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The effect of the dopamine D2 receptor antagonist raclopride on the pattern of licking microstructure induced by midazolam in the rat

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Abstract

The role of dopamine in the effects of midazolam on ingestive behaviour was investigated using microstructural analysis of licking behaviour in the rat. Midazolam (1.8 mg/kg i.p.) was administered alone or in combination with the dopamine D2 receptor antagonist raclopride (0.1 and 0.3 mg/kg i.p.). The effect on licking patterns during 60 s exposure to a range of concentrations of sucrose solution was recorded using an automated lickometer. Midazolam increased the total number of licks via an increase in mean bout duration, an effect consistent with the proposal that these drugs enhance palatability. Midazolam also decreased the intrabout lick rate, probably because of muscle relaxant effects. Pre-treatment with raclopride blocked midazolam-induced increases in mean bout duration, at doses that by themselves were ineffective, but did not reverse the decrease in intrabout lick rate. These data point to the interdependence of benzodiazepine and dopamine substrates in the mediation of palatability. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Benzodiazepine; Dopamine; Licking behaviour; Bout structure; Palatability

1. Introduction

A variety of drugs that act as agonists at benzodiazepine receptors induce a strong hyperphagic response in many species including humans (Cooper, 1980; Evans et al., 1999; Foltin et al., 1985; Haney et al., 1997; Mansbach et al., 1984). This effect can be dissociated from the anxiolytic properties of benzodiazepines (Cooper, 1980), and is most likely explained by an enhancement of palatability (Berridge and Pecina, 1995; Cooper and Higgs, 1996). Consistent with this assertion is the effectiveness of benzodiazepines in numerous behavioural paradigms thought to measure palatability, such as the taste preference (Cooper and Green, 1993; Cooper and Yerbury, 1988; Roache and Zabik, 1986), sham feeding (Cooper et al., 1997), and taste reactivity tests (Gray and Cooper, 1995; Berridge and Treit, 1986; Treit and Berridge, 1990). More recently, this palatability hypothesis has been further validated using microstructural analysis of the pattern of licking behaviour in rats ingesting liquid diets (Higgs and Cooper, 1996a, 1997, 1998).

This approach involves logging the occurrence of individual licks using an automated lickometer system (for a review of such systems, see Weijnen, 1998). The pattern of licks is then divided up into clusters, or bouts, according to a predetermined criterion. These data can then subjected to further analysis e.g. calculation of the frequency and duration of bouts. The advantage of this method is its high temporal resolution and the fact that it provides a direct metric of the behaviour used by an animal to ingest fluids. We have shown that the benzodiazepine receptor agonist midazolam selectively increases licking behaviour via an increase in the mean duration of bouts (Higgs and Cooper, 1997, 1998). This effect mirrors that observed following an increase in the concentration of palatable fluids (Davis and Smith, 1992; Spector et al., 1998) and is therefore consistent with the assertion that benzodiazepines enhance palatability. Specific benzodiazepine receptor mediation of this hedonic enhancement has also been confirmed by the finding that the increase in mean bout duration is blocked by administration of the benzodiazepine receptor antagonist flumazenil (Higgs and Cooper, 1997). Hence, convergent evidence from multiple tests indicates that benzodi-

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azepines stand as the best-documented example of drug-induced enhancement of palatability.

In contrast to behavioural examination of benzodiazepine-induced hyperphagia, relatively little is known about the neurochemical basis of this effect. Although the primary effect of benzodiazepines is to enhance gamma amino butyric acid (GABA) neurotransmission via a binding site on the $GABA_A$ receptor complex, there is some evidence to suggest that endogenous opioid activity may be involved. For example, it has been shown that benzodiazepine receptor agonists modulate the release of endogenous enkephalins in the brain (Duka et al., 1979; Wuster et al., 1980). In addition, benzodiazepine-induced hyperphagia is blocked by pre-treatment with opioid receptor antagonists (Jackson and Sewell, 1985; Stapleton et al., 1979; Britton et al., 1981). Perhaps most convincingly though, recent evidence from our laboratory using the microstructural paradigm has demonstrated that pre-treatment with the opioid receptor antagonist naloxone specifically blocks the effect of midazolam on mean bout duration (Higgs and Cooper, 1997).

