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Short communication

Increased motivation for beer in rats following administration of a cannabinoid CB_1 receptor agonist

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Abstract

A series of experiments examined the effects of the cannabinoid CB_1 receptor agonist CP 55,940 ((−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol) on the motivation to consume beer, near-beer (a beer-like beverage containing $< 0.5\%$ ethanol) and sucrose solutions in rats. The experiments employed a 'lick-based progressive ratio paradigm' in which an ever increasing number of licks had to be emitted at a tube for each successive fixed unit of beverage delivered. Break point, the lick requirement at which responding ceased, was used as an index of motivation. In the first experiment, CP 55,940 (10, 30 or 50 μg/kg) caused a dose-dependent increase in break points for beer (containing 4.5% ethanol v/v) and for near-beer. The highest (50 μg/kg) dose of CP 55,940 also significantly decreased locomotor activity. In the second experiment, CP 55,940 (10 or 30 μg/kg) dose-dependently increased break points in rats licking for 'light' beer (containing 2.7% ethanol v/v) or for a sucrose solution (8.6% w/v) containing the same number of calories as the beer. In the third experiment, the facilitatory effects of CP 55,940 (30 μg/kg) on responding for beer and near-beer were reversed by both the cannabinoid CB_1 receptor antagonist SR 141716 (*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride) (1.5 mg/kg) and the opioid receptor antagonist naloxone (2.5 mg/kg). Naloxone had a proportionally greater effect on rats licking for beer compared to near-beer, consistent with previous reports of opioid receptor mediation of alcohol craving. These results show that cannabinoids modulate the motivation for beer via both cannabinoid CB_1 receptors and opioid receptors. The similar effect of CP 55,940 on the motivation for beer, near-beer and sucrose suggests that the drug effect may reflect a general stimulatory effect on appetite for palatable beverages, although a more specific effect on the desire for alcohol cannot be ruled out.

Keywords: Cannabinoid; Cannabis; Beer; Naloxone; Sucrose; SR 141716; CP 55,940; Self-administration

1. Introduction

Recent evidence suggests that endogenous cannabinoid systems may play a key role in determining the reinforcing effects of not only cannabis, but of other abused substances including cocaine, opiates and alcohol. Much of this evidence has come from studies employing the selective cannabinoid CB_1 receptor antagonist SR 141716 (*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride). This drug was recently found to block the acquisition of conditioned place preference to cocaine in rats (Chaperon et al., 1998) and to reduce the self-administration of morphine in mice (Fratta et al., 1998). In addition, three recent studies, involving notably different methodological approaches, have indicated that SR 141716 reduces alcohol intake and alcohol craving in rats (Arnone et al., 1997; Colombo et al., 1998; Gallate and McGregor, 1999). This indicates a hitherto unexplored role for cannabinoids in influencing the desire for alcohol.

If blockade of endogenous cannabinoid systems reduces the motivation to consume alcohol then it might be reasoned that stimulation of these same systems will promote alcohol craving. This would parallel the situation seen with opioids, where naloxone has a strong inhibitory effect on alcohol consumption while morphine and other opioid receptor agonists tend to stimulate alcohol intake (Nichols et al., 1991; Herz, 1997). Interestingly, recent data suggest high levels of hazardous drinking among long-term cannabis users, a finding that is consistent with the proposition that cannabinoid receptor agonists stimulate alcohol consumption (Swift et al., 1997). In rats, however, at least

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one study has shown that acute administration of the main psychoactive constituent of cannabis, Δ^9 tetrahydrocannabinol, inhibits alcohol intake (McMillan and Snodgrass, 1991). However, this study subjected rats to food restriction and also employed ethanol in water as a test solution. These methods are questionable since few humans drink pure ethanol solutions, and food deprivation is not a prerequisite for humans to imbibe alcoholic beverages.

