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The motivation for beer in rats: effects of ritanserin, naloxone and SR 141716

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Abstract Rats were given two weeks of home cage access to either "near-beer" (a beverage that tastes like beer but contains < 0.5% ethanol v/v) or near-beer with added ethanol (4.5% v/v), which is simply referred to as "beer". The two groups of rats (near-beer and beer) were then trained on a "lick-based progressive ratio paradigm" in operant chambers in which an ever increasing number of licks had to be emitted for each successive fixed unit of near-beer or beer delivered. Break points (the ratio at which responding ceased) for near-beer and beer were approximately equal under baseline conditions. Rats were then tested for the effects of the $5HT_{2A/2C}$ receptor antagonist ritanserin (0.625, 2.5 or 10 mg/kg), the opioid receptor antagonist naloxone (0.625, 2.5 or 10 mg/kg) or the cannabinoid CB1 receptor antagonist SR 141716 (0.3, 1 or 3 mg/kg). All three drugs caused a dose-dependent reduction of break-points and locomotor activity in both the beer and near-beer groups. However, the effects of SR 141716 and naloxone, but not ritanserin, on break-points were significantly more pronounced on rats drinking beer compared to those drinking near-beer. There were no such differential effects of any of the drugs on locomotor activity across the two groups. These results suggest that both SR 141716 and naloxone differentially affect the motivation to consume alcoholic beverages and may thus have potential as drugs for the treatment of alcohol craving.

Key words Alcohol · Beer · Craving · Rat · Naloxone · SR 141716 · Ritanserin

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Introduction

Recognition of the widespread harm caused by alcohol abuse has led to urgency in the search for drugs that are effective in blocking alcohol craving. Several candidate drugs have recently emerged, and some, such as naltrexone and acamprosate, have already shown some promise in clinical practice (Spanagel and Zieglgansberger 1997; Weinreib and O'Brien 1997; Zernig et al. 1997). Preclinical studies involving rodents play a potentially important role in identifying putative anti-craving drugs that may be effective at the clinical level (Myers 1994; Spanagel and Zieglgansberger 1997). Yet studies of alcohol craving in rodents face certain difficulties. One problem is the inherent reluctance of many rodent species to consume ethanol solutions (McGregor et al. 1998). A second problem is the difficulty involved in finding a satisfactory operational definition of craving in animal subjects (Markou et al. 1993).

Recent work from our laboratory has addressed both of these issues with the development of a novel alcohol craving paradigm that uses beer as a test solution (McGregor et al. 1998; Topple et al. 1998). Beer has been chosen since 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), and will drink them to a much greater extent than equivalent strength solutions of ethanol in water (McGregor et al. 1998).

While controversy continues as to how best to measure craving in rodents, some have suggested that progressive ratio schedules of reinforcement have some utility (Markou et al. 1993; Richardson and Roberts 1996). In such paradigms, subjects have to emit a progressively greater number of responses for each successive fixed unit of reinforcement. The ratio at which the rat stops responding, known as the "break-point", is thought to offer an index of the extent to which the reinforcer is "craved". Use of progressive

ratio methodologies is common in lever press paradigms for intravenous stimulant or opiate reinforcers (Richardson and Roberts 1996). However, we have recently developed a lick-based progressive ratio paradigm that requires rats to make an ever increasing number of licks at a lick tube for a fixed volume of beer to be delivered down the tube (McGregor et al. 1998). In recent work, we have used this paradigm to assess the effects of food deprivation and cocaine on the motivation to consume beer (McGregor et al. 1998).

An important issue in identifying anti-craving compounds relates to the specificity of their effects. A drug that blocks craving for alcohol is unlikely to be clinically useful if it also blocks appetite for food or other natural reinforcers. This is not a trivial issue, since many drugs that affect alcohol intake also affect intake of palatable foods (Apfelbaum and Mandenoff 1981; Massi and Marini 1987; Schwarz-Stevens et al. 1992; Cleary et al. 1996; Arnone et al. 1997). Some researchers have suggested that rats primarily drink alcoholic beverages for their caloric content rather than for the intoxication they produce (Richter (1953), but see also Gill et al. (1996)). If this were true, then we might expect any putative anti-craving drug to exert an equivalent effect on the motivation for beer and any palatable non-alcoholic beverage. To examine and control for this, we test the effects of anti-craving drugs on the motivation to consume beer (containing 4.5% ethanol) and compare them with effects on the motivation for 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. An ideal anti-craving compound should therefore have the effect of decreasing the motivation to consume beer while barely affecting the motivation for near-beer.