Additional evidence suggests that benzodiazepine enhancement of palatability responding may also be dopamine-dependent. Schneider et al. (1986) have shown that the D1 receptor antagonist SCH23390 ((+)-7-chloro-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro(1H)-3-benzazepinemaleate) and the D2 receptor antagonist raclopride decrease overall intake in sham-feeding animals via a reduction of the size of licking bouts. This pattern of results is similar to those produced by midazolam although in the opposite direction, which is suggestive of a possible interaction between benzodiazepines and dopamine in the control of palatability. In the present experiment, we adopted the microstructural approach to investigate the possibility that endogenous dopamine release is important for benzodiazepine-induced effects on licking behaviour. The effect of pre-treatment with the dopamine D2 receptor antagonist raclopride (at doses which by themselves are behaviourally ineffective), on the pattern of licking behaviour induced by the benzodiazepine receptor agonist midazolam was examined.

2. Material and methods

2.1. Animals

Adult male hooded Lister rats (Charles River, UK) weighing approximately 400 g at the beginning of training were used. They were housed in pairs in plastic cages in a room with a constant temperature of 21 ± 2°C, and were maintained on a 12-h light:dark cycle (lights on at 0600 h). Food pellets (Special Diet services, RM1 (E), Cambridge, UK) and water were available ad lib, except during testing. All testing was conducted in the light phase between 0900 and 1200 h. The experiments were carried out in accordance with the terms of the Animals (Experimental Procedures) Act, 1986, under license from the UK Home Office.

2.2. Drugs

The dopamine D2 receptor antagonist raclopride (Sigma, Poole, UK) at doses of 0.1 and 0.3 mg/kg was dissolved in distilled water and injected intraperitoneally (i.p.) 30 min before testing. These doses were chosen on the basis of pilot studies, which had confirmed their lack of behavioural effect. The benzodiazepine receptor agonist midazolam maleate (Roche, Basel, Switzerland) was prepared for injection by dissolving in distilled water and injected i.p. 15 min prior to testing. The dose used was 1.8 mg/kg, which has been shown to enhance licking behaviour in non-deprived rats (Higgs and Cooper, 1997, 1998). All drugs were injected in a volume of 1 ml/kg.

2.3. Test solutions

Rats had access to four concentrations of sucrose solution (1%, 3%, 10% and 30%) (granulated cane sugar, Tate and Lyle, London, UK), which were made up weight/volume each day using tap water. It has been shown previously that these concentrations stimulate a range of sampling from low (approximately 50 licks in a minute) to just below asymptotic levels (approximately 300 licks in a minute) (Higgs and Cooper, 1997).

2.4. Apparatus

Testing was carried out using an MS80 multistation lick analysis system (Dilog Instruments, Tallahassee, FL, USA), which has been described in detail before (Higgs and Cooper, 1997, 1998). Briefly, rats were placed in a Perspex chamber that had an opening in the centre of the front wall allowing access to a drinking spout. Bottles containing the test solutions were mounted on a metal platform that could be moved backward and forward by a motor. This enabled several concentrations of sucrose to be presented one after another within the same session without intervention from the experimenter. The lickometer was connected to an amplifier that passed less than 60 nA through the rat every time tongue contact was made with the spout. The current was fed to a standard personal computer (Opus Technology, Surrey, UK), which stored the time of each tongue contact to the nearest millisecond.

2.5. Procedure

2.5.1. Training

A group of 10 rats were first well familiarised with the test apparatus and procedure. This involved placing each rat in the test chamber where it had access to a range of sucrose solutions presented sequentially in a different ran-

dom order each day. Each concentration was presented only once in a session for 60 s and there was an inter-trial interval of 10 s. A trial did not start until the rat had made its first lick, so each rat had a full 60 s drinking time from the first tongue contact. However, there was a time out of 200 s after which the next trial commenced if a lick had not been made. This procedure continued until steady baseline levels of licking, measured as total number of licks, were achieved (approximately 10 days). On the 2 days just prior to testing, each rat received a sham injection of distilled water to familiarise it with the injection procedure.

