates, it can be noted that studies examining the role of DA receptors yielded inconsistent results. While D1 and D3 receptors appear to be important, D2 receptor antagonists blocked opiate-induced CPP in some studies, while they were without effect in others. Morphine-induced CPP was consistently prevented by μ-antagonists such as naloxone and naltrexone, and also by κ-agonists, while the results for δ-receptor ligands are less consistent. Unlike psychostimulant-induced CPP, morphine-induced CPP appears to be strongly dependent on serotonin receptors, since a number of studies consistently reported a blockade of morphine-induced CPP by various 5-HT3 antagonists. Morphine-induced CPP was also consistently shown to be blocked by NMDA- and other glutamate antagonists. As in the case of the psychostimulants, the magnitude of morphine-induced CPP was also strongly influenced by rearing conditions or by stress.

Studies using intracranial drug application confirmed the central role of the NAS for the rewarding or aversive effects of a number of dopaminergic drugs such amphetamine, SKF 38393, quinpirole and SCH 23390, but not for cocaine. The VP was also identified as a structure from which psychostimulants can elicit rewarding effects. With respect to opiates the predominant role of the VTA for the mediation of the rewarding effects of morphine and other μ-agonists was confirmed in several studies. However, CPP could also be induced by morphine injection into the hippocampus and the PAG, but not by morphine injection into a large number of other forebrain and brainstem sites. Studies examining drug interactions also confirmed the dependence of amphetamine reward on D1 and D2 receptor-mediated mechanisms in the NAS, and also the relative independence of cocaine reward from these mechanisms. They also confirmed the importance of the VTA and the PAG for morphine-induced CPP.

The very small number of studies examining the effects of 6-OHDA lesions established the role of dopaminergic mechanisms in the VP in the mediation of cocaine-induced CPP and confirmed the importance of NAS DA for novelty-induced CPP and the unimportance of dopaminergic mechanisms in the olfactory tubercle and the visceral cortex for psychostimulant and opiate reward. A larger num-

ber of studies using excitotoxic lesions once again confirmed the importance of the NAS for amphetamine-, but not for morphine-induced CPP, and also confirmed the role of the VP, the amygdala and the thalamus in reward-related mechanisms. The selective differential importance of specific subregions of the mPFC for the CPP induced by different classes of drugs was established as well as the importance of the PPTg for the acquisition of morphine- and amphetamine-induced CPP.

Studies examining inbred strains demonstrated that different strains or lines of mice or rats can show dramatic differences with respect to the potency of drugs to induce CPP. Studies using knockout mice lacking specific receptors or transporter proteins are just beginning to emerge, but the existing results have largely confirmed the presumed role of the missing receptor or transporter in the mediation of drug reward.

Since sensitization to the effects of drugs of abuse is presumed to play an important role in the development of drug addiction (see Robinson and Berridge, 1993), the issue of sensitization has not only been addressed in locomotor studies, but also by means of place conditioning. Thus, it has been established that sensitization to the rewarding effects (and/or tolerance to the aversive effects) can heavily influence the outcome of place conditioning experiments. Cross-sensitization of the rewarding effects of drugs from different classes, such as opiates and psychostimulants, or psychostimulants and antidepressants, was also found.

Naloxone-precipitated withdrawal-induced CPA was frequently used as a model of withdrawal distress. Several drugs were found to be able to reduce withdrawal-induced CPA, most notably 5-HT3 antagonists, NMDA antagonists, α-agonists and β-antagonists.

The place preference conditioning paradigm has been extremely popular during the last decade with researchers examining the motivational effects of drugs and non-drug treatments. This popularity is at least partly due to the fact that the CPP paradigm does not require expensive technical equipment. Experiments can easily be run without automated control units, surgical preparation of the animals is not necessary (unless lesions or local injections are made), and the procedure does not involve lengthy training sessions. Once an experimental setup has been established, once it has been determined whether the setup is biased or unbiased, and once it has been confirmed that 'positive control' drugs like morphine or cocaine produce clear, reproducable CPP, the place conditioning procedure can yield sensitive and reliable measures of the motivational value of a given treatment. To exclude a possible interference of state-dependency effects, the animals should also be tested in the drugged state whenever no CPP (or CPA) was obtained in the undrugged test. Of course the CPP paradigm is no more than a model for reward and reinforcement processes. Thus, if a drug produces CPP, it does not necessarily have to be 'dismissed' as potentially addictive, and conversely, the lack of CPP does not mean that the drug is absolutely safe with respect to abuse potential. The motivational effects of drugs should be examined in all animal models available, each of which has its strengths but also its shortcomings. In the cases where this has been done in place preference conditioning as well as in self-administration and brain self-stimulation paradigms, usually a very good match was found for the results obtained with these different experimental procedures, and only combining and integrating the results of these different paradigms will yield valuable insight into the motivational properties of drugs and into the brain mechanisms of reward and reinforcement.

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