We therefore decided to re-assess this issue using a newly developed animal model of alcohol craving that uses beer as a test solution (Topple et al., 1998; McGregor et al., 1999, Gallate and McGregor, 1999). Beer is chosen because rats need very little encouragement to drink off the shelf beers (Richter, 1953; Cox and Mertz, 1985; Jones et al., 1988; Nichols et al., 1991; McGregor et al., 1999) and will drink them to a much greater extent than dilute solutions of ethanol in water (McGregor et al., 1999). Our method involves a lick-based progressive ratio paradigm that requires rats to make an ever increasing number of licks at a tube for a fixed volume of beer to be delivered down the tube. The ratio at which the rat stops responding, termed the break point, is taken as an index of the motivation or 'craving' that the rat has for beer. While lever press-based progressive ratio schedules have been much used in the intravenous drug self-administration literature (Markou et al., 1993; Richardson and Roberts, 1996) the use of lick-based progressive ratio paradigms is comparatively rare (Rodefer and Carroll, 1996; McGregor et al., 1999; Gallate and McGregor, 1999).

Our method also involves comparison of the effects of drugs on the motivation to consume beer (containing 4.5% ethanol v/v) relative to the motivation to consume near-beer (containing $< 0.5\%$ ethanol). The two test solutions, beer and near-beer, are identical in every respect except that the beer solution contains substantial quantities of ethanol. The use of near-beer offers a relatively tight control for the non-specific effects of drugs on appetite or performance (Gallate and McGregor, 1999).

In the present study, we assessed the effects of the cannabinoid CB_1 receptor agonist CP 55,940 ((−)-*cis*-3-2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroypropyl)cyclohexanol) in the lick-based progressive ratio paradigm. This drug is very similar to Δ^9 tetrahydrocannabinol in its behavioral and discriminative stimulus effects (Wiley et al., 1995) although it is approximately 30 times more potent (Little et al., 1988; Gold et al., 1992). We also tested the ability of CP 55,940 to stimulate the motivation to consume a sucrose solution. Cannabinoid CB_1 receptor agonists have been shown to stimulate intake of palatable foodstuffs in both rats (Milano et al., 1988; Williams et al., 1998) and humans (Foltin et al., 1988), and it was important to determine whether a stimulatory effect of CP 55,940 on the motivation for beer might be seen with any palatable beverage regardless of alcohol content. Finally, the study also assessed whether the cannabinoid CB_1 receptor antagonist SR 141716 and the opioid receptor antagonist naloxone might reverse the effects of CP 55,940 on the motivation for beer.

2. Materials and methods

2.1. Subjects

The subjects were a total of 64 male experimentally-naive Wistar rats weighing 450 ± 50 g. The rats were group housed in tubs of 6–8 animals on a reverse light–dark cycle (lights off at 0830 h) with ad lib access to water and standard lab chow. All behavioral testing occurred during the dark cycle.

The first 24 rats were used to test the effects of various doses of CP 55,940 on the motivation for beer and near-beer. A further 16 rats were then used to test the effects of CP 55,940 on the motivation for sucrose and 'Toohey's Blue' (a commercially available 'light' beer). The final 24 rats were used to test whether SR 141716 or naloxone could reverse the effects of a single dose of CP 55,940 (30 $\mu g/kg$) on the motivation for beer and near-beer.

All experiments adhered to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and were approved by the University of Sydney Animal Ethics Committee.

2.2. Apparatus

The apparatus was as described previously (McGregor et al., 1999; Gallate and McGregor, 1999). All behavioral testing took place in custom 'drink chambers'. These consisted of eight standard operant chambers ($30 \times 50 \times 25.5$ cm) with metal grid floors. The side walls, back wall and roof of the chambers were aluminum, while the front wall (door) was made of clear perspex. Each chamber was housed inside a light and sound attenuating wooden box ($69 \times 71 \times 61.5$ cm) with a fan fitted in the back wall which provided a low level of masking noise during testing.

A small glass tube of 5 mm diameter containing three inner stainless steel tubes of 1.5 mm diameter (hereafter known as the 'lick tube') protruded through the left side wall approximately 3 cm from the cage floor. Each lick at the tube formed a circuit between the metal tubes, the rat and the metal grid floor of the cage which was detected and counted by a Macintosh computer running 'WorkbenchMac' data acquisition software (McGregor, 1996). The lick tube was connected via plastic tubing to a solenoid valve which was in turn connected via plastic tubing to a 50-ml syringe reservoir containing the relevant beverage. The software controlled the opening of the valve so that a set amount of fluid could be delivered depending upon the number of licks emitted by the rat.