2.5.2. Testing

Following the familiarisation period, the rats received injections of drugs. A repeated-measures design was used in which each animal received injections of vehicle/vehicle, 0.1 mg/kg raclopride/vehicle, 0.3 mg/kg raclopride/vehicle, vehicle, 1.8 mg/kg midazolam, 0.1 mg/kg raclopride/1.8 mg/kg midazolam, 0.3 mg/kg raclopride/1.8 mg/kg midazolam. Following both injections, the animals were returned to the home cage until testing occurred 30 min later. A period of 48 h elapsed between subsequent test sessions, to avoid carry over effects, and the order of drug administration was randomised across rats according to a modified Latin square design. Following the injection-test interval, each rat was placed individually in the test chamber where it had access to all four concentrations of sucrose. Each concentration was presented once only for a period of 60 s. The order of presentation was randomised and there was 10 s inter-trial interval as in training.

2.6. Data analysis

The lick time data were analysed using Dilog software (Ross Henderson, DiLog Instruments, Tallahassee, FL, USA), followed by further processing using the Microsoft Excel spreadsheet programme. The lick data were first grouped into bouts by specifying an upper interlick interval of 400 ms. This definition was used because it had been established in previous studies that an interval of 400 ms was just longer than the break point in a log survivorship lot of interlick intervals (Morris, 1993). The effect of drug administration on various microstructural variables was then examined: the total number of licks, the mean bout duration, the number of bouts and the intrabout lick rate (defined as licks per second within bouts). These data were analysed using a general linear model analysis of variance (ANOVA), because, in occasional cases, there were missing cells due to the failure of some animals to lick for a particular concentration before the end of the time out period. Post hoc analysis of the main effect of drug was made using a Newman–Keuls multiple comparison test. Statistical tests were performed using Sigma Stat (Jandel, San Rafael, CA, USA, 1992–1994). A result was considered statistically significant if $P < 0.05$.

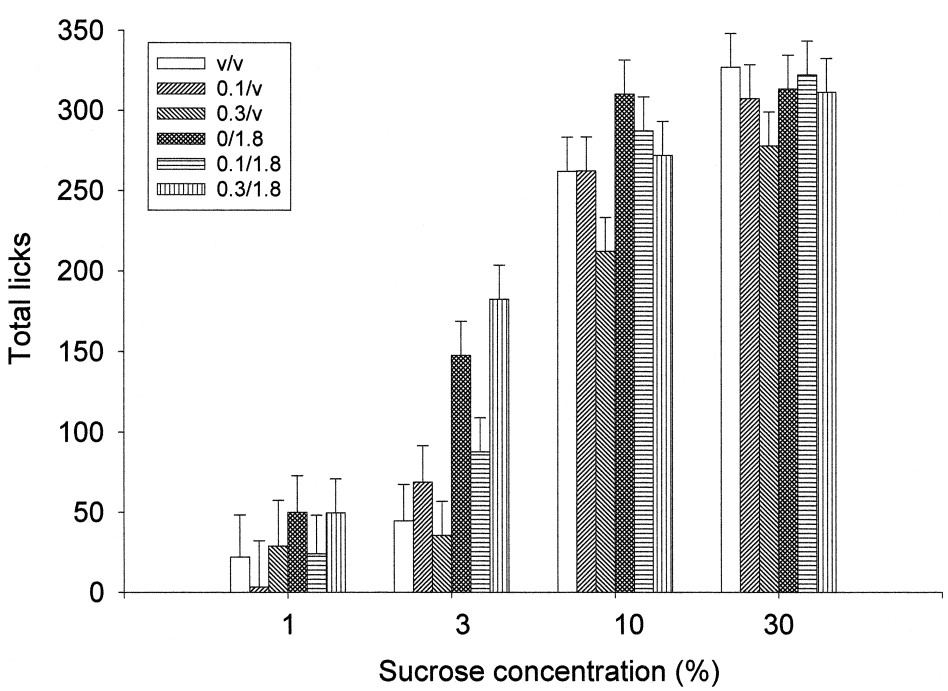

Fig. 1. Lack of attenuation of the stimulatory effect of midazolam on total number of licks by behaviourally inactive doses of raclopride. Rats ($n = 10$) were treated i.p. with 1.8 mg/kg of midazolam alone or in combination with 0.1 and 0.3 mg/kg of raclopride. Data are presented as the total number of licks averaged over all animals (±S.E.M.) for each drug condition at different levels of sucrose concentration (1–30%). Solutions were presented in a brief contact test (60 s access to each concentration within a session).

