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# THE NEUROBIOLOGY OF STARTLE

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**Abstract**—Startle is a fast response to sudden, intense stimuli and probably protects the organism from injury by a predator or by a blow. The acoustic startle response (ASR) of mammals is mediated by a relatively simple neuronal circuit located in the lower brainstem. Neurons of the caudal pontine reticular nucleus (PnC) are key elements of this primary ASR pathway.

The ASR in humans and animals has a non-zero baseline, that is, the response magnitude can be increased or decreased by a variety of pathological conditions and experimental manipulations. Therefore, the ASR has been used as a behavioral tool to assess the neuronal basis of behavioral plasticity and to model neuropathological dysfunctions of sensorimotor information processing.

Cross-species examples for the increase of the ASR magnitude are sensitization, fear-potentiation and drug-induced enhancement. Examples for the reduction of the ASR magnitude are habituation, prepulse inhibition, drug-induced inhibition and the attenuation by positive affect.

This review describes the neuronal basis underlying the mediation of the ASR, as well as the neuronal and neurochemical substrates of different phenomena of enhancement and attenuation of the ASR.

It also attempts to elucidate the biological background of these forms of behavioral plasticity. Special emphasis is put on the potential relevance of ASR modulations for the understanding of human psychiatric and neurological diseases. 

## CONTENTS



## ABBREVIATIONS

| | |
|---|---|
| ACh | Acetylcholine |
| AMPA | α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid |
| AP-5 | DL-2-Amino-5-phosphonopentanoic acid |
| ASR | Acoustic startle response |
| CCK | Cholecystokinin |
| CGS19755 | *cis*-4-Phosphonomethyl-2-piperidine-carboxylate |
| CNQX | 6-Cyano-7-nitroquinoxaline-2,3-dione |
| CRH | Corticotropin-releasing hormone |
| CS | Conditioned stimulus |
| dB | Decibel |
| DA | Dopamine |
| EPSPs | Excitatory postsynaptic potentials |
| GABA | γ-Amino-butyric acid |
| 5-HT | 5-Hydroxytryptamine (serotonin) |
| MK-801 | (5*R*,10*S*)-(+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate |
| NA | Noradrenaline |
| NAC | Nucleus accumbens septi |
| NMDA | *N*-Methyl-D-apartate |
| 6-OHDA | 6-Hydroxydopamine |
| PnC | Caudal pontine reticular nucleus |
| PPTg | Pedunculopontine tegmental nucleus |
| PPI | Prepulse inhibition |
| SOM | Somatostatin |
| SP | Substance P |
| SPL | Sound pressure level |
| US | Unconditioned stimulus |
| vHIP | Ventral hippocampus |
| VTA | Ventral tegmental area |

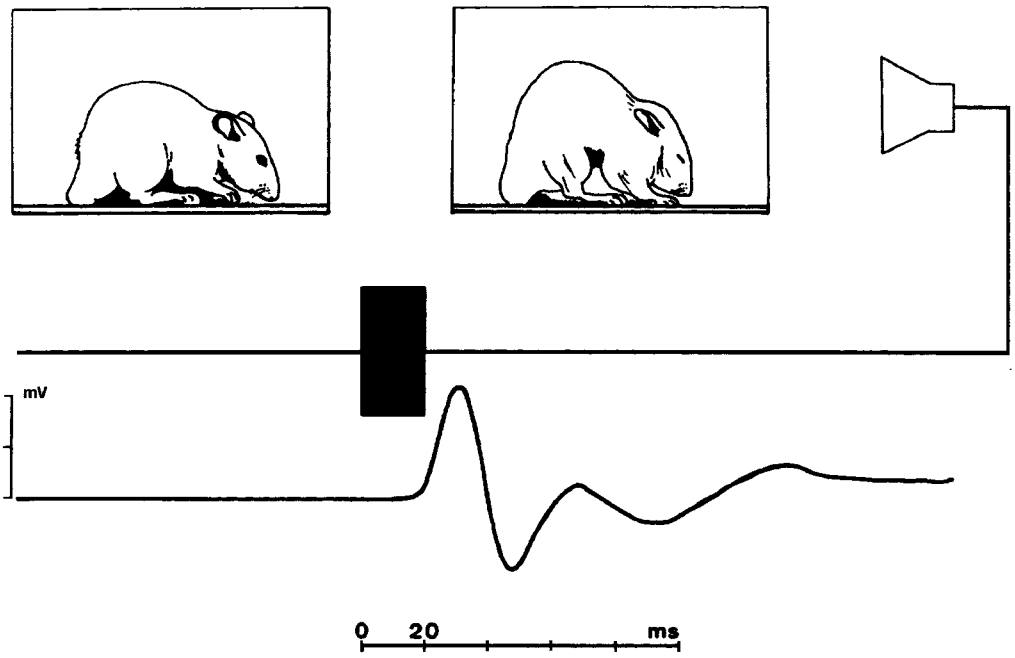


Fig. 1. The acoustic startle response in a rat *ca* 30 msec after stimulus onset. The pictures are redrawn from a film taken by Carsten Spiekermann (unpublished Diploma-thesis at the University of Tübingen) with a high-speed camera (150 frames $sec^{-1}$). The trace at the bottom of the figure shows the ballistogram of the whole-body ASR. The ASR is usually expressed as arbitrary units or in millivolts (mV) of the accelerometer output.

## 1. INTRODUCTION

Startle is a fast twitch of facial and body muscles evoked by a sudden and intense tactile, visual or acoustic stimulus. The startle pattern consists of eyelid-closure and a contraction of facial, neck and skeletal muscles (Fig. 1), as well as an arrest of ongoing behaviors and an acceleration of the heart rate. This response pattern is suggestive of a protective function of startle against injury from a predator or from a blow, and of the preparation of a flight/fight response. Startle can be elicited by acoustic, tactile and visual stimuli in a variety of animal species and in humans (Landis and Hunt, 1939). In addition, olfactory startle has been found in fish (Pfeiffer, 1962). Despite its relatively simple, reflex-like appearance, the startle response magnitude can be modulated by a variety of external and internal variables. That is to say, under appropriate experimental conditions, startle has a non-zero baseline and can be enhanced *and* attenuated. Therefore, it serves as a valuable behavioral tool to assess mechanisms of sensorimotor response plasticity. Figure 2 summarizes the most commonly investigated phenomena of startle plasticity. By far the greatest amount of data on the neurobiology of startle has been gathered on the acoustic startle response (ASR) of mammals, mostly of rats, mice, cats and of humans. The ASR can be elicited in rats and humans using identical stimulus parameters to generate equal response patterns. The results obtained in studies with animals have repeatedly been generalized to humans, which implies that research into the neuronal mechanisms underlying the ASR and its various forms of plasticity in rats may help to understand human sensorimotor integration. This article summarizes recent findings related to the neuronal and neurochemical mechanisms mediating and modulating the ASR.

The ASR becomes functional immediately after the onset of hearing, which is around postnatal day 12 in rats (Sheets *et al.*, 1988; Kungel *et al.*, 1996). The ASR magnitude and latency are influenced by the stimulus intensity (Pilz *et al.*, 1987, 1988), the interstimulus interval (Davis, 1970), ongoing motor behavior (Wecker and Ison, 1986; Plappert *et al.*, 1993), and is variable among individuals (Plappert *et al.*, 1993). It is also influenced by genetic differences (Glowa and Carl, 1994; Paylor and Crawley, 1997), by the diurnal rhythm (Davis and Sollberger, 1971; Chabot and Taylor, 1992), by the sensory environment [e.g. background noise: Hoffman and Fleshler (1963); illumination: Walker and Davis (1997b); prepulses: Reijmers and Peeters (1994); Hoffman and Ison (1980)] and by drugs (Davis, 1980). The ASR is also modulated by a variety of experimental changes in the perceptual or emotional state of the organism: the ASR magnitude can be enhanced by conditioned and unconditioned aversive events (Davis, 1996; Davis *et al.*, 1997). It can be attenuated by the repeated presentation of startling stimuli [habituation; Davis and File (1984)], by prior presentation of a prepulse [prepulse inhibition (PPI) and latency facilitation; Hoffman and Ison (1980)] or by positive affect (Lang *et al.*, 1990; Schmid *et al.*, 1995). The changes in magnitude of the ASR by systemical or intracerebral application of drugs have been widely used to assess the respect-

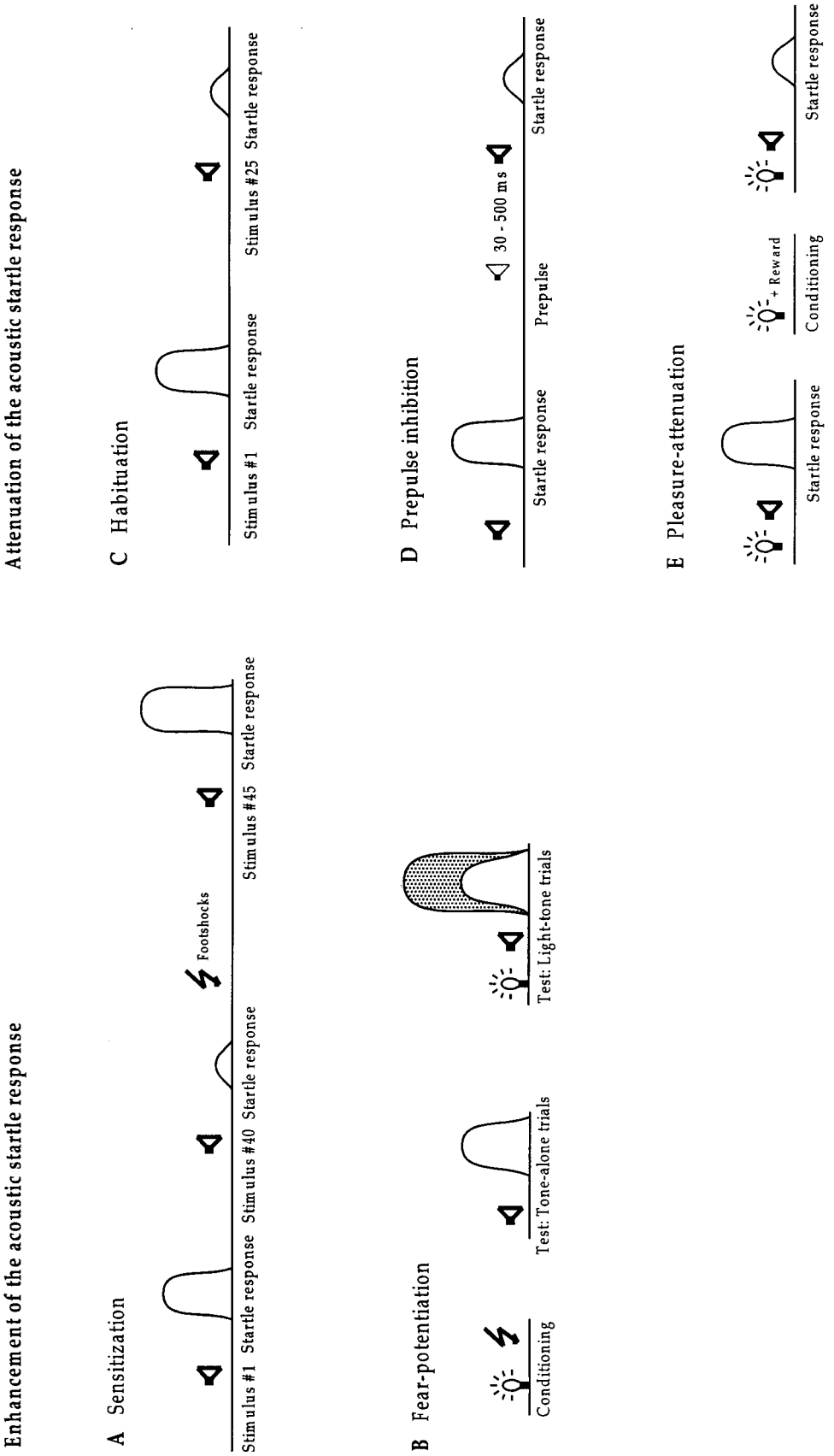


Fig. 2. Pictograms summarizing the most commonly investigated modulations of the ASR magnitude. The stippled area in B is a measure of fear.