The chambers incorporated two passive infra-red motion detectors (Jaycar, Sydney) which were located in the

center of each aluminum side wall at the same height as the rat. These detectors allowed measurement of locomotor activity by the rat throughout the test chamber. The detectors were customized so that they were sensitive to relatively small movements of the head and body of the rat, but generally did not trigger when the rat was licking at the lick tube. The outputs of the detectors were also sent to the computer and this allowed measurement of the total number of seconds spent moving in each test session. Measurement of activity allowed determination of whether any reduction in licking might be due to a general depressant effect of a drug.

2.3. Drugs and beverages

Rats in the 'near-beer' conditions in the first and third experiments were given 'Birell's Premium' (Coopers, South Australia), which contains $< 0.5\%$ ethanol by volume. Rats in the 'beer' groups received this solution with 4.0% ethanol (v/v) added. As in previous studies (Nichols et al., 1991; Topple et al., 1998; McGregor et al., 1999; Gallate and McGregor, 1999) the beer was decarbonated prior to use in experiments by being placed on a magnetic stirrer for approximately 20 min. The beer was presented to the rats at room temperature.

In the second experiment, the beer used was 'Toohey's Blue' (Toohey's, Lidcombe, Australia), a commercially available 'light beer' which contains 2.7% ethanol (v/v). The other rats in the second experiment were given 8.6% sucrose solution, made by dissolving granulated table sugar in tap water. The 8.6% concentration was used since it is isocaloric with the 'Toohey's Blue' beer.

CP 55,940 (Pfizer) was initially dissolved in 100% ethanol. Tween 80 was added to this solution and the ethanol completely evaporated under a stream of nitrogen gas to give a final solution of 1:39 (Tween 80:saline). SR 141716 (Sanofi Recherche), a selective cannabinoid CB_1 receptor antagonist (Rinaldi-Carmona et al., 1994), was similarly prepared to give a final dilution of 1:19 (Tween 80:saline). Naloxone (Research Biochemicals) was prepared in an identical fashion to SR 141716 so that the two antagonist drugs used were matched for vehicle.

All drugs were injected i.p. in a volume of 1 ml/kg 15 min prior to behavioral testing. Identical solutions minus the drugs were used in the vehicle conditions.

2.4. Effects of CP 55,940 on the motivation for beer or near-beer

In the first experiment, three doses of CP 55,940 were tested, namely 10, 30 and 50 μg/kg. These doses span the behaviorally effective range according to previous experiments from this laboratory, with the highest 50 μg/kg dose causing a pronounced decrease in locomotor activity (McGregor et al., 1996a,b; Arnold et al., 1998) and marked c-*fos* expression in several brain regions (McGregor et al., unpublished data). In preliminary experiments we determined that a 100 μg/kg dose of CP 55,940 produced an almost complete cessation of responding for beer or sucrose (data not shown), so doses higher than 50 μg/kg were not used.

The experiment involved two groups, a beer group ($n = 12$) and near-beer group ($n = 12$) and four phases as follows.

2.4.1. Home cage pre-exposure

During this 21-day phase, groups of rats were given daily access to a total of 365 ml near-beer or beer (divided between six rats) in a 24-h period in their home cages. Rats in the beer group were given near-beer for the first three days of this phase, then near-beer + 2% ethanol for the following 3 days and then near-beer + 4% ethanol for the remainder of the experiment. Rats in the near-beer group were given only near-beer. On every day of this phase, the groups of rats drank the entire 365 ml of beer or near-beer that was available.

2.4.2. Drink training

At the end of the pre-exposure phase, home cage access to beer or near-beer ceased and rats were switched to 30 min access to 20 ml of either beer or near-beer (according to group allocation) each day in the drink chambers. For every three licks that the rat made at the lick tube, a 0.05-ml drop of beer or near-beer was delivered. This phase continued for a total of 5 days by which time, as described previously (McGregor et al., 1999), most rats were drinking all of the available fluid in each test session.