3. Results

3.1. Total licks

A two-way repeated-measures ANOVA revealed a significant main effect of sucrose concentration ($F_{(3,27)} = 133.78$, $P < 0.01$). Fig. 1 shows that the overall levels of licking increased with increasing concentration. There was also a significant main effect of drug treatment ($F_{(5,45)} = 6.38$, $P < 0.01$), and a significant sucrose concentration × drug treatment interaction ($F_{(15,119)} = 2.18$, $P < 0.05$). Fig. 1 shows that, at the highest concentration of sucrose, there was probably a ceiling effect and no further increase due to midazolam could be seen. Therefore, post hoc analysis on the main effect of drug treatment across all concentrations was carried out. This revealed that overall, midazolam significantly increased the total number of licks ($P < 0.01$), and this increase was not attenuated by pre-treatment with raclopride. Fig. 1 shows that at all concentrations of sucrose, the highest dose of raclopride especially, failed to reverse the increase in total number of licks brought about by midazolam. Additionally, administration of raclopride alone (0.1 and 0.3 mg/kg) did not significantly alter the total number of licks. Fig. 1 shows that this was the case at each concentration of sucrose, although at 10% and 30% concentrations there was a tendency for the 0.3 mg/kg dose of raclopride to reduce total number of licks.

3.2. Mean bout duration

Main effects of sucrose concentration ($F_{(3,27)} = 19.28$, $P < 0.01$ and drug treatment ($F_{(5,45)} = 6.78$, $P < 0.01$) were found, but no significant sucrose concentration × drug treatment interaction ($F_{(15,119)} = 1.28$, $P > 0.05$). Fig. 2 shows that as the concentration of sucrose increased so did the mean bout duration. Post hoc analysis of the main effect of drug treatment showed that the vehicle/vehicle condition differed significantly from the vehicle/midazolam condition ($P < 0.01$). As shown in Fig. 2, midazolam increased the mean bout duration compared with the control condition at the 3%, 10%, and 30% concentrations, although this effect was less marked for the 1% sucrose condition. There was no significant effect of raclopride when administered alone on mean bout duration, but co-administration of raclopride (0.1 and 0.3 mg/kg) and midazolam attenuated the increase in mean bout duration bought about by midazolam ($P < 0.01$). Fig. 2 shows that despite the non-significant interaction term, this reversal was more evident at the higher concentrations of sucrose.