ive drug effects on sensorimotor reactivity in animals and humans (Davis, 1980; Davis *et al*., 1993). Briefly, anxiogenic drugs, for example yohimbine (Morgan III *et al*., 1993; Fendt *et al*., 1994a), and drugs that reduce the inhibitory neurotransmission in the CNS, for example, the glycine receptor antagonist strychnine (Kehne and Davis, 1984; Koch and Friauf, 1995), enhance the ASR, whereas drugs that reduce overall excitability of the CNS, such as ethanol or diazepam attenuate the ASR (Berg and Davis, 1984; Grillon *et al*., 1994a). Most anxiolytic drugs reduce only the fear- or anxiety-enhanced ASR and have no effect on the baseline ASR magnitude (Davis *et al*., 1993; Hijzen *et al*., 1995; Walker and Davis, 1997a). These various forms of modulation of the ASR magnitude are probably due to an enhancement or an inhibition, respectively, of the information transfer between the sensory receptors and the motor effector systems and, hence, knowledge of the pathway that mediates the ASR is a necessary prerequisite for the understanding of the modulation of the ASR.

## 2. A HYPOTHETICAL NEURONAL CIRCUIT MEDIATING THE ASR

The ASR is elicited by acoustic stimuli with an intensity $>80$ dB sound pressure level (SPL) and a steep rise time (Davis, 1984; Pilz *et al*., 1987). The ASR has a short latency of *ca* 10 msec measured electromyographically in neck- or limb muscles (Caeser *et al*., 1989; Cassella *et al*., 1986) and is mediated by a pathway located in the ponto-medullary brainstem that has been extensively studied in rats [Davis *et al*. (1982a); Davis (1984); Frankland *et al*. (1995); Lee *et al*. (1996); Leitner *et al*. (1980); summarized in Yeomans and Frankland (1996); Koch and Schnitzler (1997)]. It has been speculated that the ASR of mammals is probably homologous to the flight response observed in fish that is mediated by a brainstem escape network including the Mauthner cells (Eaton *et al*., 1991; Pfeiffer, 1962). Based on the short latency of the ASR in rats it was assumed that the primary neuronal pathway is composed of a small number of neurons con-

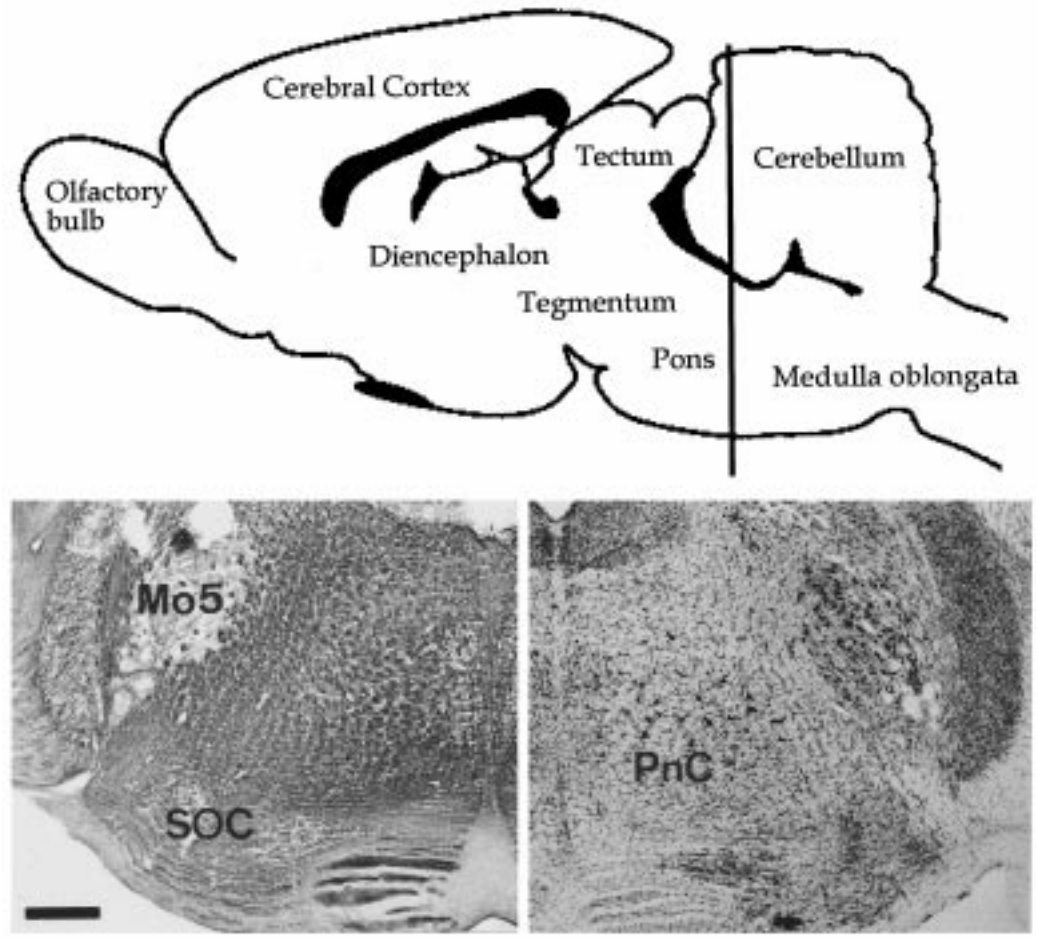


Fig. 3. Drawing of a parasagittal section through the rat brain showing the location of the caudal pontine reticular nucleus (PnC; vertical line). Bottom, photomicrographs of frontal sections through the PnC stained with gold chloride for myelin (left) and Nissl-stained with thionine (right). Note the cluster of giant neurons in the center of the PnC. Mo5, motor trigeminal nucleus; SOC, superior olivary complex. Bar = 500 $\mu$m.

nected serially by chemical synapses, and that this pathway is located near the primary auditory pathway. Consequently, all of the ASR circuits proposed so far include synaptic relays in the cochlear nuclear complex, in the nearby reticular formation and in cranial and spinal motorneurons [summarized in Yeomans and Frankland (1996)].

The first systematic study of a primary startle pathway of rats was published in 1982 by Davis and his colleagues (Davis *et al*., 1982a). On the basis of anatomical tracing experiments, electrical stimulation and electrolytic lesions, these authors suggested that the pathway mediating the ASR consists of the auditory nerve, the ventral cochlear nucleus, the dorsal nucleus of the lateral lemniscus, the caudal pontine reticular nucleus (PnC), spinal interneurons and spinal motor neurons (Davis *et al*., 1982a). A pivotal role of the PnC (Fig. 3) in the mediation of the ASR was confirmed by a series of other studies in cats (Wu *et al*., 1988), rats (Koch *et al*., 1992; Yeomans *et al*., 1993; Lingenhöhl and Friauf, 1994; Lee *et al*., 1996) and mice (Carlson and Willott, 1998). Detailed electrophysiological and neuroanatomical studies revealed that the subpopulation of giant (soma diameter $> 40\ \mu$m) reticulospinal neurons of the PnC receive direct acoustic input from different nuclei of the central auditory pathway, including the dorsal and ventral cochlear nucleus, the lateral superior olive and from neurons of the cochlear root nucleus, a ganglion located within the auditory nerve, (Kandler and Herbert, 1991; Lingenhöhl and Friauf, 1992, 1994; Lee *et al*., 1996). The auditory afferents mainly project to the contralateral PnC (Davis *et al*., 1982a; Frankland *et al*., 1995; Lingenhöhl and Friauf, 1992, 1994). Furthermore, the PnC is innervated by other parts of the pontine reticular formation which also receive auditory input, for example, the ventrolateral tegmental nucleus (Herbert *et al*., 1997; Yeomans and Frankland, 1996). However, a recent lesion study has excluded a crucial role of the ventrolateral tegmental nucleus for the ASR (Lee *et al*., 1996). PnC neurons project onto facial, cranial and spinal motor neurons (Lingenhöhl and Friauf, 1992, 1994) and can therefore be regarded as sensorimotor interfaces for the facial and somatic components of the ASR. While it has been claimed that for the ASR of the facial musculature (head startle) the gigantocellular nucleus of the medullary reticular formation appears to be more important than the PnC (Pellet, 1990), our data have shown that the blockade of glutamate receptors in the PnC reduce the startle-like electromyograms recorded from the musculus temporalis and musculus levator auris to a similar extent than the whole body ASR (Krase *et al*., 1993), suggesting that the head-startle is also mediated by the PnC.

In humans, a distinction is being made between the auditory blink reflex and the ASR measured in the musculus orbicularis oculi. The auditory blink reflex is mediated by a mesencephalic circuit, shows a short latency and habituates at a slow rate. In contrast, the ASR is usually recorded in the musculus orbicularis oculi, habituates rapidly, has a relatively long latency (ca 60 msec) and is evoked by a bulbopontine circuit including projections to the seventh cranial nerve (Brown *et al*., 1991a). In the human PnC, a few large neurons are found that project to the spinal cord and to cranial and facial motor nuclei (Martin *et al*., 1990). Hence, the anatomical substrate that corresponds to the cerebral structures that mediate and modulate the ASR in rats is present in the human brain as well.