In the present study, we sought to develop this paradigm further by testing the effects of three drugs that have shown clinical or preclinical potential in blocking alcohol craving. Naloxone, an opioid receptor antagonist, has been shown to reduce alcohol intake in numerous studies with rodents (Herz 1997), and the closely related drug, naltrexone has now been specifically approved in the United States for treatment of alcohol craving in humans (Weinreib and O'Brien 1997). The $5HT_{2A/2C}$ receptor antagonist ritanserin has also been found to reduce alcohol consumption in animal studies (Meert et al. 1991; Panocka and Massi 1992), although the effect is somewhat equivocal (Myers and Lankford 1993; Panocka et al. 1993). Clinical results with ritanserin have also been mixed (Monti and Alterwain 1991; Johnson et al.1996). Finally, two recent studies with rats have indicated that the cannabinoid CB1 receptor antagonist SR 141716 reduces alcohol intake in rats (Arnone et al. 1997; Colombo et al. 1998). This has suggested a hitherto unexplored role for the endogenous cannabinoid system of the brain in mediating the reinforcing effects of alcohol.

Materials and methods

Subjects

The subjects were 48 male Wistar rats of approximately 120 days of age at the start of the experiment. They were housed in groups of six in large plastic tubs with ad libitum access to food and water in a reverse light-dark cycle colony (lights off at 8.30 a.m., lights on 8.30 p.m.). All behavioral testing occurred during the dark cycle. The first 24 rats were used to test the effects of ritanserin while the remaining 24 were tested with naloxone, followed 3 weeks later by SR 141716. Within each batch of 24 rats, 12 received near-beer throughout the experiment while the other 12 received 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.

Apparatus

Apart from the initial home cage phase of the experiment (see below), rats received beer or near-beer in custom "drink chambers". These consisted of eight standard operant chambers ($30 \times 50 \times 25.5$ cm) with metal grid floors as described previously (McGregor et al. 1998; Topple et al. 1998). 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 black 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 beer or near-beer. 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 a rat, but generally did not trigger when the rat was licking at the lick tube. The output 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.

Drugs and beverages

Rats in the near-beer groups were given "Birrell's Premium" (Coopers Ltd, South Australia), which contains < 0.5% ethanol by volume. Rats in the "beer" groups received this same solution with 4.0% additional ethanol. As in previous studies (Nichols et al. 1991; McGregor et al. 1998; Topple et al. 1998) the beer was decarbonated prior to use in experiments by being left uncapped overnight and was presented to the rats at room temperature.

SR 141716 (Sanofi Recherche), a selective antagonist at the CB1 cannabinoid receptor (Rinaldi-Carmona et al. 1994), was initially dissolved in 100% ethanol. Tween 80 was added to this solution

and the ethanol completely evaporated under a stream of nitrogen gas. The resulting solution was diluted with 0.9% saline to give a final dilution of 1:19 (Tween 80:saline). Ritanserin (Jansenn-Cilag) was similarly dissolved to a final dilution of 1:9 (Tween 80:saline). Naloxone (Research Biochemicals) was dissolved in saline.

Three doses of each drug were tested, namely 0.3, 1 and 3 mg/kg SR 141716, 0.625, 2.5 and 10 mg/kg naloxone and 0.625, 2.5 and 10 mg/kg ritanserin. Dose ranges for each drug were chosen on the basis of key recent studies on the effects of these drugs on ethanol consumption in rats (Panocka and Massi 1992; Davidson and Amit 1996; Arnone et al. 1997).

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

Procedure

The first experiment assessed the effects of ritanserin and the second tested the effects of naloxone and SR 141716. Identical training procedures were followed in each experiment, involving two groups (beer and near-beer) and four different phases which occurred over consecutive days: home cage pre-exposure, drink training, progressive ratio training and drug testing.

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 3 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. On every day of this phase, the groups of rats drank the entire 365 ml beer or near-beer that was available.

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 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. 1998), most rats were drinking all of the available fluid in each test session.

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 with ratios for each successive trial derived from the following equation (see McGregor et al. 1998): licks required for 0.1 ml drop of beer or near-beer = $3 + 0.005 \times (0.25 \times \text{trial})^3$.

Previous work from our laboratory (McGregor et al. 1998) has shown that this equation is optimal, since it ensures 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 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. Four rats from the ritanserin group (two beer and two near-beer) either failed to show adequate intake or stable baseline responding and were dropped from the study, leaving an n of 10 per group. Immediately following this last baseline session, drug testing commenced.

