The involvement of 5-hydroxytryptaminergic and dopaminergic mechanisms in the eating induced by buspirone, gepirone and ipsapirone

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- 1 The roles of 5-hydroxytryptamine (5-HT) and dopamine systems in mediating the increased feeding induced by buspirone, gepirone and ipsapirone were investigated.
- 2 All three compounds induced dose-dependent increases in food intake when administered subcutaneously to free feeding rats. Buspirone was effective over a narrower dose range than either gepirone or ipsapirone, and the maximal effect observed was smaller than the effects elicited by gepirone and ipsapirone.
- 3 Depletion of brain 5-HT with parachlorophenylalanine (PCPA) prevented the effects of equi-effective doses of gepirone (2.5 mg kg⁻¹) and ipsapirone (2.5 mg kg⁻¹), but failed to prevent buspirone (1 mg kg⁻¹)-induced eating. Thus buspirone does not appear to interact with 5-HT systems to elicit feeding.
- 4 Gepirone (0.2 µg) and ipsapirone (0.04 and 0.2 µg) increased food intake when injected into the dorsal raphe nucleus (DRN), presumably by inhibiting the activity of DRN 5-hydroxytryptaminergic afferents. Buspirone (0.04–5 µg) was ineffective when injected into the DRN.
- 5 Pretreatment with haloperidol (0.1 mg kg⁻¹, 30 min) significantly attenuated the effects of equi-effective doses of buspirone, gepirone and ipsapirone, indicating that these drugs interact with dopaminergic systems to increase feeding.
- 6 Previously it has been shown that each of these drugs increases striatal dopamine activity. Increased dopaminergic neurotransmission in the striatum induces a general behavioural activation, which under certain conditions facilitates feeding. It is possible that this mechanism underlies the behavioural effects of buspirone, gepirone and ipsapirone. The effects of gepirone and ipsapirone probably involve an indirect action to inhibit the activity of DRN 5-hydroxytryptaminergic afferents, whereas buspirone interacts directly with dopaminergic systems.

Introduction

The centrally acting 5-hydroxytryptamine_{1A} (5-HT_{1A}) agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) induces a variety of behavioural effects when administered peripherally to rats. These effects include the 5-HT motor syndrome (Tricklebank *et al.*, 1984), increased consumption of hypertonic saline (Cooper & Desa, 1987), anxiolytic-like activity (reviewed by Dourish, 1987; Traber & Glaser, 1987) and antidepressant-like activity (Kennett *et al.*, 1987; Cervo *et al.*, 1988). In free-feeding rats 8-OH-DPAT increases food intake (Dourish *et al.*, 1985), and the underlying mechanism of this particular response has received considerable experimental attention.

Depletion of brain 5-HT by parachlorophenylalanine (PCPA) (Dourish *et al.*, 1986a) or 5,7-dihydroxytryptamine (Bendotti & Samanin, 1986) blocks 8-OH-DPAT-induced eating, indicating that presynaptic elements of 5-hydroxytryptaminergic neurotransmission are required for the expression of this behaviour. Electrophysiological studies have shown that 8-OH-DPAT markedly inhibits the activity of 5-hydroxytryptaminergic neurones, notably those arising from the dorsal raphe nucleus (DRN) (Sprouse & Aghajanian, 1987). This effect may occur from an agonist action at receptors which normally regulate impulse flow in DRN neurones, and which are located in the somatodendritic region of the cells (Aghajanian *et al.*, 1987). That the DRN is important in mediating 8-OH-DPAT-induced eating is shown by the finding that microinjection of 8-OH-DPAT into the DRN elicits a feeding response comparable to that observed after

peripheral injection (Bendotti & Samanin 1986; Hutson *et al.*, 1986; Fletcher & Davies, 1989). A consequence of this decreased activity of DRN neurones is a reduction in 5-HT turnover in various forebrain regions (Hutson *et al.*, 1986; Hamon *et al.*, 1988; Hjorth & Magnusson, 1988). Thus, it is suggested that 8-OH-DPAT elicits feeding by reducing 5-hydroxytryptaminergic neurotransmission arising from the raphe nuclei. This is in keeping with the current views of the role of 5-HT in controlling feeding behaviour (Blundell, 1984). Since injection of 8-OH-DPAT into the DRN also induces anxiolytic-like (Higgins *et al.*, 1988) and antidepressant-like (Cervo *et al.*, 1988) actions, this mechanism is also thought to underlie these effects of 8-OH-DPAT.