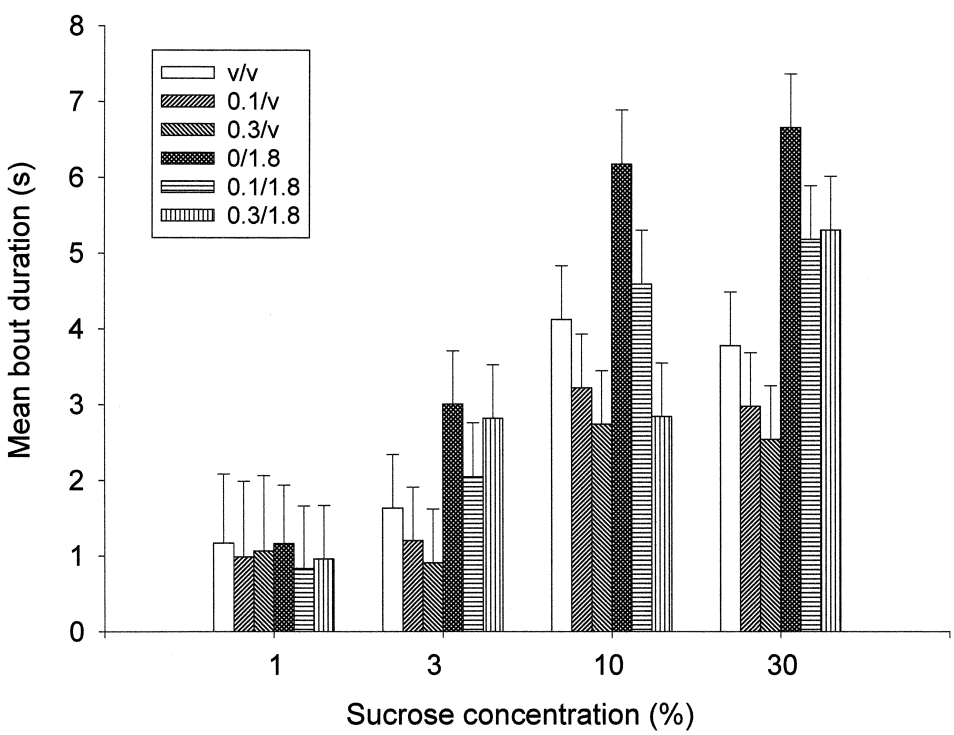

Fig. 2. Attenuation of the stimulatory effect of midazolam on mean bout duration by behaviourally inactive doses of raclopride. Rats ($n = 10$) were treated i.p. with 1.8 mg/kg of midazolam alone or in combination with 0.1 and 0.3 mg/kg of raclopride. Data are presented as the mean bout duration averaged over all animals (±S.E.M.) for each drug condition at different levels of sucrose concentration (1–30%). Solutions were presented in a brief contact test (60 s access to each concentration within a session).

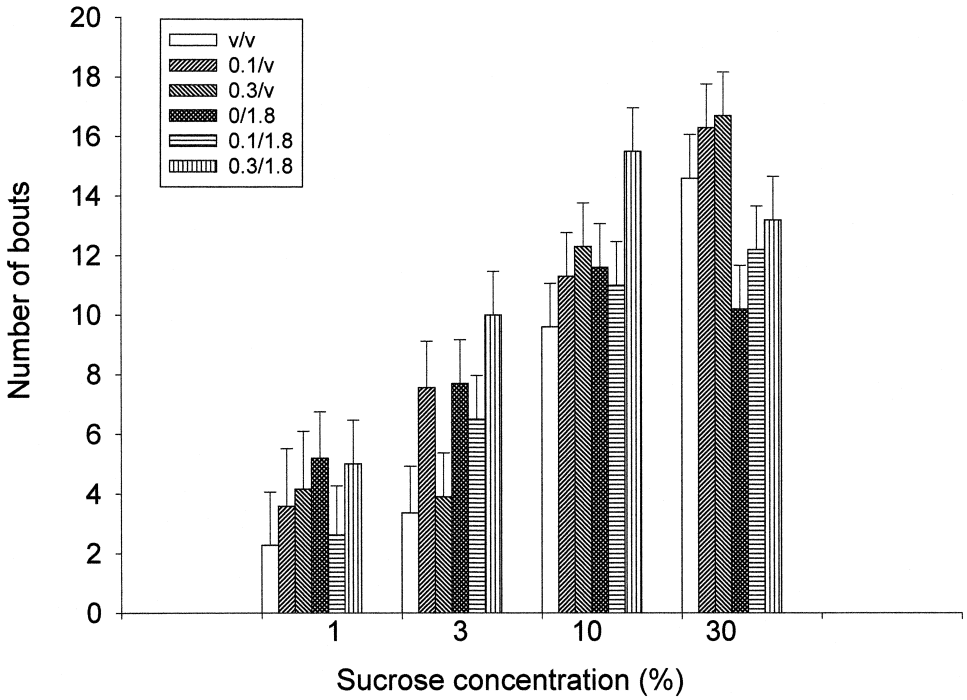

Fig. 3. Effect of drug treatment on number of bouts. Rats ($n = 10$) were treated i.p. with 1.8 mg/kg of midazolam alone or in combination with 0.1 and 0.3 mg/kg of raclopride. Data are presented as the number of bouts averaged over all animals (±S.E.M.) for each drug condition at different levels of sucrose concentration (1–30%). Solutions were presented in a brief contact test (60-s access to each concentration within a session).