A behavioral study in rats indicated that the ASR magnitude correlates significantly with the number of PnC giant neurons (Koch *et al*., 1992). Extracellular single unit recordings (Ebert and Koch, 1992) and intracellular recordings (Lingenhöhl and Friauf, 1992, 1994) from rat reticulospinal PnC giant neurons *in vivo* during acoustic stimulation revealed a high excitation threshold of *ca* 75 dB, a short mean excitatory postsynaptic potentials (EPSP) latency of *ca* 2.6 msec and a mean spike latency of 4.4 msec, which fits well with the short latency of the ASR. A recent study investigated the intrinsic membrane properties of PnC neurons after intracellular current pulse injections in a rat brain slice preparation. PnC giant neurons showed a relatively low membrane resistance and a long membrane time constant (Wagner and Mack, 1998), indicating a relatively low firing threshold and the capacity to temporally integrate various synaptic inputs. A low firing threshold after direct intracellular current injection and a high threshold of excitation of PnC neurons after acoustic stimulation suggests that the relatively high excitation threshold of the ASR is located at the sensory side of the ASR pathway, that is, *before* the PnC. It has also been shown that the acoustically evoked activity of PnC neurons can be modulated in the same way as the ASR in awake animals. An enhancement of the EPSP amplitude of giant PnC neurons was found after electrical stimulation of the amygdala and a reduction of the EPSP by a prepulse, or by increasing the rise time of the acoustic stimulus (Lingenhöhl and Friauf, 1994; Wu *et al*., 1988). Likewise, the spike activity of PnC neurons is enhanced after electrical stimulation of the amygdala (Koch and Ebert, 1993). In mice, a correspondence of the neuronal activity in the PnC with the behavioral characteristics of the ASR (dependency upon latency, threshold and PPI) was demonstrated (Carlson and Willott, 1998). While these studies strongly indicate that the PnC is the most important brainstem site for the evocation of the ASR, other brain nuclei than the PnC may also play a role as premotor relays that mediate the ASR [summarized in Yeomans and Frankland (1996)]. Thus, the possibility of different parallel pathways mediating different aspects of the ASR cannot be excluded.

Interestingly, the EPSPs recorded intracellularly from PnC neurons show multiple peaks ('shoulders') that occur at constant latencies, suggestive of excitatory input to the PnC with different latencies from multiple afferent systems (Lingenhöhl and Friauf, 1994). Consistent with this interpretation, tracing experiments revealed auditory input from the dorsal and ventral cochlear nucleus, lateral superior olive, cochlear root nucleus, and input from other nuclei of the reticular formation (Herbert *et al*., 1997; Kandler and Herbert, 1991; Koch *et al*., 1993; Lee *et al*., 1996; Lingenhöhl and Friauf, 1994). On the

basis of electrophysiological data, it was argued that neither the dorsal cochlear nucleus, nor the nuclei of the lateral lemniscus can be critically involved in the mediation of the fast components of the ASR [Lingenhöhl and Friauf (1994); see also Koch and Schnitzler (1997)]. The study by Lee and co-workers indicates that the ASR is mediated by a serial trisynaptic pathway comprising the cochlear root neurons, the PnC and motor neurons (Lee *et al*., 1996). However, since action potentials were recorded from PnC neurons at latencies of *ca* 5 msec (Ebert and Koch, 1992; Lingenhöhl and Friauf, 1994), and since the ASR latency is *ca* 10 msec for the whole body ASR, indirect pathways conveying excitatory auditory input to the PnC perhaps via reticular relay nuclei (Davis *et al*., 1982a; Frankland *et al*., 1995; Herbert *et al*., 1997; Yeomans and Frankland, 1996), as well as interneurons in the spinal cord (Kehne *et al*., 1986) are likely to mediate and modulate components of the ASR. Consistent with this, a recent lesion study has shown that the dorsal cochlear nucleus contributes to the ASR elicited by high intensity (=110 dB) stimuli (Meloni and Davis, 1998). Presently, the model of a primary ASR circuit where the PnC is the most important sensorimotor interface, receiving auditory evoked excitatory input at different latencies from various brainstem nuclei is probably the most widely accepted one (Fig. 4). In this model the input from the cochlear root nucleus to the PnC has the shortest latency and excites PnC giant neurons very fast, leading to a depolarization of the neurons close to firing threshold, preparing them for the subsequent excitatory synaptic inputs arriving from other auditory and reticular nuclei.

However, it is still not clear which subregion of the PnC mediates the ASR. While initially a prominent role for giant PnC neurons was generally agreed upon (Koch *et al*., 1992; Lingenhöhl and Friauf, 1994; Yeomans and Frankland, 1996), the study by Lee *et al*. (1996) showed that excitotoxic lesions of the ventrolateral PnC abolished the ASR, although in that region only few giant neurons are normally found [Fig. 3 here and Fig. 5 in Lee *et al*. (1996)]. Recent lesion experiments in our laboratory have partially confirmed these findings, but have also shown that the lateral superior olive, which projects to the PnC giant neurons, is also important for the ASR (T. Wagner and M. Fendt, unpublished observations). Therefore, it cannot be excluded that ventrolateral PnC lesions attenuated the ASR so effectively because they also compromised the functioning of the lateral superior olive. Moreover, there are still no lesion data available that show that lesions restricted to the medial part of the PnC do *not* abolish the ASR. Clearly, a systematic lesion study is required to settle the issue of the roles of different subregions of the PnC in the mediation of the ASR.

Neuropharmacological studies have shown that glutamate is probably the excitatory transmitter of auditory input to PnC neurons. The fast ionotropic receptors of the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-subtype are more important for the excitatory action of glutamate on PnC neurons (Ebert and Koch, 1992), although *N*-methyl-D-apartate (NMDA) receptors in the PnC do also contribute to the evocation of the ASR (Krase *et al*., 1993; Miserendino and Davis, 1993). Acoustically evoked action potentials of PnC neurons are blocked by iontophoretic application of the inhibitory transmitter γ-amino-butyric acid [GABA (Kungel *et al*., 1994)] and the ASR can be enhanced by blockade of GABA receptors in the PnC, which indicates that GABA exerts an inhibitory effect on the ASR (Birnbaum *et al*., 1997). Since stimulation of the inhibitory glycine receptors with β-alanine, or blockade of glycine receptors with strychnine in the PnC did not affect the ASR magnitude or habituation, it can be concluded that glycine at the level of the PnC does not play an inhibitory role on the ASR (Koch and Friauf, 1995), although at the spinal motor neuron level this transmitter is very important for the ASR (Kehne *et al*., 1981; Kehne and Davis, 1984; Koch *et al*., 1996a).

## 3. ENHANCEMENT OF THE ASR

Because startle can be regarded as a protective response, it is intuitively expected that the ASR should be enhanced in threatening situations or following an aversive event. In fact, the ASR of rats has consistently found to be enhanced in the presence of a cue predicting an aversive event [fear-potentiated startle, see e.g. Davis *et al*. (1993)], as well as during presentation of loud noise (Davis,

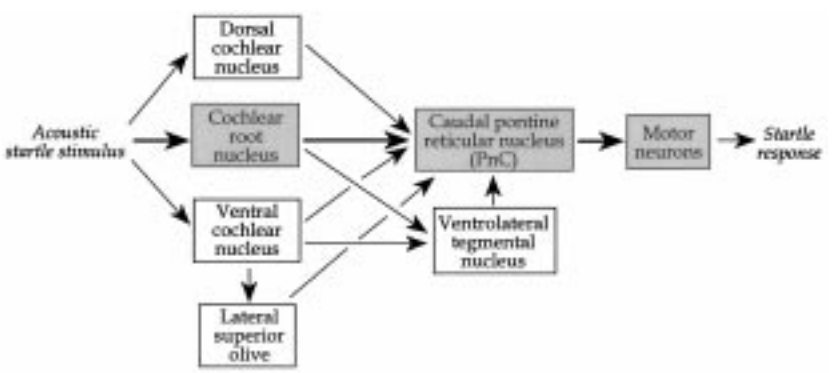


Fig. 4. A hypothetical primary ASR pathway. The bold arrows and the lightly shaded boxes symbolize the probably fastest route of transmission of acoustic input into the motor output.

1974; Gerrard and Ison, 1990; Schanbacher *et al*., 1996), or bright illumination (Walker and Davis, 1997b), and after electric footshock (Davis, 1989). The ASR is also enhanced after lesions of the septum (Decker *et al*., 1995; Melia and Davis, 1991; Melia *et al*., 1991), by olfactory bulbectomy (McNish and Davis, 1997), as well as by stimulation of the amygdala (Koch, 1993; Koch and Ebert, 1993; Rosen and Davis, 1988; Yeomans and Pollard, 1993) or the ventral tegmental area (VTA) and the lateral periaqueductal gray (Borowski and Kokkinidis, 1996). Furthermore, systemic or intracerebral application of a variety of drugs can increase the ASR magnitude (Davis, 1980). It is not always easy to tell, however, whether a drug-induced enhancement of the ASR is related to the induction by the drug of an aversive emotional state [e.g. by an increase of anxiety, Grillon *et al*. (1994a); Morgan III *et al*. (1993)] or simply due to a reduction of synaptic inhibition within the primary reflex pathway, for example, by blockade (Kehne *et al*., 1981; Kehne and Davis, 1984; Koch and Friauf, 1995) or mutation of the inhibitory glycine receptors on motor neurons (Brown *et al*., 1991b; Koch *et al*., 1996a), or by the blockade of the GABAergic neurotransmission in the PnC (Birnbaum *et al*., 1997).

The ASR is also enhanced in human patients suffering from anxiety disorders (Grillon *et al*., 1994b, 1996), in humans anticipating shock (Grillon *et al*., 1991), in the presence of an unpleasant odor (Ehrlichman *et al*., 1995), or while viewing aversive pictures (Lang *et al*., 1990; Patrick *et al*., 1996). As a matter of fact, an enhanced startle response is one of the diagnostic criteria for post-traumatic stress disorder (*Diagnostic and Statistical Manual IV of Mental Disorders*, American Psychiatric Association). Although the neuronal basis of the different forms of enhancement of the ASR were investigated mainly in rats, it can be assumed that similar brain mechanisms contribute to pathological anxiety in humans and to fear-conditioning in animals (Lang, 1995). While a distinction can be made between conditioned (fear) and unconditioned (anxiety) forms of ASR enhancement, it should be noticed that anxiety disorders such as post-traumatic stress disorder usually are caused by an explicit traumatic experience that resembles fear-conditioning. In fact, there is a considerable overlap between the brain structures that mediate the conditioned and unconditioned forms of aversive information processing. However, these different phenomena of enhancement of the ASR (see below) also offer the possibility for a distinction between different brain mechanisms of aversive information processing.