2.4.3. Progressive ratio training

This phase also involved access to either beer or near-beer in the drink chambers but under a progressive ratio schedule of reinforcement where an increasing number of licks had to be given for each successive 0.1 ml unit of reinforcement. This schedule was implemented in software as reported previously (McGregor et al., 1999) using the equation

$$\text{licks required} = 3 + \left(0.005\left[(0.25\,\text{trial})^3\right]\right)$$

The schedule ensured that (a) most rats receive a reasonable amount of the test solution in a session (approximately 8–11 ml) but not a maximal amount that would induce satiety (i.e., 20–30 ml), and (b) most rats achieve a break point within a 1-h test session, with the break point defined as the ratio reached where no further licks are emitted for a period of 10 min or more. When this condition was not met, the break point was simply defined as the highest ratio completed by the rat during the test session. However, this happened only very rarely in test sessions. Following 14 days of baseline training on the progressive ratio schedule the mean break point in all rats showed less than 5% deviation from day to day.

2.4.4. Drug testing

Drug testing occurred over 8 consecutive days using a within-subjects design where each rat received each dose of CP 55,940 and vehicle in a randomized order. A drug dose was given every second day and on intervening days rats were run in the standard paradigm without injection to ensure that baseline levels of responding had recovered.

2.5. Effects of CP 55,940 on the motivation for beer or sucrose

Rats in this experiment were trained to respond under a progressive ratio paradigm as described for the first experiment above except that (1) the rats were given no initial home cage exposure phase, and (2) the test solutions were either Toohey's Blue beer in the 'beer' group ($n = 8$) or 8.6% sucrose solution in the 'sucrose' group ($n = 8$). The use of a different beer in this experiment allowed the generality of the effects obtained in Experiment 1 to be assessed. The home cage exposure phase was omitted because our previous results show that high levels of Toohey's Blue intake are obtained without initial home cage access to the beer being required (McGregor et al., 1999).

Drug testing with CP 55,940 occurred over 6 consecutive days with a drug test every second day in which each rat was tested with CP 55,940 (10 or 30 μg/kg) and vehicle in a randomized order. On the days in between drug tests, rats were run in the standard paradigm without injection to ensure that baseline levels of responding had recovered.

2.6. Reversal of CP 55,940 effects with naloxone or SR 141716

Rats in this experiment were trained to consume beer ($n = 12$) or near-beer ($n = 12$) in the drink chambers under a progressive ratio schedule in an identical fashion to that described for the first experiment.

Drug testing occurred over 8 consecutive days with a drug test every second day in which each rat was tested in a randomized order with (1) vehicle + vehicle, (2) CP 55,940 (30 μg/kg) + vehicle, (3) CP 55,940 (30 μg/kg) + SR 141716 (1.5 mg/kg), and (4) CP 55,940 (30 μg/kg) + naloxone (2.5 mg/kg). The single doses of SR 141716 and naloxone were chosen on the basis of pilot experiments in which a wider dose range of each drug was explored in small groups of rats. Again, on the days in between drug tests, rats were run in the standard paradigm without injection to ensure that baseline levels of responding had recovered.

2.7. Data analysis

In each experiment, data for break point and locomotor activity were compared across conditions using planned contrasts. A Bonferroni procedure was used in which the α rate was divided by the number of contrasts to determine the threshold for significance.

In the first experiment, the contrasts (two-way ANOVAs) compared the beer and near-beer groups across the following conditions: (1) vehicle v CP 55,940 (10 μg/kg), (2) vehicle v CP 55,940 (30 μg/kg) and (3) vehicle v CP 55,940 (50 μg/kg). Bonferroni corrections modified the threshold of statistical significance to $0.05/3 = 0.0166$.

In the second experiment the contrasts (two-way ANOVAs) compared the beer and sucrose groups across the following conditions: (1) vehicle v CP 55,940 (10 μg/kg) and (2) vehicle v CP 55,940 (30 μg/kg), The threshold for significance in this case was $0.05/2 = 0.025$.