3.3. Number of bouts

The effect of drug administration on the number of bouts for each concentration of sucrose is shown in Fig. 3. There were main effects of both sucrose concentration ($F_{(3,27)} = 27.63,\ P < 0.01$) and drug treatment ($F_{(5,45)} = 2.62,\ P < 0.05$) and a significant interaction between these two factors ($F_{(15,119)} = 2.82,\ P < 0.01$). Fig. 3 shows that

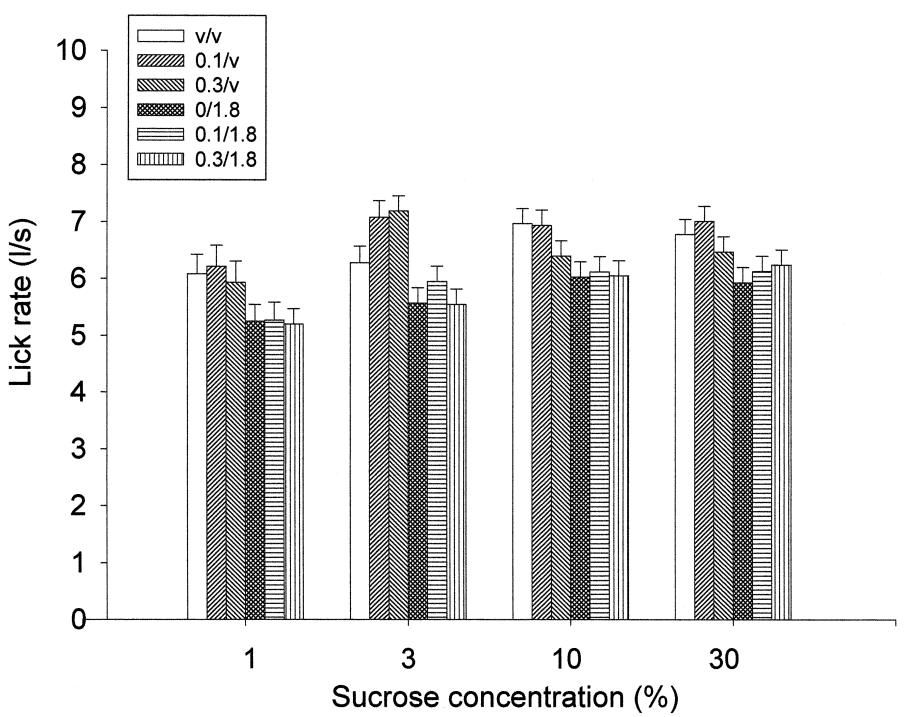

Fig. 4. Lack of reversal of the depressant effect of midazolam on intrabout lick rate by behaviourally inactive doses of raclopride. Rats ($n = 10$) were treated i.p. with 1.8 mg/kg of midazolam alone or in combination with 0.1 and 0.3 mg/kg of raclopride. Data are presented as the intrabout lick rate averaged over all animals (±S.E.M.) for each drug condition at different levels of sucrose concentration (1–30%). Solutions were presented in a brief contact test (60 s access to each concentration within a session).

as concentration increased there was an increase in bout number. An analysis of drug effect at each level of concentration was carried out to determine the nature of the interaction. No significant effect of drug was found at the 1% sucrose concentration. At the 3% and 10% concentrations of sucrose, the combination dose of 1.8 mg/kg midazolam and 0.3 mg/kg raclopride increased bout number significantly compared to the control condition ($P < 0.05$). At the highest concentration of sucrose (30%), midazolam in combination with the vehicle brought about a significant decrease in bout number ($P < 0.01$).