### 3.1. Sensitization

Sensitization is the enhancement of a response following a strong stimulus that is probably mediated by heterosynaptic facilitation (Kandel, 1976). The ASR-sensitizing effects of 0.6–1 mA electric footshocks peak after *ca* 10 min and last *ca* 30–40 min [Davis (1989); Fig. 2(A)Fig. 5]. Most ASR sensitization studies are based on a dishabituation design,

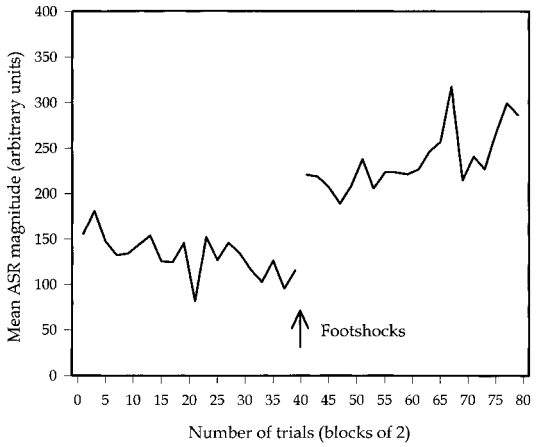


Fig. 5. Sensitization of the ASR by electric footshocks (0.6 mA) presented at trigger No. 40 [data are from 11 rats adapted from Schanbacher *et al*. (1996)]. Note that footshocks enhance the ASR to a magnitude that is above the initial ASR magnitude before habituation.

because the pre-shock ASR magnitude after repeated presentation of startling stimuli is already habituated and is then compared with the ASR after shocks [Fig. 2(A)]. In the first systematic study of sensitization of the ASR by electric footshocks, Davis has shown that dishabituation does in fact contribute to the enhancement of the ASR by aversive events (Davis, 1989). However, since usually the aversive shock increases the ASR magnitude above the initial level (i.e. before habituation, see e.g. Figure 5) the term sensitization should be used for this enhancement of the ASR. Sensitization has been considered as a non-associative form of learning, because the organism does not associate a particular event with the strong or noxious sensitizing stimulus. However, there might be associative elements in this form of learning, such as rapid conditioning to background cues (Pilz, 1996). In order to minimize background cue conditioning, Davis designed an experiment where footshocks and ASR tests were conducted either under different lighting conditions or under constant lighting conditions and found that the rats of both groups showed equally strong ASR potentiation after the footshocks. From these results he concluded that background-conditioning does not contribute substantially to the enhancement of the ASR by footshocks (Davis, 1989). A recent paper has shown that shock sensitization of the ASR is mediated by context conditioning (Richardson and Elsayed, 1998).

Lesion and drug infusion experiments revealed that the amygdala is important for the sensitizing effects of electric footshocks (Fendt *et al*., 1994a; Hitchcock *et al*., 1989; Sananes and Davis, 1992; Schanbacher *et al*., 1996). It should be noted that the startling stimuli themselves are aversive and may induce a state of fear or anxiety (Borszcz *et al*., 1989; Leaton and Cranney, 1990), and field potentials specifically related to the ASR were recorded in the basolateral amygdala (Ebert and Koch, 1997), suggesting that the aversive character of the startling stimulus is due to activation of the amygdala.

Sensitization of the ASR by footshocks influences the primary startle circuit at the level of the PnC (Boulis and Davis, 1989; Davis *et al*., 1982b) probably by a direct projection from the medial part of the central amygdaloid nucleus descending via the caudal division of the ventral amygdalofugal pathway to the PnC (Hitchcock *et al*., 1989; Koch and Ebert, 1993; Rosen *et al*., 1991). However, there are also relay nuclei interposed between the central amygdala and the PnC that contribute to sensitization, such as the periaqueductal gray (Fendt *et al*., 1994b), the laterodorsal tegmental nucleus (Hitchcock *et al*., 1989; Hitchcock and Davis, 1991; Krase *et al*., 1994; Kungel *et al*., 1994), and the deep mesencephalic nuclei (Frankland and Yeomans, 1995). Although a prominent role in the enhancement of the ASR of these PnC afferents is already clear, we do not yet know if the ASR-sensitizing effects of these projections are mediated by a presynaptic facilitation of the auditory afferents or by a postsynaptic excitation of the PnC neurons. Although direct connections between this part of the primary ASR pathway and state-regulating systems such as the amygdala and the periaqueductal gray are well described, it is important to keep in mind that not all of the ASR modifications need to be mediated by a specific interaction with the PnC. An enhancement of the ASR by aversive events could also be mediated by the release of stress hormones or by neurotransmitters that may not directly affect the PnC, but rather facilitate neuronal transmission on the sensory or motor side of the ASR pathway.

It has to be noted that the behavioral background of sensitization is different from that of conditioned fear: while sensitization reflects an immediate response to an actual aversive stimulus or to danger, the conditioned aversive stimulus *predicts* the occurrence of an aversive or threatening event. Consistent with this, the enhancement of the ASR by electric footshocks, or by bright illumination, or by some neuropeptide agonists outlasts the duration of an aversive stimulus, whereas in fear-potentiation, the ASR is only momentarily enhanced in the presence of the aversive conditioned stimulus (CS), suggesting that there are probably different neuronal or neurochemical factors involved in these two phenomena of ASR potentiation. The differentiation between phasic and tonic forms of adverse emotions is important for psychopharmacologist who attempt to develop drugs that ameliorate anxiety but do not dampen the protective responses to dangerous situations. While lesion studies showed that there is a considerable overlap of the structures mediating phasic and tonic forms of ASR-potentiation, recent data suggest that there are important distinctions to be made between the mechanisms underlying sensitization, enhancement by stress and fear-potentiation of the ASR. A long-lasting enhancement of the ASR has been shown by infusions of corticotropin-releasing hormone (CRH) into the lateral ventricle (Swerdlow *et al*., 1989; Liang *et al*., 1992; Lee *et al*., 1994) into the PnC (Birnbaum and Davis, 1998), or after infusion of cholecystokinin [CCK; Fendt *et al*. (1995)] or substance P [SP (Krase *et al*., 1994)] into the PnC or into the amygdala (Frankland *et al*., 1997), indicating that these peptides are involved in sensitization. Sensitization of the ASR by footshocks can also be blocked by the injection of SP antagonists into the PnC (Krase *et al*., 1994), or by infusion of the $\alpha_2$-adrenergic agonist ST-91 (a clonidine analogue) into the amygdala (Fendt *et al*., 1994a).

While initially no explicit distinction was made between fear and anxiety in the fear-potentiated startle paradigm (Davis, 1986), it became clear in recent years that the fear-potentiated ASR clearly reflects a rapid conditioned response to the fear-provoking stimulus, and does therefore not provide an ideal model for the tonic states of anxiety in humans. Anxiety is not related to a certain stimulus but is characterized by a more general state of discomfort and apprehension. On the basis of this distinction, Davis and colleagues have recently attempted to distinguish between the neuronal mechanisms of fear and anxiety using different forms of enhancement of the ASR (Davis *et al*., 1997; Lee and Davis, 1997a,b; Walker and Davis, 1997a). Recent experiments in rats revealed that the enhancement of the ASR by bright illumination or by the intracerebroventricular infusion of CRH is mediated by pathways that partially differ from those mediating footshock-induced sensitization or fear-potentiation of the ASR (Fig. 7). The bed nucleus of the stria terminalis obviously plays an important role in the ASR-enhancing effects of stress and anxiety and is probably of minor relevance for fear-potentiation of the ASR. The hippocampus is also involved in the enhancement of the ASR by CRH, but not in fear-potentiation of the ASR. Amygdaloid nuclei are necessary for both fear-potentiation and sensitization of the ASR, as well as in the potentiation of the ASR by bright illumination, but are not involved in the enhancement of the ASR by CRH. It is not yet known by which cerebral route stress ultimately potentiates the ASR. Since the bed nucleus of the stria terminalis projects to the PnC, it is conceivable that at least a part of the impact of stressors on the ASR are mediated by a direct projection from the bed nucleus of the stria terminalis to the PnC, although an indirect route from the bed nucleus of the stria terminalis to the PnC via the amygdala is also possible (Davis, 1996; Davis *et al*., 1997; Lee and Davis, 1997b; Walker and Davis, 1997a).

### 3.2. Fear-Conditioning

The fear-potentiated startle paradigm was introduced in 1951 (Brown *et al*., 1951), and was thoroughly investigated later by Davis and his associates (Davis *et al*., 1993). In this model, the animals are trained to associate a neutral stimulus, for example, a light or a tone, with an aversive stimulus, such as a mild electric footshock. After a few pairings, the CS induces a state of fear as measured, among other variables, by a potentiation of the ASR. It is important to note that the state of fear, not the potentiation of the ASR is the conditioned response to the CS [Fig. 2(B)Fig. 6]. Notably, the presentation of the CS also elicits a variety of other adverse reactions, such as freezing, blood pressure elevation, bradycardia (Davis, 1992; Le Doux,

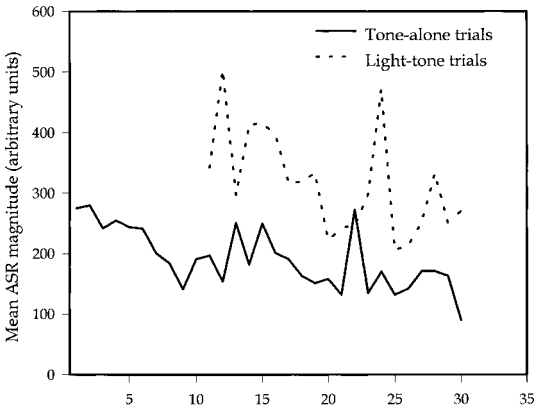


Fig. 6. Fear-potentiation of the ASR. The stippled line reflects the ASR magnitude of light-tone trials after fear conditinioning to a light stimulus. Note that the figure depicts a pseudo time-course, because during the tests the tone-alone and light-tone trials are presented in a randomized order (unpublished data from 16 rats; courtesy of Dr Markus Fendt).