In the final experiment the contrasts (two-way ANOVAs) compared the beer and near-beer groups across the following conditions: (1) (vehicle + vehicle) v (CP 55,940 + vehicle), (2) (vehicle + vehicle) v (CP 55,940 + SR 141716), and (3) (vehicle + vehicle) v (CP 55,940 + naloxone). The threshold for significance in this case was $0.05/3 = 0.0166$.

3. Results

3.1. Effects of CP 55,940 on the motivation for beer or near-beer

The data for the first experiment are shown in Fig. 1. Analysis showed a significant overall increase in break point with the 10 μg/kg dose of CP 55,940 ($F(1,22) = 21.72$, $P < 0.0001$) as well as the 30 μg/kg dose ($F(1,22) = 40.01$, $P < 0.0001$) and the 50 μg/kg dose ($F(1,22) = 17.19$, $P < 0.001$). There were no significant group effects or group × drug interactions, indicating similar effects of the drug in the beer and near-beer groups.

Analysis of locomotor activity showed a strong trend towards decreased activity with the 10 μg/kg dose ($F(1,22) = 4.63$, $P = 0.043$) and the 30 μg/kg dose ($F(1,22) = 6.08$, $P = 0.021$), and a significant reduction with the 50 μg/kg dose ($F(1,22) = 29.62$, $P < 0.001$). Again, there were no significant group effects or group by drug interaction effects, indicating similar effects of the drug in the beer and near-beer groups.

3.2. Effects of CP 55,940 on the motivation for beer or sucrose

The data for the second experiment are shown in Fig. 2. Analysis indicated that break points were significantly increased by both the 10 μg/kg dose ($F(1,14) = 6.93$, $P < 0.025$) and the 30 μg/kg dose ($F(1,14) = 22.19$, $P < 0.001$). There were no significant effects of group and no group × drug interactions suggesting that the effects of the drug were similar in the beer and sucrose groups.

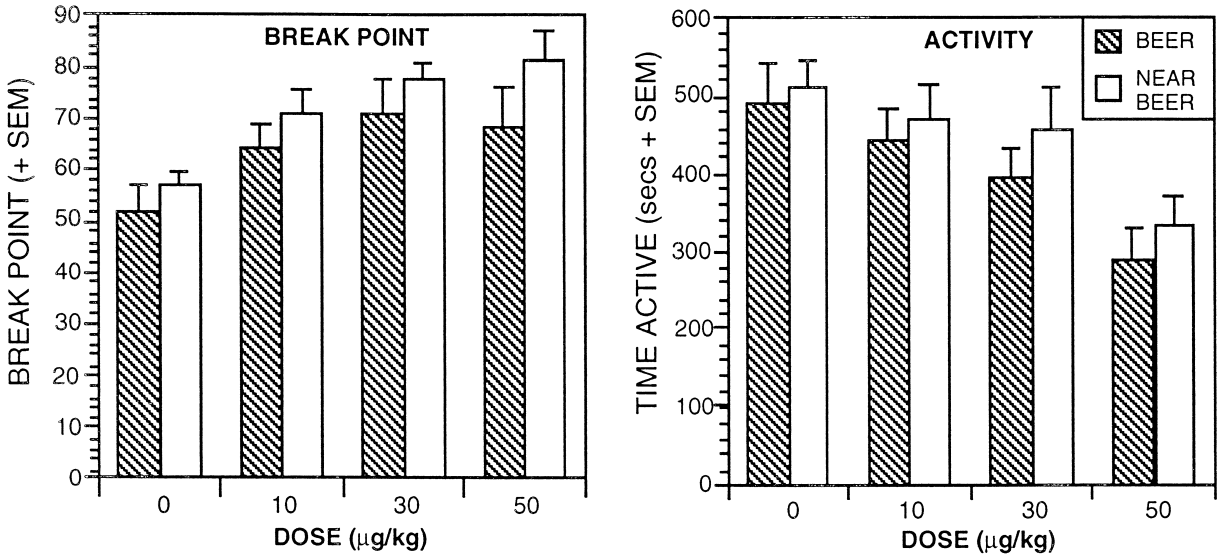

Fig. 1. Effects of CP 55,940 on break points for beer or near-beer (left) and on locomotor activity (right).