3.4. Intrabout lick rate

ANOVA revealed significant main effect of both sucrose concentration ($F_{(2,27)} = 5.72$, $P < 0.01$) and drugs treatment ($F_{(5,45)} = 9.1$, $P < 0.01$), but no significant concentration × treatment interaction ($F_{(15,119)} = 1.09$, $P > 0.05$). There was decrease in intrabout lick rate with increasing sucrose concentration. The effect of drug administration on the intrabout lick rate is shown in Fig. 4. Raclopride administered by itself (0.1 and 0.3 mg/kg) did not significantly alter the intrabout lick rate at any sucrose concentration. Midazolam brought about a significant decrease in the rate of licking within bouts ($P < 0.01$). Fig. 4 shows that this was true for all concentrations of sucrose. Post hoc analysis also showed that this decrease was not reversed by pre-treatment with either dose of raclopride. Fig. 4 shows that this pattern of results was consistent across all concentrations of sucrose.

4. Discussion

In the present study, midazolam exerted two distinct effects on the licking behaviour for sucrose in non-deprived rats. First, it increased the total number of licks for sucrose by a selective increase in the mean duration of bouts of licking. This result confirms earlier findings (Higgs and Cooper, 1997, 1998), and therefore suggests that benzodiazepine-induced lengthening of licking bouts is a robust phenomenon. It has been shown that bout duration varies monotonically as a function of the concentration of carbohydrate solutions (Davis, 1973, 1998; Davis and Smith, 1992; Spector et al., 1998). This effect contrasts with that of food deprivation, which increases bout number, suggesting that bout size may be useful measurement of solution palatability (Spector et al., 1998). Hence, we and others have argued that benzodiazepines promote the palatability of sucrose and other solutions (Berridge and Pecina, 1995; Cooper and Higgs, 1996).

There is a second effect of midazolam, however, which is unrelated to its putative effect on solution palatability: a significant decrease in the rate of licking within bouts (intrabout lick rate), which is normally maintained at a constant level. We think that this effect is more closely related to motoric effects, since benzodiazepines are known to have muscle-relaxant effects (File, 1982), and this may interfere with the steady rate of licking, which is controlled by a motor pattern generator (Travers et al., 1997). Hence, within the same study, licking analysis provides two measures, one of which may be viewed as an index of palatability, while the other may reflect a side effect on the performance of the licking response.

It is of considerable significance, therefore, that pre-treatment with raclopride (at doses which, when given alone, have little behavioural effect) should selectively block the midazolam-induced increase in the mean bout duration of licking. This result implies that the effect of midazolam on the mean bout duration is dopamine-dependent, whereas its effect on the intrabout lick rate is not. Hence, the data suggest that midazolam's enhancement of sucrose palatability may be mediated, at least in part, by dopamine mechanisms.

The suggestion that dopamine may mediate the palatability effects of benzodiazepines is consistent with the hedonia hypothesis of dopamine function (Wise et al., 1978), but stands in contrast to other theories, such as the 'incentive salience' hypothesis (Berridge, 1996; Berridge and Robinson, 1998), which argue that dopamine is not involved in mediating hedonic reactivity or palatability. According to the incentive salience hypothesis, palatability or food 'liking' is dissociable both psychologically and neuroanatomically from food 'wanting' (Berridge, 1996; Berridge and Robinson, 1998), dopamine being important for the latter, but not the former. This hypothesis is based on the findings of taste reactivity studies showing that manipulations altering brain dopamine systems appear to have no effect on palatability responding as measured by the taste reactivity test (Berridge and Valenstein, 1991; Berridge et al., 1989; Pecina et al., 1997). Importantly, these authors have also shown that benzodiazepine-induced increases in hedonic reactivity remain intact in rats with 6-hydroxy-dopamine lesions of dopamine projections from the midbrain to targets in the dorsal and ventral striatum (Berridge and Robinson, 1998).