Buspirone and its structural analogues, gepirone and ipsapirone represent a group of non-benzodiazepine anxiolytic compounds which exhibit many of the same properties of 8-OH-DPAT. All three compounds are 5-HT_{1A} agonists (Peroutka, 1985; 1986; McMillen *et al.*, 1987) which reduce 5-HT turnover (Hjorth & Carlsson, 1982; McMillen *et al.*, 1987; Hamon *et al.*, 1988) by inhibiting the activity of DRN neurones (VanderMaelen *et al.*, 1986; McMillen *et al.*, 1987; Sprouse & Aghajanian, 1987). In behavioural tests these drugs, like 8-OH-DPAT, show anxiolytic activity (reviewed by Dourish, 1987), increase the consumption of hypertonic saline (Cooper & Desa, 1987) and increase food intake (Dourish *et al.*, 1986b; Gilbert & Dourish, 1987; Gilbert *et al.*, 1988; Neill & Cooper, 1988). It is possible that buspirone, gepirone and ipsapirone act via the same mechanism as 8-OH-DPAT to exert their behavioural effects. However, there is a lack of direct experimental evidence showing that 5-hydroxytryptaminergic neurones, and particularly those arising from the DRN, are involved in mediating the behavioural effects of buspirone, gepirone and ipsapirone. Several differences in the behavioural effects of these compounds have been noted. For example, all

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four compounds, including 8-OH-DPAT, block the fear-potentiated startle reaction (Davis *et al.*, 1988; Mansbach & Geyer, 1988), but in the case of buspirone 5-hydroxytryptaminergic systems are not involved (Davis *et al.*, 1988). Buspirone has been shown also to affect unpunished responding in pigeons, whereas gepirone and 8-OH-DPAT do not (Barrett *et al.*, 1988). Additionally these compounds differ in their ability to elicit the 5-HT syndrome (Smith & Peroutka, 1986). In regard to the effects of these drugs on feeding, gepirone induces a strong feeding response, whereas ipsapirone appears only to be weakly active (Gilbert & Dourish, 1987). Together these results suggest that a single common mechanism may not underlie the behavioural effects of these drugs.

The present experiments were undertaken to examine the mechanism(s) involved in mediating the effects of buspirone, gepirone and ipsapirone on feeding. Specifically, the effects of these drugs were investigated in PCPA-treated rats to examine whether 5-hydroxytryptaminergic systems are required for the actions of these drugs. In order to determine the possible importance of the DRN, the effects of these drugs on feeding were examined following direct injection into the DRN. Previously it has been suggested that 8-OH-DPAT-induced eating is mediated ultimately by an increase in nigrostriatal dopamine activity (Fletcher, 1987; Montgomery *et al.*, 1988; Fletcher & Davies, 1989). Therefore, the possible involvement of a dopaminergic mechanism in the effects of buspirone, gepirone and ipsapirone was assessed by investigating the actions of these drugs in rats pretreated with the dopamine receptor antagonist haloperidol.

Methods

Male Sprague-Dawley rats weighing 270–420 g at the start of the experiments were used. They were housed individually in hanging wire-mesh cages in a temperature-controlled room ($22 \pm 1^\circ\text{C}$) under a 12 h light-dark cycle (lights on at 08 h 00 min). Food and water were available at all times. All animals were handled for several minutes on at least three occasions before the experiments began.

Procedure

On test days the procedure was identical in all experiments. One hour before drug injection fresh food was placed on the floor of each animal's cage. This procedure together with the frequent handling minimizes the amount of food consumed under control conditions during testing. Each rat was then removed from the home cage, injected and returned to the home cage, together with a weighed amount (approximately 25–35 g) of fresh food. One hour later food intakes were determined by reweighing to the nearest 0.1 g the remaining food plus any spillage collected on paper towels placed beneath the cages.

Effects of peripherally injected buspirone, gepirone and ipsapirone on food intake

Three separate groups of rats were used in three different experiments to examine the effects of various doses of peripherally administered buspirone ($n = 8$), gepirone ($n = 8$) and ipsapirone ($n = 8$) on food intake over a 1 h period. The first group was tested on different occasions following an injection of 0.3125, 0.625, 1.25, 2.5 or 5 mg kg^{-1} buspirone hydrochloride (Bristol-Myers, Wallingford, CT) or 0.9% saline; the second group was injected with 0.3125, 0.625, 1.25, 2.5 or 5 mg kg^{-1} gepirone hydrochloride (Bristol Myers) or saline; the third group was tested with 0.625, 1.25, 2.5, 5 and 10 mg kg^{-1} ipsapirone hydrochloride (Miles Inc., West Haven, CT) or saline. For each experiment a repeated measures design was used, with each rat receiving every dose of the

appropriate test drug, and saline in a randomized order, with at least 3 drug-free days between successive tests. All drugs were injected subcutaneously (s.c.) in a volume of 1 ml kg^{-1} .