Analysis of locomotor activity showed a strong trend towards a decrease in activity with the 10 μg/kg dose ($F(1,14) = 5.13$, $P = 0.04$) and a significant reduction with the 30 μg/kg dose ($F(1,14) = 8.60$, $P < 0.025$). There was also a strong tendency towards a group × drug interaction effect with the 10 μg/kg dose ($F(1,14) = 4.16$, $P = 0.06$) suggesting a greater locomotor suppressant effect of this dose in rats receiving alcohol.

3.3. Reversal of CP 55,940 effects with naloxone or SR 141716

The data for the third experiment are shown in Fig. 3. One rat from the near-beer group did not complete the experiment due to highly variable intake during baseline. Analysis indicated that break points were significantly increased by the 30 μg/kg dose of CP 55,940 ($F(1,21) = 37.82$, $P < 0.0001$). In contrast, the combination of CP 55,940 and SR 141716 produced break points that did not differ from vehicle ($F(1,21) = 1.09$, $P = 0.3$), while the combination of CP 55,940 and naloxone caused a significant decrease in break points ($F(1,21) = 11.81$, $P < 0.01$).

There was also a significant group × drug interaction effect on break points with the combination of CP 55,940 and naloxone ($F(1,21) = 11.59$, $P < 0.01$). This reflects a decrease in the break point with the naloxone and CP 55,940 combination in the beer group but not in the near-beer group. There was also a near-significant group × drug interaction effect with the contrast comparing CP 55,940 and vehicle, suggestive of a greater facilitation in the near-beer group ($F(1,21) = 4.40$, $P = 0.048$).

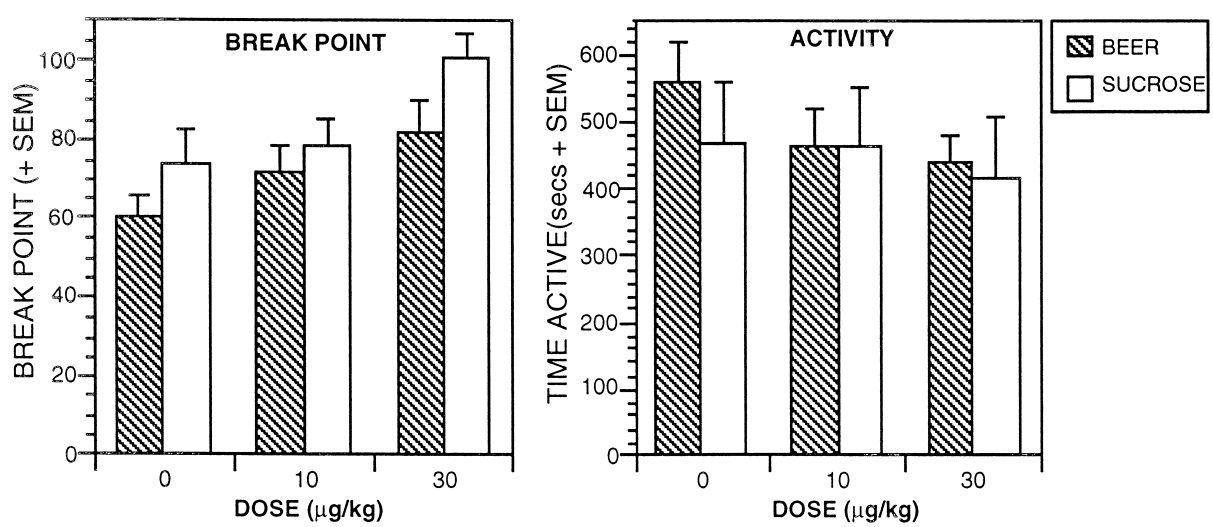

Fig. 2. Effects of CP 55,940 on break points for beer or sucrose (left) and on locomotor activity (right).