Our present results might be interpreted as providing evidence against the incentive salience hypothesis, because in contrast to the taste reactivity studies cited above, we have provided evidence of dopaminergic blockade of benzodiazepine-induced increases in palatability. However, it may be necessary to temper this strong conclusion because of the prospect that unlike taste reactivity, mean bout duration may not provide a direct measure of the palatability response. It is possible that rather than constituting an expression of palatability, mean bout duration reflects an appetitive response to perceived palatability. As such, this measure may reflect wanting which is triggered in response to changes in liking, as opposed to just changes in liking. In this case, it might be argued that raclopride is blocking the appetitive response to benzodiazepine-induced enhancement of palatability, rather than the en-

hancement of palatability itself. Such an interpretation would be more consistent with the incentive salience hypothesis of dopamine function. Further investigation of the variables affecting mean bout duration is required before explanations of the present results couched in terms of dopaminergic effects on either hedonia or incentive salience can be adequately distinguished.

Regardless of the specific role of dopamine in blocking benzodiazepine-induced increases in mean bout duration, this effect is consistent with several other observations that benzodiazepine associated reward is disrupted by dopaminergic manipulation. For example, diazepam-induced self-administration and place conditioning are both blocked by the dopamine receptor antagonist haloperidol (Pilotto et al., 1984; Spyraki and Fibiger, 1988). In addition, an intact dopamine system is required for place preference conditioning by diazepam (Spyraki and Fibiger, 1988).

One possible explanation for the effects of dopamine receptor antagonists on benzodiazepine reward is that benzodiazepines cause release of dopamine in reward-related brain areas. This interpretation is in agreement with electrophysiological evidence showing that the benzodiazepine receptor agonist diazepam increases neuronal firing in mesolimbic and dopamine systems (O'Brien and White, 1987), and in vitro data suggesting that diazepam causes release of dopamine in the striatum (Mitchell and Martin, 1980). However, there is also contradictory evidence from microdialysis experiments showing that benzodiazepines decrease turnover and release of dopamine in the nucleus accumbens (Finlay et al., 1992; Invernizzi et al., 1991; Zetterström and Fillenz, 1990). This paradoxical dissociation between the electrophysioloigcal/behavioural and microdialysis data remains to be fully explained and deserves further investigation. It should be noted however, that the microdialysis studies used relatively high doses of benzodiazepines. At high doses, diazepam blocks adenosine uptake, which may lead to a decrease in dopamine release indirectly (Phillis et al., 1980; Michaelis et al., 1979). It is also worth noting that mesolimbic dopamine activity has been linked to the reinforcing and dependence inducing properties of drugs of abuse (Di Chiara and North, 1992; Koob, 1992; Robinson and Berridge, 1993). Therefore, an effect of benzodiazepines on this system would be consistent with the abuse liability of these compounds (DeWit and Griffiths, 1991; Woods et al., 1987).

The failure of raclopride to reverse the increase in total number of licks (despite the significant reduction in mean bout duration) is probably related to the fact that in combination with midazolam, the highest dose of raclopride significantly increased the number of bouts and this served to counteract the decrease in mean bout duration. The reason for this effect is not clear but may relate to the blockade of midazolam-induced mean bout duration. Dopamine receptor antagonists have been shown occasionally to effect paradoxical increases in responding for rewards. This has been explained in terms of a reduction in hedonic pleasure resulting in an increase in responding for the less rewarding stimulus (Wise et al., 1978). Therefore, it is possible that as a consequence of the reduction in benzodiazepine-induced palatability, the rate at which the rats came back to sample from the drinking spout was increased.

The present results do not provide any information concerning the neural substrate for benzodiazepine/dopamine interactions although it is likely that brainstem structures are involved. It has been shown that injection of midazolam directly into the fourth ventricle and parabrachial nucleus of the brainstem increase consumption of a palatable mash diet in non-deprived rats (Higgs and Cooper, 1996b,c). Fourth ventricular injections of diazepam also enhance hedonic reactions to intra-oral sucrose infusions (Pecina and Berridge, 1996). Potential interactions between brainstem benzodiazepines sites and forebrain dopamine systems in the control of palatability requires further investigation.

In summary, we have extended knowledge of the neurochemical mechanisms underlying the hyperphagic effects of benzodiazepine receptor agonists by demonstrating blockade of midazolam-induced increases in mean bout duration by the dopamine D2 receptor antagonist raclopride. These data point to the interaction of GABA/benzodiazepine and dopaminergic systems in the control of palatability.

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