1996). The usually applied Pavlovian conditioning procedure involves one or two training sessions including 10–20 pairings of a 3.7 sec light with a 0.5 sec electric footshock of moderate intensity (0.6 mA) presented 3.2 sec after the light onset. Tests of fear-conditioning are normally performed 4–24 hr after conditioning. Acoustic startle stimuli are presented during the presentation of the CS (light-tone trials) or in the absence of the light (tone-alone trials) and the differences in ASR magnitude between tone-alone and light-tone trials provide the operational measure for fear (Fig. 6). It has to be noted, however, that rats show remarkably low levels of fear-potentiation of the ASR when they were trained with high levels (e.g. 1.6 mA) of electric shocks. A possible explanation for the non-monotonic relationship between fear-conditioning and shock intensity might be that intense footshocks trigger an active rather than a passive defense mode that reduces fear-potentiation of the ASR (Walker and Davis, 1997c; Walker *et al*., 1997). Fear-potentiation of the ASR is specific to the stimulus modality used for the acquisition of fear and does not generalize to stimuli of other modalities (Falls and Davis, 1994). Fear-potentiation of the ASR shows a remarkable temporal specificity, that is, the ASR is maximally potentiated if the startling noise pulse is presented at exactly that time after light onset at which the shock was given during conditioning. This observation was interpreted as being indicative of anticipatory fear (Davis *et al*., 1993). Fear-potentiated ASR is a cross-species phenomenon that is also observed in humans (Grillon and Davis, 1997). This is important, because the verbal report of a state of fear in humans that accompanies the potentiation of the ASR, and the other physiological markers of this aversive state corroborate the idea that the physiological signs of fear in experimental animals and in humans reflect the operation of analogous processes across species. The assumption that the aversive CS evokes a state of fear in rats and humans is further buttressed by the finding that fear-potentiation of the ASR can be reduced or blocked by a variety of anxiolytic drugs (Davis, 1979; Davis *et al*., 1993; Hijzen *et al*., 1995; Josselyn *et al*., 1995; Patrick *et al*., 1996).

The neuronal basis of the fear-potentiated ASR has been investigated by various groups and these investigations have yielded a relatively complete picture of the circuits through which fear enhances the ASR (Fig. 7). The amygdaloid complex plays an important role in the acquisition and the expression of conditioned fear. Lesions of the central, or the basolateral nucleus of the amygdala block the occurrence of fear in the fear-potentiated startle paradigm (Davis *et al*., 1993). The association between neutral and aversive stimuli occurs in the lateral/basolateral nuclei of the amygdala (Campeau and Davis, 1995a; McKernan and Shinnick-Gallagher, 1997; Miserendino *et al*., 1990; Rogan *et al*., 1997) where inputs from cortical and thalamic sensory regions converge with inputs from nociceptive brain nuclei such as the parabrachial nuclear complex and the posterior intralaminar thalamic nuclei (Davis *et al*., 1994, Shi and Davis, 1999). The perirhinal cortex conveys the visual or auditory CS to the amygdala (Campeau and Davis, 1995a; Rosen *et al*., 1992). Microinjections of the NMDA-antagonist DL-2-amino-5-phosphonopentanoic acid (AP-5) into the basolateral amygdala also prevent the acquisition of fear in this paradigm, indicating that an NMDA-receptor mediated process in the amygdala is involved in the association between the neutral stimulus and the aversive event (Campeau *et al*., 1992; Gewirtz and Davis, 1997; Miserendino *et al*., 1990). Amygdaloid noradrenaline is obviously not involved in the acquisition of fear in this paradigm (Miserendino *et al*., 1990) in contrast to other phenomena of the acquisition of aversive memory (McGaugh, 1989), and in contrast to sensitization of the ASR by footshocks (Fendt *et al*., 1994a). The association between the unconditioned stimulus (US) and the CS probably changes the properties of intraamygdaloid circuits (Campeau and Davis, 1995a; McKernan and Shinnick-Gallagher, 1997; Rogan *et al*., 1997), so that the presence of the CS after training enhances the neuronal activity of the central amygdaloid nucleus which, in turn, increases the excitability of PnC neurons and leads to an enhanced ASR. Electrically evoked startle is potentiated by a light predicting shock when the startle response is elicited upstream from the PnC, suggesting that the ASR circuit receives its input from the fear circuit at the level of the PnC (Davis *et al*., 1993). The transmitter of this direct amygdaloreticular output pathway could be glutamate and/or CRH, since local injections of AP-5 (Fendt *et al*., 1996a) or α-helical CRH, the specific antagonist of CRH (Fendt *et al*., 1997) into the PnC prevent fear-potentiation of the ASR. The expression of conditioned fear was also blocked by injection into the amygdala of the glutamate receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) (Kim *et al*., 1993), indicating that the intraamygdaloid projections that are activated by the CS use glutamate acting at the AMPA/kainate receptor to convey their information onto the amygdaloid output neurons. Interestingly, the dopaminergic projection

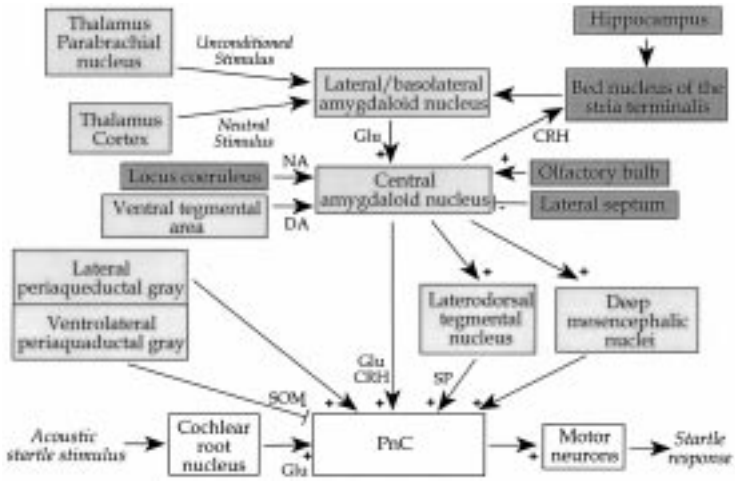


Fig. 7. A hypothetical circuit mediating fear-potentiation and sensitization of the ASR, as well as the enhancement of the ASR by stress. The lightly shaded boxes symbolize brain areas involved in fear-potentiation *and* sensitization. The darkly shaded boxes symbolize brain areas that are only involved in sensitization or stress-induced enhancement of the ASR. CCK, Cholecystokinin; CRH, corticotropin-releasing hormone; DA, dopamine; Glu, glutamate; NA, noradrenaline; SOM, somatostatin; SP, substance P; +, excitatory; −, inhibitory transmitter action.

from the VTA to the amygdala is also involved in the expression of fear-potentiation of the ASR (Borowski and Kokkinidis, 1996; Lamont and Kokkinidis, 1998). Normally, fear-conditioning to the experimental context also occurs and it has been shown that, in contrast to other fear-conditioning paradigms, the effect of contextual fear on the ASR is obviously not mediated by the hippocampus (McNish *et al*., 1997). Interestingly, fear-potentiation of the ASR can be reacquired after destruction of the amygdala by extensive training (Kim and Davis, 1993) if the lesions were inflicted to the rats after an initial fear-conditioning. However, it is presently unknown which brain structure is responsible for reacquisition of fear in this paradigm. In any event, it is clear from these findings that while the amygdala is crucial for the acquisition and expression of fear, other brain areas may take over some of the functions of the amygdala.

Recent studies indicate that synaptic relays are interposed between the amygdala and the PnC which are also important for fear-potentiation of the ASR and for the enhancement of the ASR by footshocks. The deep mesencephalic nuclei are the target of fibers of the caudal ventral amygdalofugal pathway transmitting the startle-enhancing effects of the amygdala onto the PnC, to medullary brainstem structures or maybe directly to the spinal cord (Frankland and Yeomans, 1995; Yeomans and Pollard, 1993). In addition, the midbrain periaqueductal gray also plays an important role for the sensitization of the ASR by footshocks (Fendt *et al*., 1994b), as well as for the expression (Fendt *et al*., 1996b; Fendt, 1998) and for the suppression (Fendt *et al*., 1996c; Fendt, 1998; Walker *et al*., 1997) of fear-potentiated ASR. The dorsolateral and the ventrolateral parts of the periaqueductal gray play opposite roles in the regulation of fear [summarized in Fendt and Fanselow (1999); Walker and Davis (1997c)]. The laterodorsal tegmental nucleus also projects to the PnC (Koch *et al*., 1993) and plays a role for fear-potentiated ASR (Hitchcock and Davis, 1991). Taken together, the amygdala probably serves as a command center for the enhancement of the ASR and influences the ASR via multiple descending parallel and serial chains of nuclei including the periaqueductal gray, the laterodorsal tegmental nucleus and the deep mesencephalic nuclei (Fig. 7). Each of these relay nuclei is connected to different somatosensory and autonomic brain centers. The input from this complex set of brain nuclei to the PnC determines the degree of enhancement of the ASR. The involvement of different output systems of the amygdala provides the substrate for a fine-tuning of the life-protecting responses to stimuli which signify danger, depending upon the specific constellation of internal and external conditions of a given situation.

### 3.3. Inhibition of Fear-Potentiated Startle

Fear-potentiation of the ASR can be reduced by most of those experimental manipulations that commonly affect Pavlovian conditioning, such as extinction, conditioned inhibition and latent inhibition. These phenomena of suppression of fear in rats are not only of theoretical interest, but may also expand our knowledge about the mechanisms that control fear in humans, and this knowledge might help to develop strategies for the suppression of pathological fear in humans.

An extinction training involves the repeated non-reinforced presentation of the CS after fear-conditioning and leads to a reduction of fear-potentiated ASR. Extinction must not be confused with forgetting, and obviously involves an overlearning process that requires an NMDA receptor-dependent process in the amygdala (Falls *et al*., 1992).

Latent inhibition is a phenomenon of retarded conditioning after non-reinforced presentation of the prospective CS before training. Latent inhibition has been measured in a variety of Pavlovian and

instrumental conditioning paradigms (Lubow, 1997). We have recently demonstrated latent inhibition of the fear-potentiated ASR in rats. Preexposition of rats to a light stimulus retards the subsequent conditioning to that stimulus by pairing the light with footshocks. Preexposed rats show significantly less fear-potentiation of the ASR than non-preexposed rats (Schauz and Koch, 1998, 1999). The mechanisms underlying latent inhibition of fear-potentiation of the ASR are presently under investigation. The deficit in the CS–US association could be due to inattention during conditioning caused by the repeated non-reinforced preexposure to the CS. Alternatively, latent inhibition could be due to the failure to acquire, or express the conditioned response due to an interference of conflicting CS-representations (CS relevant vs CS irrelevant) during training or during the behavioral test. Latent inhibition of various conditioned emotional response is regulated by a network of forebrain nuclei including the nucleus accumbens and the entorhinal cortex (Weiner and Feldon, 1997), but it is presently unclear if these circuits also affect latent inhibition of the fear-potentiated ASR. Our data indicate that the nucleus basalis magnocellularis, which provides the cholinergic input to the cortex and the amygdala, and which is important for attentional and mnemonic processes, is not necessary for latent inhibition of fear-conditioning (Schauz and Koch, 1999).