Drug testing

Drug testing for each drug occurred over 8 consecutive days using a within-subjects design where each rat received each dose of the drug and vehicle in a randomized order. A drug dose was given every second day and 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.

In the second experiment, where the same rats were tested first on naloxone and then on SR 141716, a 3-week gap was interspersed between the two drug testing phases. For the first 2 weeks of this interval, rats were returned to home cage access to either beer or near-beer as described above. On the third week, rats were run on the progressive ratio paradigm to re-establish baseline responding.

Statistics

Data for break-point and locomotor activity under vehicle and the three drugs doses were compared across the beer and near-beer groups using planned contrasts. The effects of drug doses were analyzed via linear and quadratic trend analysis (Keppel 1991). Of interest was the possibility of a group by linear (or quadratic) trend interaction effect which would suggest that a given drug was differentially affecting the motivation to consume beer relative to near-beer. The significance level used for all contrasts was 0.05.

Results

The data for break-point and locomotor activity for the three drugs tested are shown in Fig. 1.

Ritanserin

Comparison of beer and near-beer groups for break points under ritanserin showed no significant effect of group ($F < 1.4$). There was a significant linear trend with dose ($F1,18 = 51.38$, $P < 0.001$) but no significant quadratic trend ($F < 1$). There were no significant group by linear or quadratic trend interactions ($Fs < 1$), suggesting that the drug doses had essentially the same effect on beer and near-beer break-points.

With respect to locomotor activity, there was no significant group effect ($F < 1$). There was a significant overall linear trend with dose ($F1,18 = 35.86$, $P < 0.001$) but no significant quadratic trend ($F < 1$). The group by linear or quadratic trend interaction effects were not significant ($Fs < 1$). These data show that ritanserin produced an overall dose-dependent