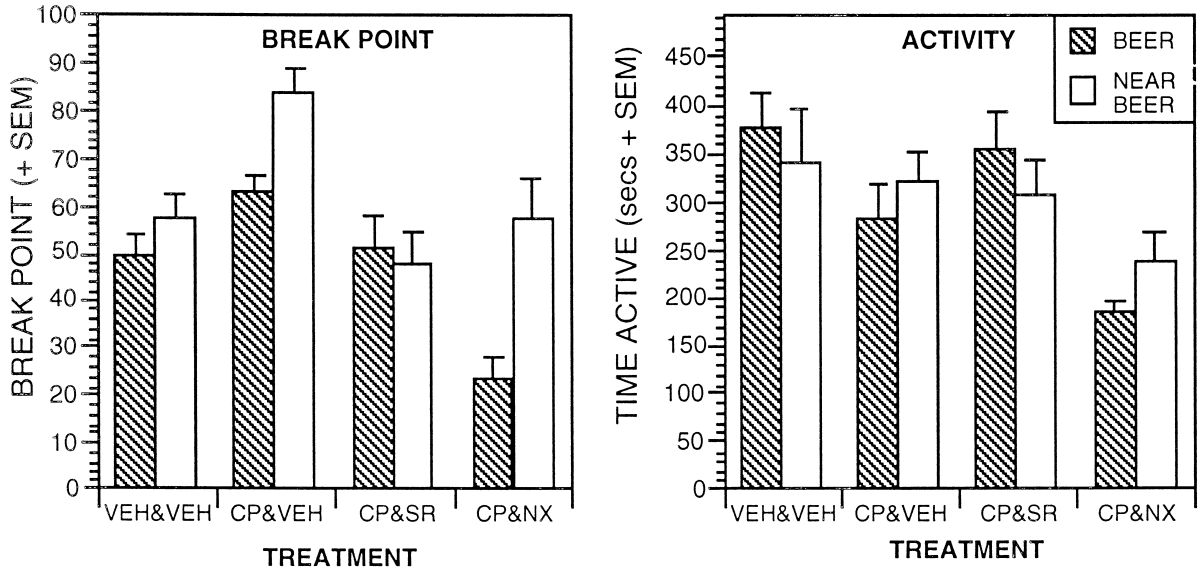

Fig. 3. Effects of CP 55,940 either alone or in combination with SR 141716 (1.5 mg/kg) or naloxone (2.5 mg/kg) on break points for beer or near-beer (left) and on locomotor activity (right). Abbreviations: VEH = vehicle, CP = CP 55,940, NX = naloxone, SR = SR 141716.

There was only a tendency towards an inhibition of locomotor activity with either the 30 μg/kg dose ($F(1,21) = 2.83$, $P = 0.11$) or the combination of CP 55,940 and SR 141716A ($F < 1.8$). However, the combination of CP 55,940 and naloxone produced a strong overall inhibitory effect on locomotor activity ($F(1,21) = 23.88$, $P < 0.001$).

4. Discussion

The present results show a clear facilitatory effect of the cannabinoid CB_1 receptor agonist CP 55,940 on the motivation to consume beer in rats. The effect was dose-dependent with a peak at 30 μg/kg and was cannabinoid CB_1 receptor mediated since SR 141716 was able to completely block the facilitation. As such these results support the hypothesis that stimulation of cannabinoid CB_1 receptors may promote alcohol craving.

Some caution is necessary in this conclusion, however, since the effect of CP 55,940 was seen across beverages containing different ethanol concentrations and was also seen with sucrose solution, which contains no alcohol. There was even some suggestion of a greater facilitatory effect of CP 55,940 in the near-beer group than the beer group in the final experiment. This invites the speculation that the facilitatory effect on beer intake represents little more than an increase in the desire to consume any palatable beverage, regardless of whether it contains alcohol or not. This would be in line with the known stimulatory effects of cannabinoid CB_1 receptor agonists on consumption of palatable foods seen in both humans and rats (Foltin et al., 1986, 1988; Milano et al., 1988; Mattes et al., 1994; Williams et al., 1998). This situation is reminiscent of a previous study that documented a facilitatory influence of morphine on beer intake in rats (Nichols et al., 1991). The authors were unable to determine in this case whether this effect represented anything more than a general stimulatory effect on appetite for any palatable beverage.