Fear-potentiation of the ASR can also be reduced by a conditioned inhibitor, that is, by a stimulus that has been associated with the absence of the aversive event during fear-conditioning (Falls and Davis, 1997). In this model of conditioned inhibition of fear the rats were trained with a stimulus which predicts an electric footshock (e.g. light → shock) and with a compound stimulus that predicts the absence of the shock (e.g. noise + light → no shock). After training the rats showed a potentiated ASR in the presence of the light, but no fear-potentiation when the light was preceded by the noise as conditioned inhibitor (Falls and Davis, 1995). The investigation into the neuronal mechanisms underlying conditioned inhibition of fear is particularly interesting, because this might help to develop potential therapeutic strategies to amend pathological fear in humans. However, the brain regions that mediate conditioned inhibition of fear in the potentiated ASR paradigm are still largely unknown. Obviously, neither the amygdala (Falls and Davis, 1995), nor the prefrontal (Gewirtz *et al*., 1997) or the perirhinal (Falls *et al*., 1997) cortex are necessary for the fear-reducing effect of a conditioned inhibitor. An extensive study using the induction by the conditioned inhibitory stimulus of the immediate-early gene *c-fos* revealed a change in neuronal activity of a variety of brain structures. The structures where *c-Fos* expression was most reliably associated with the presence of the conditioned inhibitor were the bed nucleus of the stria terminalis, the septohypothalamic nucleus, the locus coeruleus, as well as the laterodorsal and pedunculopontine tegmental nucleus (PPTg) (Campeau *et al*., 1997). Since recent lesion studies revealed that the septohypothalamic nucleus and the red nucleus are not involved in conditioned inhibition of fear (M. Fendt and M. Davis, unpublished data), further experiments are now necessary to scrutinize the role of the locus coeruleus, the laterodorsal and pedunculopontine tegmental nuclei, and the bed nucleus of the stria terminalis in conditioned inhibition. A recent brain stimulation study by Fendt has shown that different parts of the periaqueductal gray are involved in conditioned and unconditioned inhibition of fear (Fendt, 1998).

## 4. ATTENUATION OF THE ASR

### 4.1. Habituation

Habituation is a theoretical construct referring to the reduction in magnitude of the ASR after repeated presentation of the startling stimulus that is not due to muscle fatigue or blunting of sensory receptor responsiveness (Davis and File, 1984; Christoffersen, 1997). Within-session, or short-term habituation, that is, the decline of the ASR magnitude following repeated presentation of startling stimuli within a single test session [Fig. 2(C)Fig. 8] is distinguished from between-session habituation, or long-term habituation (i.e. the reduction of the ASR magnitude of the first trial amplitude across several test sessions). Habituation is regarded as a form of non-associative learning, which means that the response decrement solely depends upon the US presentation. The term non-associative refers to the fact that the response eliciting stimulus itself fails to predict any biologically important event and, hence, is no longer behaviorally relevant. Short-term habituation of the ASR is probably due to a deficit in central nervous gating mechanisms that normally function to dampen unnecessary responding to innocuous stimuli (Davis and File, 1984; Geyer *et al*., 1990). Probably the most influential theory of habituation is the *dual-process theory* (Groves and Thompson, 1970), which postulates the existence of two independent and opposing mechanisms in the central nervous system (habituation and sensitization) the net result of which is measured as the decline of the response magnitude across the different trials. Consonant with this theory, it is assumed


Fig. 8. Short-term (within-session) habituation of the ASR (unpublished data from 10 rats).

that each startling stimulus has both sensitizing and habituating properties (Borszcz *et al*., 1989; Leaton and Cranney, 1990; Ornitz and Guthrie, 1989) and that the time course of an ASR test session (e.g. Figure 8) reflects the net result of a central nervous computation of these two interfering processes.

The neuronal mechanisms underlying short-term habituation are still unclear. As habituation occurs without increasing the threshold of the ASR, it has been assumed that short-term habituation occurs downstream from the site determining the threshold of the ASR, probably at the connection between neurons of the cochlear nuclei with the PnC neurons (Pilz and Schnitzler, 1996). The repeated activation of these synapses of the primary ASR pathway might lead to synaptic depression, either by attenuating presynaptic transmitter release or by lowering the sensitivity of postsynaptic receptors. These processes of within-session reduction of the ASR magnitude are referred to as 'intrinsic' mechanisms, because they act within the stimulus–response pathway. Alternatively, the activation of inhibitory projections from brain sites outside the ASR pathway could also attenuate the sensorimotor information transfer within the primary ASR circuit, which would represent a form of 'extrinsic' modulation. Because decerebrated rats (bearing knife cuts at the level of the midbrain colliculus inferior) still showed short-term habituation of the ASR, it was suggested that short-term habituation occurs within the ASR pathway itself and not via inhibitory extrinsic brain sites (Fox, 1979; Leaton *et al*., 1985). Yet, these decerebration experiments only proof that brain structures situated rostral from the stimulus–response pathway do not mediate short-term habituation, but they do not rule out the possibility that inhibitory neurotransmitters released by interneurons that are located within the stimulus–response pathway at the same segmental level of the brain as the primary ASR circuit reduce synaptic transmission and lead to habituation. However, since the inhibitory transmitters glycine and GABA do not affect short-term habituation (Birnbaum *et al*., 1997; Kehne *et al*., 1981; Kehne and Davis, 1984; Koch and Friauf, 1995) other inhibitory transmitters have to be tested in behavioral experiments, in order to clarify if an extrinsic inhibitory mechanism accounts for short-term habituation. Another possible mechanism underlying habituation would be the inhibition of release from the auditory PnC afferents of the excitatory transmitter glutamate through the activation of inhibitory presynaptic autoreceptors (probably metabotropic glutamate receptors). Serotonin receptors are important for short-term habituation of tactile startle (Geyer and Tapson, 1988), but it is still unclear where this transmitter interacts with the pathway mediating tactile startle.

Long-term habituation is probably due to the fact that the US (and the experimental context) do not predict a biologically significant event (Leaton, 1974; Marlin and Miller, 1981). The neuronal substrates involved in long-term habituation of the ASR include the mesencephalic reticular formation (Jordan, 1989; Jordan and Leaton, 1983), the medial cerebellum (Leaton and Supple, 1986, 1991; Lopiano *et al*., 1990), the ventral periaqueductal gray (Borszcz *et al*., 1989) and different cortical areas (Groves *et al*., 1974), indicating an extrinsic mechanism of ASR suppression. Some of these brain sites have direct projections to the PnC (Koch *et al*., 1993; Fendt *et al*., 1994b; Rosen *et al*., 1991), but it is still not known at which site of the primary ASR pathway the ASR is inhibited in the course of long-term habituation.

### 4.2. Prepulse Inhibition

The ASR magnitude is reduced if a distinctive non-startling tactile (Pickney, 1976), visual (Campeau and Davis, 1995b) or acoustic (Hoffman and Ison, 1980) stimulus is presented 30–500 msec before the startling stimulus [Fig. 2(D)]. This phenomenon is termed PPI and is used as an operational measure for sensorimotor gating mechanisms (Hoffman and Ison, 1980). The limitation of sensory information processing pathways of the brain to cope with the surplus of sensory input bound to gain access to cognitive centers or motor output pathways necessitates mechanisms that restrict the access of behaviorally irrelevant stimuli to the effector pathways. The startling stimulus could interfere with prepulse processing either by backward masking, or the motor events associated with the ASR could disrupt prepulse processing. The mechanism of inhibition of contemporaneous sensory or motor events that would interfere with the ongoing processing of the prepulse, reflects a fundamental principle of the neuronal control of behavior which is necessary for stimulus recognition and for the sequential organization of behavior (Norris and Blumenthal, 1996). PPI already occurs on the first prepulse-pulse trial (Fig. 9), indicating that PPI does not require learning. Interestingly, the reduction of the ASR magnitude by a prepulse is usually accompanied by a reduction in the peak latency of the ASR (Hoffman and Ison, 1980; Swerdlow *et al*., 1992a). The neuronal mechanisms underlying latency re-

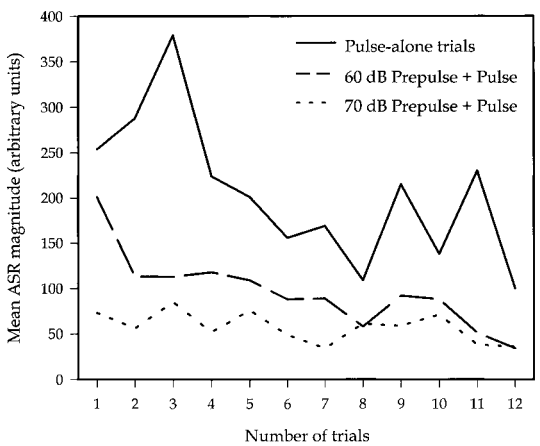


Fig. 9. Prepulse inhibition of the ASR with prepulses of two different intensities. The figure depicts a pseudo time-course, because during the tests the pulse-alone and the different prepulse-pulse trials are presented in a randomized order [data are from eight rats, adapted from Koch (1998)].

duction are still unknown but pharmacological treatments that affect PPI but not latency reduction suggest that these phenomena are independent (Swerdlow *et al*., 1992a). Repeated prior exposure to prepulses does not reduce the ability of subsequent prepulses to inhibit the ASR (Wu *et al*., 1984; Blumenthal, 1997). PPI is increased with increasing prepulse intensity and is maximal at prepulse durations of 10–20 msec (Reijmers and Peeters, 1994; see also Fig. 9). Although PPI shows a high test–retest reliability in humans (Schwarzkopf *et al*., 1993b), PPI in rats has been shown to habituate (i.e. declines across trials of a test session) if prepulses close to the detection threshold were used, which possibly reflects reduced attention that may lead to reduced prepulse detection (Gewirtz and Davis, 1995). The optimal interstimulus interval between the prepulse and the startling pulse is almost similar in rats [100 msec, Hoffman and Ison (1980)] and in humans [120 msec, Graham and Murray (1977)]. PPI can be expressed as a percentual or an absolute difference between the ASR magnitudes presented in the absence and in the presence of a prepulse (Davis, 1988). Since relative (percentual) differences have been found to remain constant under a variety of conditions that increase or decrease the ASR magnitude (Ison *et al*., 1997; Koch and Friauf, 1995; Swerdlow *et al*., 1992a) it can be concluded that the ASR and PPI are mediated by different pathways and that PPI is best expressed as percent scores rather than as absolute difference scores (Ison *et al*., 1997).