Effects of PCPA on feeding induced by buspirone, gepirone and ipsapirone

Three groups of rats were used in three different experiments to examine the effects of PCPA treatment on the eating induced by 1 mg kg^{-1} buspirone ($n = 7$), 2.5 mg kg^{-1} gepirone ($n = 7$) and 2.5 mg kg^{-1} ipsapirone ($n = 6$). The drug treatment protocol was identical for each experiment. Before the experiments each rat was administered 3 ml kg^{-1} distilled water via a stomach tube. Then, 3–4 days later 1 h food intakes were determined on two consecutive days following injection (s.c.) with saline or the appropriate test drug. On each of these days approximately half of the rats received saline, and the remainder the test drug. Four days later each rat was administered 400 mg kg^{-1} parachlorophenylalanine (PCPA) ethyl ester (Sigma Chemical Co., St. Louis, MI) dissolved in distilled water (3 ml kg^{-1}) via a stomach tube. On the third and fourth days after PCPA treatment, 1 h food intakes were determined, again following injection (s.c.) with saline or the test drug as described above. This dose and time schedule of PCPA treatment depletes whole brain 5-HT content by approximately 90% (Fletcher, 1989).

Effects of dorsal raphe nucleus injection of buspirone, gepirone and ipsapirone on food intake

Three groups of rats were used to examine the effects of buspirone, gepirone and ipsapirone on food intake following injection into the DRN.

Surgery Before these experiments each rat (weighing 270–320 g) was anaesthetized with $40\text{--}50\text{ mg kg}^{-1}$ sodium pentobarbitone (Nembutal, Abbott Laboratories) and placed in a stereotaxic frame. A 22 g stainless steel guide cannula (Plastic Products, Roanoke, VA) cut to 15 mm in length was implanted, aimed at a site 4 mm above the DRN. With the incisor bar set at 3.3 mm below interaural zero the following coordinates were used (relative to interaural zero): AP + 1.2 mm, Lat – 1.6 mm, V + 7.8 mm according to the atlas of Paxinos & Watson (1985). The cannula was lowered at an angle of 20° to the vertical to avoid damaging the sagittal sinus. Each cannula was secured by acrylic cement which was held in place by 4 stainless steel screws drilled into the skull. A 28 g stainless steel stylet served to keep the cannula patent. Animals were allowed at least 7 days to recover before testing began; during this period each rat was handled frequently and familiarized with the injection procedure.

Drug delivery At the time of drug injection each rat was removed from the home cage and lightly restrained by hand. Drugs were injected into the DRN through a glass capillary tube ($70\text{--}90\text{ }\mu\text{m}$ diameter) connected to a manually operated 5 ml Hamilton syringe via a length of plastic tubing. The glass capillary was housed inside a 15 mm length of stainless steel tubing, and could be extended 4 mm beyond the guide cannula to penetrate the DRN (See Azami *et al.*, 1980 for full details of the microinjection assembly). Each drug solution was delivered in a volume of $0.5\text{ }\mu\text{l}$ (in a sterile 0.9% saline vehicle) over a period of 1 min, and the needle was left in place for a further 30 s.

One group of rats ($n = 8$) was tested following injection of saline, 0.2, 1 and $5\text{ }\mu\text{g}$ of buspirone HCl; a second group ($n = 9$) received injections of saline, 0.04, 0.2, 1 and $5\text{ }\mu\text{g}$ gepirone HCl; the third group ($n = 9$) received injections of saline, 0.04, 0.2, 1 and $5\text{ }\mu\text{g}$ ipsapirone HCl. A minimum of 3 days elapsed between successive drug treatments and doses were administered in a randomised order. Following completion of these studies all rats were tested after administration of $1\text{ }\mu\text{g}$

8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) HBr (RBI, Wayland, MA).

Verification of injection sites After completion of the experiments all rats were anaesthetized with Nembutal, injected with 0.5 µl fast green dye into the DRN, and perfused intracardially with 4% formalin. The brain was removed and standard histological procedures were used to determine the injection sites. Results from animals with injection sites located outside the DRN were not used in the final analysis.

Effects of haloperidol on feeding induced by buspirone, gepirone and ipsapirone

Three groups of rats were used to examine the effects of haloperidol on the eating induced by 1 mg kg⁻¹ buspirone (*n* = 8), 2.5 mg kg⁻¹ gepirone (*n* = 6) and 2.5 mg kg⁻¹ ipsapirone (*n* = 6). The drug treatment protocol was identical in each experiment. Animals were first injected s.c. with 0.1 mg kg⁻¹ haloperidol (RBI) or its vehicle, 0.1 M tartaric acid (adjusted to pH 6 with 2N NaOH) in a volume of 1 ml kg⁻¹. Thirty minutes later the animals were injected s.c. with the appropriate test drug or saline. Food intakes were determined 1 h later as described above. Repeated measures designs were used in each experiment, with every rat receiving all 4 possible drug combinations. Animals were tested first with saline and the appropriate drug, given in a counterbalanced order, following the vehicle pretreatment, and subsequently, in a counterbalanced order, following haloperidol treatment. At least 3 days elapsed between successive drug treatments.