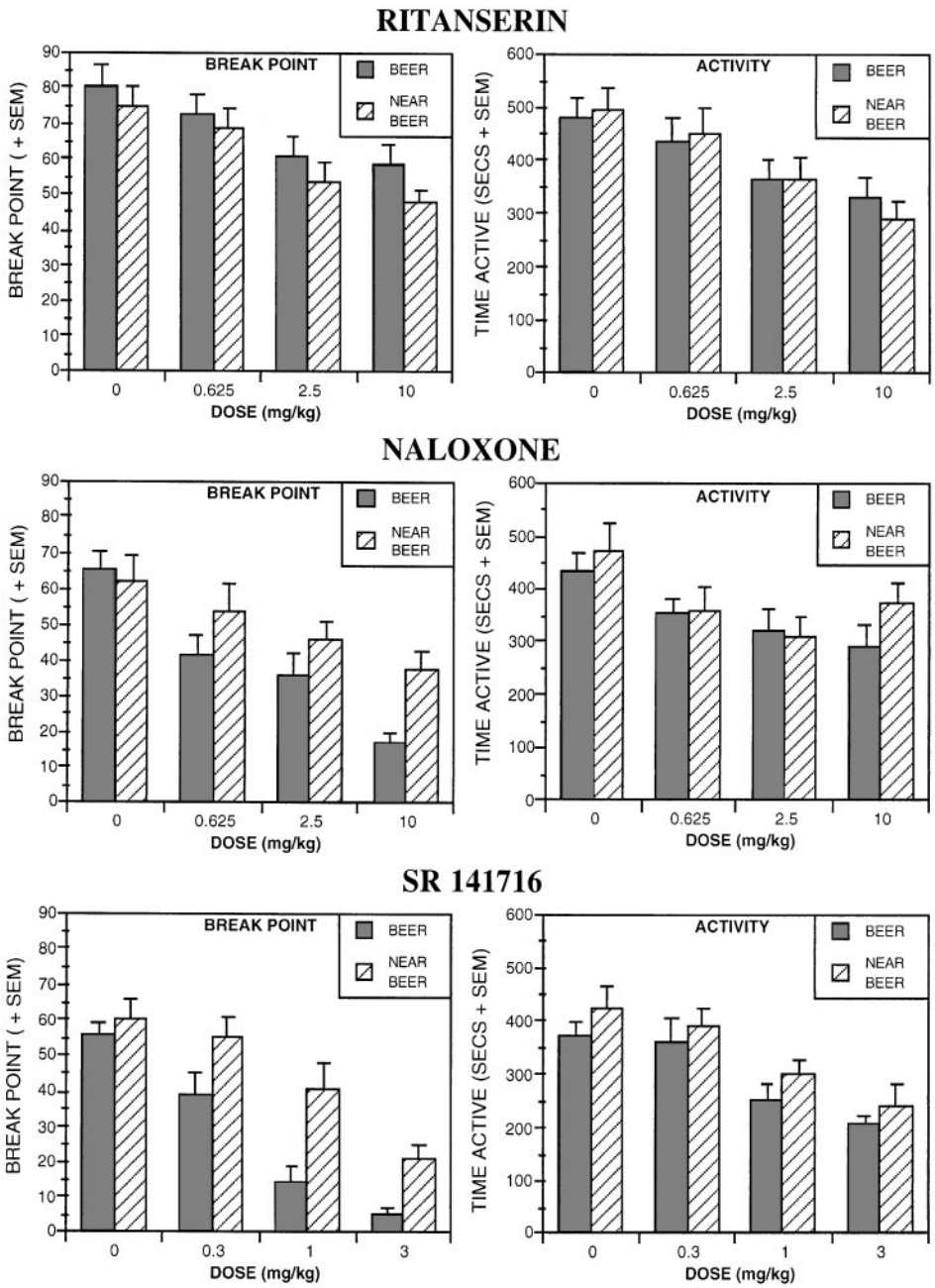

Fig. 1 Effects of ritanserin (*upper*), naloxone (*middle*) and SR 141716 (*lower*) on break-points (*left*) for beer ■ or near-beer ▨ and locomotor activity (*right*)

decrease in locomotor activity that was similar across the beer and near-beer groups.

Naloxone

Comparison of beer and near-beer groups for break-points under naloxone showed a tendency towards a significant group effect ($F1,22 = 3.21$, $P = 0.087$). There was a significant linear trend with dose ($F1,22 = 100.98$, $P < 0.001$) but no significant quadratic trend ($F < 1$). There was a significant group by linear trend interaction ($F1,22 = 8.30$, $P < 0.01$), suggesting that the drug doses had a differential effect on beer and near-beer break-points. There was no significant group by quadratic trend effect ($F < 1$). It can be seen from Fig. 1 that the group by linear trend interaction reflects naloxone causing greater decreases in break-points for beer than for near-beer.

With respect to locomotor activity, there was no significant group effect ($F < 1$). There was a significant overall linear trend with dose ($F1,22 = 16.15$, $P < 0.001$) and a significant quadratic trend ($F1,22 = 7.02$, $P < 0.05$). The group by linear or quadratic trend interaction effects were not significant ($Fs < 2.2$). The significant linear trend reflects an overall dose-related decrease in locomotor activity with naloxone. However,

it is clear from Fig. 1 that the drug effect is not exclusively linear, since there is a small upturn in locomotor activity in the near-beer group with the highest naloxone dose. This non-linear effect is reflected in the significant overall quadratic trend that was obtained.

SR 141716

Comparison of beer and near-beer groups for break-points under SR 141716 showed a significant effect of group ($F1,22 = 8.47$, $P < 0.01$). There was also a significant overall linear trend with dose ($F1,22 = 220.37$, $P < 0.001$) but no significant quadratic trend ($F < 1$). The group by linear trend interaction approached significance ($F1,22 = 4.24$, $P = 0.051$) and a significant group by quadratic trend interaction was found ($F1,22 = 5.25$, $P < 0.05$). These results suggest that the drug had a differential action on the beer and near-beer groups. As can be seen in Fig. 1, SR 141716 appeared to have a more profound inhibitory effect on break-points for beer compared to near-beer.

With respect to locomotor activity, there was no significant group effect ($F < 1.4$). There was a significant overall linear trend with dose ($F1,22 = 66.62$, $P < 0.001$) but no significant overall quadratic trend ($F < 1$). The group by linear or quadratic trend interaction effects were not significant ($Fs < 1$). These results show that SR 141716 caused an overall dose-dependent decrease in locomotor activity, with a similar effect across the beer and near-beer groups.

Discussion

The present study introduces a potentially useful methodology for studying the effects of drugs on the motivation to consume alcohol. The use of beer as a test solution allows rapid acquisition of alcohol intake as witnessed by the high levels of home cage and limited access consumption during the acquisition phases of the experiment. This intake occurs without recourse to food deprivation, selective breeding, sucrose fading or any of the other artificial techniques that are often employed to make rats drink dilute ethanol solutions (Deitrich 1992).