The brain mechanisms underlying the mediation of PPI are still not fully understood. The attenuating effect on the ASR of acoustic prepulses probably affects the primary ASR pathway at the level of the PnC (Carlson and Willott, 1998; Lingenhöhl and Friauf, 1994; Willott *et al*., 1994; Wu *et al*., 1988) probably by activation of an inhibitory cholinergic (muscarinic) projection from the PPTg to the PnC (Koch *et al*., 1993; Swerdlow and Geyer, 1993a). Lesions of the inferior colliculus disrupt PPI by auditory prepulses (Leitner *et al*., 1980, 1981; Leitner and Cohen, 1985; Li *et al*., 1998) suggesting that the ascending auditory pathway activates a PPI circuit at the level of the midbrain. We have shown that excitotoxic lesions of the superior colliculus also impair PPI (Fendt *et al*., 1994c). The superior colliculus projects to the PPTg and receives input from different sensory modalities (auditory, tactile and visual) which reduce the ASR when given as prepulses (Blumenthal and Gescheider, 1987; Campeau and Davis, 1995b; Leitner, 1988; Pickney, 1976). A primary PPI circuit for auditory prepulses could therefore be composed of the lower parts of the ascending auditory system (cochlear nuclei, superior olivary complex and nuclei of the lateral lemniscus), the inferior colliculus, the superior colliculus and the PPTg which conveys inhibitory cholinergic input to the PnC. Behavioral data make a role for classical inhibitory transmitters (e.g. GABA and glycine) in the mediation of PPI at the level of the PnC very unlikely (Koch and Friauf, 1995; Birnbaum *et al*., 1997). It should be noted, however, that lesions of the PPTg do not completely block PPI, which means that there must be another pathway that conveys the effect of prepulses onto the primary ASR circuit.

There has been a debate about whether PPI reflects a sensorimotor gating mechanism that *facilitates* attention (Graham, 1975), or whether PPI *requires* attention towards the prepulse in order to function effectively. It appears as if this debate is largely based on different concepts of attention, which will be discussed in Chapter 4.3.

### 4.3. Regulation of PPI

PPI of the ASR is reduced in a variety of neuropsychiatric disorders that are characterized by a general reduction of the ability to gate intrusive sensory, motor or cognitive information, for example in schizophrenia, schizotypal personality disorder, Huntington's disease, obsessive compulsive disorder, Tourette's syndrome and attention deficit disorder [summarized in Swerdlow and Geyer (1998)]. There has been a discussion whether deficits in PPI reflect a sensorimotor gating deficit (leading to compromised processing of the prepulse) or an impairment of attention leading to a reduced detectability of the prepulse (Campeau and Davis, 1995b; Davis *et al*., 1990; Dawson *et al*., 1993; Grillon *et al*., 1992; Swerdlow *et al*., 1992a). The term '*preattentive* filter mechanism', introduced by Graham (1975) for the description of PPI in humans, was coined to describe a mechanism that protects stimulus processing beyond the mere perceptual level and thereby facilitate stimulus recognition. That is to say that the term preattentive should not indicate that PPI occurs *before* perceptional attentional mechanisms. Swerdlow and co-workers have repeatedly shown that treatments that impair PPI do not affect the reduction in ASR peak latency that occurs concomitant to PPI, indicating that the animals are still able to detect the prepulse under conditions that reduce PPI (Swerdlow *et al*., 1992a). On the other hand, PPI-disrupting treatments (such as systemic application of phencyclidine or apomorphine, see below) do also impair the detection of a prepulse in a combined fear-potentiation/PPI-paradigm suggesting that they reduce PPI by an impairment of the detection of the prepulse (Varty *et al*., 1997). Also, in humans PPI is enhanced if the subjects attended to the prepulse (Blumenthal and Flaten, 1994; Filion *et al*., 1993; Jennings *et al*., 1996). Obviously, there are important attentional components involved in PPI, indicating that the PPI mechanism is more than a pure sensorimotor gate that is a prerequisite for attention. Attentional ('top–down') mechanisms obviously affect PPI at the perceptual level, whereas higher levels of stimulus processing (cognitive processes) are protected by the gating mechanism underlying PPI.

Reduced PPI is observed under a variety of experimental conditions in animals, such as fluctuating ovarian hormones (Koch, 1998), manipulation of different transmitter systems, brain lesions [summarized in: Koch and Schnitzler (1997); Swerdlow *et al*. (1992a), breeding conditions Geyer *et al*. (1993); Ellenbroek *et al*. (1995)], strain differences (Varty and Higgins, 1994; Paylor and Crawley, 1997) and, as mentioned above, in certain neuropsychiatric dis-

eases in humans [summarized in: Geyer and Braff (1987); Swerdlow and Geyer (1998)].

The most conspicuous finding of recent animal research is a disruption of PPI under the influence of an overactive mesoaccumbal dopamine (DA) system (Rigdon, 1990; Swerdlow *et al*., 1994), for example, after excessive stimulation of DA $D_2$ receptors on medium spiny neurons of the ventral striatum (nucleus accumbens) (Swerdlow *et al*., 1990b) and the medial striatum [Swerdlow *et al*. (1992a,b); Wan and Swerdlow (1993); Wan *et al*. (1994); but see also Schwarzkopf *et al*. (1993a); Wan *et al*. (1996b)].

PPI deficits were also seen after blockade of 5-$HT_2$ receptors (Sipes and Geyer, 1994) or stimulation of 5-$HT_1$ receptors (Rigdon and Weatherspoon, 1992), after blockade of the noradrenergic system (Saitoh *et al*., 1986), knockout of $\alpha_2$-noradrenergic receptors (Sallinen *et al*., 1998), after stimulation of $\alpha_1$-adrenergic receptors (Carasso *et al*., 1998) and after blockade of non-competitive NMDA receptors (Al-Amin and Schwarzkopf, 1996; Bakshi *et al*., 1994; Kretschmer and Koch, 1998; Mansbach, 1991) or after blockade of the glycine-site of the NMDA receptor (Furuya and Ogura, 1997; Kretschmer and Koch, 1997). Pharmacologically induced PPI-deficits and the antagonism of these behavioral effects has frequently been used to assess the potential neuroleptic activity of drugs (Hoffman and Donovan, 1994; Johansson *et al*., 1994, 1995; Swerdlow and Geyer, 1993b; Swerdlow *et al*., 1991; Schwarzkopf *et al*., 1993b). PPI deficits induced by systemic or intra-accumbal application of DA agonists can effectively be restored by classical antipsychotic agents such as haloperidol (Swerdlow *et al*., 1994). Most interestingly, though, PPI deficits induced by systemic apomorphine were only partially antagonized by local microinfusion of the DA antagonist haloperidol into the nucleus accumbens and other brain sites, suggesting that haloperidol acts on multiple brain substrates to affect PPI (Hart *et al*., 1998). Enhanced PPI is found after neuroleptic treatment if the basal PPI performance is low (Depoortere *et al*., 1997).

Several investigators have attempted to explain the reduction of PPI by the manipulation of selective transmitter systems in terms of neuronal circuits. The nucleus accumbens septi (NAC) is one of the centers of convergence of several transmitter systems that regulate PPI. The NAC receives a dense dopaminergic innervation from the VTA, and excessive DA receptor stimulation or a lesion-induced DA receptor supersensitivity in the NAC reduces PPI [summarized in Swerdlow *et al*. (1992a)]. Because a disturbance of the interaction between glutamate and DA plays a role in the etiology of schizophrenia, a role of the glutamate–DA interaction in the NAC in the regulation of PPI was thoroughly investigated. Since PPI-deficits induced by non-competitive NMDA antagonists cannot be antagonized by DA antagonists (Keith *et al*., 1991), a direct effect of NMDA receptor blockers on PPI via the DA system can be excluded. Intra-accumbal application of the non-competitive NMDA-antagonist dizocilpine *enhances* PPI (Reijmers *et al*., 1995), whereas intraaccumbal infusion of competitive NMDA antagonists, or glycine-site NMDA antagonists reduce PPI [Kretschmer and Koch (1997, 1998); but see: Bakshi *et al*. (1998)]. Since striatal DA release is to some extent under the control of cortical and limbic glutamatergic afferents, one of the research aims was to investigate whether DA-glutamate interactions are important for the regulation of PPI. The NAC receives a direct projection from the ventral hippocampus (vHIP) (Groenewegen *et al*., 1987) and these hippocampal fibers converge on spiny NAC neurons with dopaminergic afferents from the VTA (Totterdell and Smith, 1989; Sesack and Pickel, 1990). Stimulation of the hippocampal afferents enhances DA release from VTA terminals probably via a direct presynaptic glutamatergic mechanism mainly in the shell region of the NAC (Blaha *et al*., 1997; Brudzynski and Gibson, 1997). PPI is reduced after chemical stimulation of the vHIP with the acetylcholine (ACh) muscarinic receptor agonist carbachol (Caine *et al*., 1991, 1992), with the glutamate agonist NMDA (Wan *et al*., 1996a; Klarner *et al*., 1998) or with the GABA antagonist picrotoxin (Japha and Koch, 1999). This PPI-disruptive effect is also seen after transsynaptic stimulation of ACh release in the vHIP via the medial septum (Koch, 1996). Since, however, the DA antagonists spiperone (Caine *et al*., 1991) or haloperidol (Wan *et al*., 1996a) do not ameliorate the PPI-disruptive effects of vHIP stimulation, this effect is probably mediated by a DA-independent mechanism. Reduced PPI is also found after intra-NAC core infusion of the glutamate agonist AMPA and this effect was reduced by co-administration of haloperidol, suggesting that in the NAC core a presynaptic DA–glutamate interaction regulates PPI (Wan *et al*., 1995; Wan and Swerdlow, 1996). The stimulation of the vHIP leads to a profound PPI-deficit that is accompanied by a strong expression of the neuronal activity marker *c-Fos* in a variety of corticolimbic forebrain structures (NAC, septal nuclei and different parts of the piriform and prefrontal cortex). In this study, the PPI deficit was still present on the day after hippocampal stimulation (Klarner *et al*., 1998). These behavioral and functional mapping data suggest that PPI is regulated by a complex pattern of long-lasting activity in an interrelated set of forebrain areas.

An important role of the prefrontal cortex in the PPI-deficits of schizophrenia patients has been reported recently (Hazlett *et al*., 1998). Glutamatergic afferents from the medial prefrontal cortex may also play a role in the regulation of DA release in the NAC and in the regulation of PPI. Depletion of DA from the rat medial prefrontal cortex by 6-hydroxydopamine (6-OHDA) lesion (Bubser and Koch, 1994; Koch and Bubser, 1994), blockade of prefrontocortical DA receptors (Ellenbroek *et al*., 1996) or disinhibition of medial prefrontocortical neurons by local infusion of the GABA antagonist picrotoxin (Japha and Koch, 1999) reduces PPI and this effect was antagonized by haloperidol. A hypofunction of prefrontocortical DA leads to excessive DA release in the NAC core region, because the reduction of the mainly inhibitory influence of DA on the glutamatergic cortical

output neurons enhances the excitatory output from the cortex to the VTA. Hence, the medial prefrontal cortex enhances accumbal DA release probably via its glutamatergic projection to the VTA (Karreman and Moghaddam, 1996; Taber and Fibiger, 1995), although an interaction of prefrontal glutamatergic afferents and tegmental DAergic afferents in the NAC is also possible.