Nonetheless, some arguments can be made in favour of the hypothesis that cannabinoids specifically affect the craving for alcohol. In recent work involving the same lick-based progressive ratio paradigm used in the present study we have found that SR 141716 exerts a much more powerful inhibitory effect on the motivation for beer than for near-beer (Gallate and McGregor, 1999). This was taken as evidence for a relatively specific mediation of alcohol craving by cannabinoid CB_1 receptors. It might then be asked why SR 141716 did not exert a greater effect on the motivation for beer than near-beer when given in conjunction with CP 55,940 in the present study. The answer is presumably that the dose given (1.5 mg/kg) was sufficient to cancel out the effects of CP 55,940, but not to have any further inhibitory effect. Our previous work has shown that an effective dose of SR 141716, when given alone, for decreasing the motivation for beer and near-beer is 1–3 mg/kg (Gallate and McGregor, 1999). It is therefore conceivable that a 3 mg/kg dose of SR 141716 dose would not only reverse the facilitatory effects of CP 55,940 seen in the present study, but also act further to inhibit the motivation for near-beer and (in particular) beer.

In contrast to SR 141716, the combination of naloxone with CP 55,940 resulted in a much greater inhibitory effect in the motivation for beer relative to near-beer. Thus while naloxone merely reversed the facilitatory effects of CP 55,940 in the near-beer group, it caused a further dramatic inhibition of responding in rats given beer. In previous

work we have shown that naloxone given alone exerts a greater inhibitory effect on the motivation for beer compared to near-beer (Gallate and McGregor, 1999), consistent with other demonstrations of opioid receptor mediation of the reinforcing effects of alcohol (Herz, 1997).

There may be two actions of naloxone with respect to the present data: a reversal of the general stimulatory effect of CP 55,940 on appetite which applies to both beer and near-beer conditions, and a more specific inhibitory effect on the desire for alcohol which applies only to the beer condition. The former effect is seen in the existing literature with evidence that naloxone can reverse the facilitatory effect of Δ^9 tetrahydrocannabinol on the intake of palatable mash (Williams et al., 1998) and on feeding elicited by stimulation of the lateral hypothalamus in rats (Trojniar and Wise, 1991). Such results suggest that cannabinoids modulate appetite, not directly, but via an indirect influence on brain opioid systems. Evidence for an opioid component of cannabinoid action with respect to analgesia (Smith et al., 1998) and reinforcement (Gardner and Lowinson, 1991; Tanda et al., 1997) has also been reported.

It is notable that the combination of naloxone and CP 55,940, unlike the SR 141716 and CP 55,940 combination, caused a significant reduction in locomotor activity in the near-beer and beer groups, with the effect particularly strong in the latter group. The exact significance of this effect is unclear, although it is interesting to note that naloxone appears to magnify rather than reverse the locomotor suppressant effects of the cannabinoid. There is at least one previous report that naloxone, at doses similar to that used in the present study, reduces spontaneous activity and exploration in rats (Lukaszewska and Klepaczewska, 1997). The present result may then simply reflect the summation of separate inhibitory effects of CP 55,940 and naloxone on locomotor activity. The intake of considerable levels of alcohol, in the beer group rats, may explain why locomotor activity is even further suppressed in this group.

Finally, it is worth noting that the present study introduces a method with which the stimulatory effects of drugs on the desire for both alcoholic and non-alcoholic beverages can be readily assessed. In our experience, documenting such stimulatory effects using free access paradigms can be very difficult, since rats will tend to drink palatable solutions such as beer or sucrose in maximal amounts under baseline conditions. This avid consumption results in a ceiling effect, making it difficult to show any increased motivation produced by a drug. In contrast, under the progressive ratio paradigm used here, rats do not achieve intakes that will cause satiety, so that an upward shift in motivation produced by a drug treatment can be readily assessed.

In conclusion, the present paper shows that moderate doses of a cannabinoid CB_1 receptor agonist clearly stimulate the motivation to consume palatable beverages in rats. Whether there is also a specific enhancement of the motivation to consume alcohol will have to be decided by further, more refined, experimentation.

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