The use of near-beer offers a potentially powerful control for the effects of drugs on appetite. As noted above, it is important to show that a drug that has anti-craving potential does not block appetite for food as well as alcohol. The fact that naloxone and SR 141716 affected the motivation for beer more profoundly than that for near-bear, suggests that both of these drugs have at least a partly specific anti-alcohol effect. This differential effect also suggests that the alcohol in beer serves as an important factor modulating its intake. In other words, the rats are unlikely to be drinking the beer for its palatability alone. This observation tends to rebut the suggestion of Richter, more than 45 years ago, that beer and wine are simply treated as "foods" by rodents (Richter 1953).

Nonetheless, it should be noted that adding ethanol to near-bear (as was done to make the beer used in the present study) also adds calories. It therefore remains possible that the differential effect of naloxone and SR 141716 on beer compared to near-beer reflects an effect related to the higher calorie content of the beer. While future studies may be necessary to rule out this hypothesis completely, we have previously found that SR 141716 has a greater inhibitory effect on the intake of beer than on the intake of a calorie-matched sucrose solution (McGregor et al. 1997). This observation, in combination with the present results, suggests that the SR 141716 effect is best explained as an effect on the motivation for alcohol.

An interesting aspect of the present data is the clear qualitative difference between ritanserin and the other two drugs. Not only were the absolute magnitudes of effects with ritanserin small, but ritanserin had an almost equivalent inhibitory effect on break points for beer and near-beer. This suggests a non-specific rather than a specific effect on the motivation to consume ethanol. Since ritanserin tends to increase rather than decrease food intake in rats (Massi and Marini 1987; Fletcher1988), it is unlikely that this non-specific effect is a simple suppression of appetite. More likely, the effect reflects a depression of ongoing activity by higher doses of ritanserein, as has been documented in at least one previous study (Peltier et al. 1994). These results with ritanserin are also consistent with previous studies that have failed to show a specific effect on ethanol intake in rats with this drug (Myers and Lankford 1993; Panocka et al. 1993). In addition, clinical experience with ritanserin has been rather disappointing, with key studies showing at best only marginal effects (Naranjo et al. 1995; Johnson et al. 1996).

In contrast, both naloxone and SR 141716 showed promising results, causing a significantly greater suppression of beer than near-beer intake. In the case of naloxone, many animal studies have demonstrated a suppression of ethanol intake in rats treated with this drug (Myers and Critcher 1982; Sandi et al. 1988; Froehlich et al. 1990; Davidson and Amit 1996). However, naloxone is also found to suppress intake of palatable foodstuffs (Apfelbaum and Mandenoff 1981; Schwarz-Stevens et al. 1992; Cleary et al. 1996), raising doubt about the specificity of the alcohol effect (Herz 1997). The present data show that indeed, naloxone is able to suppress intake of a palatable beverage containing minimal ethanol (namely near-beer), but that its effect on an ethanol containing solution is proportionately greater. These results concur with recent reports that the closely related drug, naltrexone, exerts a specific anti-craving effect for alcohol in humans (O'Brien et al. 1996; Weinrieb and O'Brien 1997).

With respect to SR 141716, only two studies have so far tested the effects of this drug on ethanol intake in rats (Colombo et al. 1998; Arnone et al. 1997). Both have reported a suppression of intake of dilute ethanol solutions. However, in one of these studies, the intake of sucrose pellets was also suppressed (Arnone et al. 1997), a general effect on appetite that has recently been replicated in marmosets (Simiand et al. 1998). This raises the same question as with naloxone regarding the specificity of the effect of SR 141716 on alcohol consumption. The present data help to clarify this issue by showing a much more powerful suppression of beer intake compared to near-beer intake with SR 141716. The fact that the drug had equivalent suppressant effect on locomotor activity in the beer and near-beer groups shows that the greater effect on responding for beer was not due to a synergistic effect of SR 141716 and ethanol on general locomotor activity.

Overall, these results suggest that both opioid and cannabinoid neural systems play an important role in mediating ethanol reinforcement. While this role of opioid systems has already been well documented and discussed (Herz 1997), the role of cannabinoid systems has only emerged very recently (Arnone et al. 1997; Colombo et al. 1998). With the benefit of hindsight, this role should not be particularly surprising, given the similar euphorogenic effects of alcohol and cannabis, their frequent co-abuse (Swift et al. 1997) and their synergistic effects on behaviour (Chesher et al. 1976). It would be of great interest to determine the exact mechanism whereby ethanol interacts with brain cannabinoid systems, with one clear possibility being that it enhances the release or blocks the reuptake of endogenous cannabinoid ligands such as anandamide.

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