The prominent role of accumbal DA for PPI is further supported by work showing that other transmitters (e.g. adenosine), or neuropeptides (e.g. neurotensin and CCK) that may interact with DA are also important for the regulation of PPI in the NAC (Feifel and Swerdlow, 1997; Feifel *et al*., 1997; Feifel and Minor, 1997; Hauber and Koch, 1997; Koch and Hauber, 1998).

The neuronal substrates of the reduction of PPI by NMDA antagonists are still not completely understood. It has consistently been found that non-competitive NMDA antagonists (e.g. MK-801, phencyclidine and ketamine) reduce PPI after systemic application (Mansbach, 1991). These PPI-disruptive effects are not antagonized by DA antagonists (Keith *et al*., 1991), but only by atypical neuroleptics (Bakshi *et al*., 1994; Johansson *et al*., 1994), by nitric oxide synthase inhibitors (Johansson *et al*., 1997), or by the $\alpha_1$-noradrenergic antagonist prazosin (Bakshi and Geyer, 1997). We do not yet exactly know where in the brain the blockade of NMDA receptors by non-competitive antagonists affects PPI. Local infusion of MK-801 into the NAC either *enhance* PPI (Reijmers *et al*., 1995) or show no effect on PPI (Bakshi and Geyer, 1998), whereas infusion into the basolateral amygdala or into the dorsal hippocampus reduces PPI (Bakshi and Geyer, 1998). In this context, it is interesting to note that lesions of the basolateral amygdala also impair PPI (Decker *et al*., 1995; Wan and Swerdlow, 1997) and this effect has been suggested to be mediated by an amygdaloid projection to the ventral pallidum (Wan and Swerdlow, 1997). Remarkably, there is a clear difference between the effects on PPI of competitive NMDA antagonists and the non-competitive open-channel blockers of the NMDA receptor. Earlier studies had shown that systemically applied competitive NMDA antagonists do not affect PPI (Swerdlow *et al*., 1992a), whilst recent studies revealed that intraaccumbal administration of AP-5 (Kretschmer and Koch, 1997, 1998; Reijmers *et al*., 1995) or the glycine-site NMDA receptor antagonist 7-chlorokynurenic acid (Kretschmer and Koch, 1997, 1998) reduce PPI. Likewise, systemic application of the competitive NMDA receptor antagonist CGS19755 or intracerebroventricular administration of 7-chlorokynurenic acid also reduce PPI (Furuya and Ogura, 1997).

A series of elegant studies have shown that the overactivity of the mesoaccumbal DA system affects the PPI-mediating circuit by a GABAergic projection from the NAC to the ventral pallidum, from where a GABAergic projection descends to the PPTg (Swerdlow *et al*., 1990a; Kodsi and Swerdlow, 1994, 1995, 1997). Obviously, the ventral pallidum is also a target for the PPI-regulating effects of seroto-

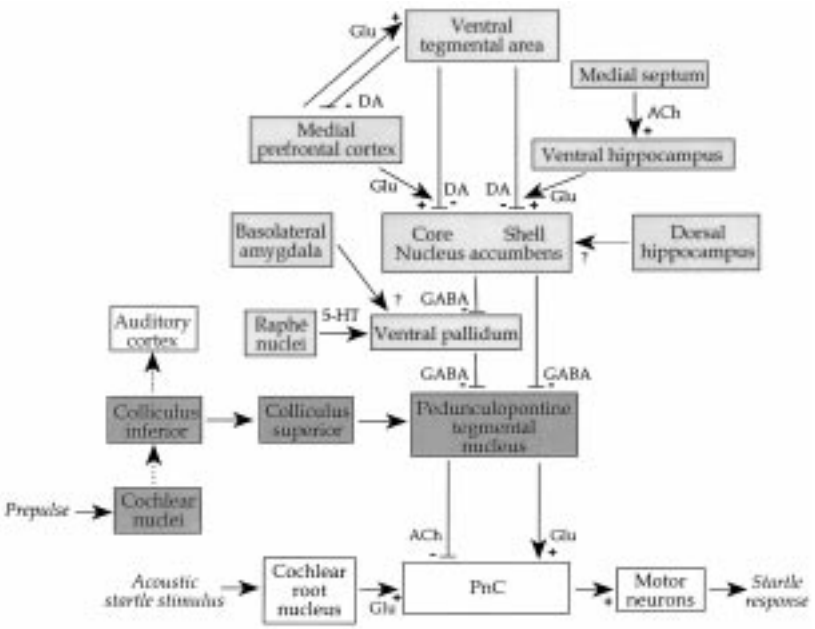


Fig. 10. A hypothetical circuit mediating PPI of the ASR and some of its modulations. ACh, Acetylcholine; DA, dopamine; GABA, $\gamma$-aminobutyric acid; Glu, glutamate; 5-HT, serotonin; +, excitatory; –, inhibitory transmitter action; ?, direct interaction is uncertain. The darkly shaded boxes symbolize brain nuclei involved in the mediation of PPI and the lightly shaded boxes symbolize brain structures that modulate (reduce) PPI. Stippled arrows symbolize that other relay nuclei are interposed between the respective brain structures. It should be noted that in this and in the other circuit diagrams the temporal information is neglected. The transmission velocities of the different parts of these pathways differ due to differences in conduction velocities, as well as in pre- and postsynaptic transmitter actions.

nin receptor antagonists (Sipes and Geyer, 1997). Recently it has been shown that only the PPI-deficits induced by an overactivity of the DA system, but not those induced by systemic or intraaccumbal blockade of NMDA receptors are mediated by the NAC-ventral pallidal output pathway (Kretschmer and Koch, 1997, 1998). The present hypothetical pathway is proposed to delineate possible substrates of regulation of PPI (Fig. 10).

PPI is also reduced by selective breeding (Ellenbroek *et al.*, 1995; Ellenbroek and Cools, 1998), by rearing rats in social isolation (Geyer *et al.*, 1993), by an elevation of female sex steroid hormones in rats (Koch, 1998) and humans (Swerdlow *et al.*, 1997), and is affected by strain differences (Varty and Higgins, 1994; Paylor and Crawley, 1997). Although it has been shown that isolation-rearing-induced PPI-deficits are reversed by the neuroleptics seroquel or olanzapine (Bakshi *et al.*, 1998), it is still not clear which parts of the above neuronal circuits affecting PPI are compromised by the experimental manipulation of developmental and physiological conditions.

### 4.4. Pleasure-Attenuation

The theoretical concept of motivational priming [as proposed e.g. by Konorski (1967); Dickinson and Dearing (1979)] attempts to explain the observation that protective behaviors that are adaptive in dangerous or threatening contexts are facilitated by aversive motivation, whereas they tend to be attenuated by positive affect. Drawing on this concept, Lang and his co-workers have found that in humans the ASR magnitude is increased in an aversive context and decreased if elicited in a pleasant ('hedonic') emotional context [Lang *et al.* (1990); Lang (1995); see also: Ehrlichman *et al.* (1995)]. Enhanced ASR in the context of fear and anxiety was discussed in Section 3. The attenuation of the ASR during a presumed hedonic state has also been shown in rats [Fig. 11; Schmid *et al.* (1995)]. Here, a Pavlovian conditioning procedure was applied, during which food-deprived rats were trained to associate palatable food and sucrose with a light CS. After conditioning the ASR magnitude was found to be reduced in the presence of the CS predicting food [Fig. 2(E)]. This effect was termed pleasure-attenuation of the ASR and probably reflects a mechanism of state-dependent gating of the ASR, capitalizing on the idea of drive and antidrive developed by Konorski (1967), which predicts that behaviors that are normally released by aversive events are attenuated in a pleasant context.

The first experiments into the neuronal basis of pleasure-attenuated ASR have shown that 6-OHDA lesion of the NAC, but not excitotoxic lesion of the amygdala, prevent the attenuation of the ASR in the presence of a rewarding stimulus (Koch *et al.*, 1996b). These findings suggests that parts of the mesoaccumbal-pallidal circuitry that governs reward-related behavior (Robbins and Everitt, 1996) are important for the reduction of the ASR in the presence of a stimulus that predicts reward. Recent experiments have shown that while instrumental responding for reward in a lever-pressing paradigm

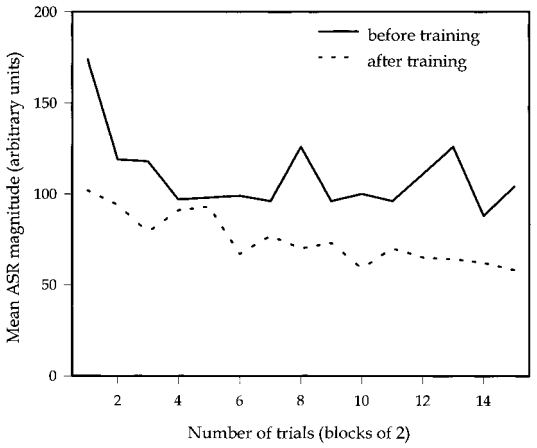


Fig. 11. Pleasure-attenuation of the ASR. The figure shows the time course of the ASR in 19 rats in the presence of a light before (———) and after (– – –) the light had been paired with palatable food and sucrose [data are adapted from Schmid *et al.* (1995)]. No differences between ASR magnitudes before and after training are found in a pseudoconditioned control group (data not shown).

is reduced following intraaccumbal infusion of DA antagonists, the reduction of the ASR in the presence of a light predicting reward is not (A. Schmid and M. Koch, unpublished observations). Since 6-OHDA lesions of the NAC performed before training impairs pleasure-attenuation of the ASR (Koch *et al.*, 1996b), but blockade of NAC DA $D_1$ or DA $D_2$ receptors after conditioning does not, it can be concluded that accumbal DA is important for the acquisition, but not for the expression of this form of ASR gating. It is unclear, however, how reward-related brain areas interact with the primary ASR circuit so as to inhibit the ASR.

## 5. CONCLUSION

The ASR is a simple reflex-like behavior that can be reliably elicited and exactly quantified in a variety of experimental animals and in humans. It is mediated by a relatively simple oligosynaptic pathway located in the pontine brainstem and is modulated by perceptual (prepulses) and state (positive or negative affect) variables and by a variety of drugs. Hence, the ASR can be used as a behavioral tool to assess brain mechanisms of sensorimotor integration in mammals. The PnC is one of the key elements of the primary ASR circuit, because it mediates the ASR and it is also the recipient of ASR-modulating input from a variety of other brain areas that enhance the ASR by aversive states or which reduce the ASR by prepulses. In that brain nucleus, the particularly large giant neurons play an important role for the evocation of the ASR. Hence, this brain region can be regarded as a sensorimotor-motivational interface for the ASR, where the modulation of a behavior can be studied at the cellular level in mammals.

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* References that are helpful to a reader new to the subject.