Results

Effects of peripherally injected buspirone, gepirone and ipsapirone on food intake

The effects on food intake of peripheral injection of buspirone, gepirone and ipsapirone are shown in Figure 1. One way analyses of variance showed significant main effects of buspirone ($F(5,35) = 5.5$, $P < 0.001$), gepirone ($F(5,35) = 7.7$, $P < 0.001$) and ipsapirone ($F(5,35) = 5.7$, $P < 0.001$) doses. Thus, each drug produced dose-dependent increases in food intake. In the case of buspirone food intake was increased by doses of 0.625 and 1.25 mg kg⁻¹ only; further increases in dose did not elicit eating above control levels. For gepirone and ipsapirone an increase in dose resulted in progressive increments in food intake across the entire dose ranges tested. It can be seen also that the eating responses induced by the highest doses of gepirone and ipsapirone were somewhat greater than the maximal increase in food intake induced by buspirone.

Effects of PCPA on feeding induced by buspirone, gepirone and ipsapirone

Figure 2 illustrates the effects of 5-HT depletion produced by PCPA on the increased food intake induced by equi-effective doses of buspirone, gepirone and ipsapirone. Results were analysed by separate two-way analyses of variance with PCPA treatment and drug treatment as factors. Significant main effects of buspirone ($F(1,6) = 25.7$, $P < 0.003$), gepirone ($F(1,6) = 28.1$, $P < 0.002$) and ipsapirone ($F(1,5) = 51.3$, $P < 0.001$) confirmed that overall each drug increased food intake relative to saline treatment. More importantly, significant interactions between PCPA treatment and buspirone ($F(1,6) = 6.9$, $P < 0.05$), gepirone ($F(1,6) = 25.9$, $P < 0.013$) and ipsapirone ($F(1,6) = 51.3$, $P < 0.001$) were found. Tests of simple main effects further confirmed that each drug significantly enhanced food intake relative to saline injection under the vehicle pretreatment condition ($F(1,6) = 19.7$, 42.8 and

Figure 1 The effects of different doses of (a) buspirone, (b) gepirone, (c) ipsapirone, and saline (Sal) on food intakes. Columns represent mean intakes (g) over 1 h and bars show s.e.mean. * $P < 0.05$, ** $P < 0.01$ —significantly different from saline, Dunnett's test.

$F(1,5) = 42.3$, respectively, all $P < 0.005$). The PCPA treatment significantly attenuated the eating induced by gepirone ($F(1,6) = 22.6$, $P < 0.01$) and ipsapirone ($F(1,5) = 26.4$, $P < 0.004$) but not buspirone ($F(1,6) = 1$, $P > 0.3$). In all three experiments a slight increase in food intake was observed in animals treated with PCPA and injected with saline.

Effects of DRN injection of buspirone, gepirone and ipsapirone on food intake

The effects of different doses of buspirone, gepirone and ipsapirone, and a single dose of 8-OH-DPAT, on food intake following direct injection into the DRN are shown in Figure 3. The data, including responses to 8-OH-DPAT, were analysed by one-way analysis of variance for each experiment. In the buspirone study a significant treatment effect was observed ($F(4,28) = 10.7$, $P < 0.0001$), but this was due entirely to the increase in food intake observed with 1 µg 8-OH-DPAT. None of the doses of buspirone significantly altered food intake. In an additional group of ten rats injected with saline and 0.04 µg buspirone no effect on food intake was observed (saline, 0.3 ± 0.2 g, 0.04 µg buspirone, 0.5 ± 0.3 g, $t(9) = 0.5$, $P > 0.1$). Significant treatment effects were observed also in the gepirone ($F(5,40) = 3.6$, $P < 0.01$) and ipsapirone ($F(5,40) = 3.98$, $P < 0.01$) studies. Gepirone was effective only at a dose of 0.2 µg, while ipsapirone increased food intake at 0.04

Figure 2 The effects of parachlorophenylalanine (PCPA) treatment (400 mg kg^{-1}) and its vehicle (Veh) on eating induced by (a) 1 mg kg^{-1} buspirone, (b) 2.5 mg kg^{-1} gepirone, (c) 2.5 mg kg^{-1} ipsapirone (hatched columns) and saline (open columns). Columns represent mean food intakes (g) recorded over 1 h and bars show s.e.mean. ** $P < 0.01$ —significantly different from vehicle-buspirone treatment.

and $0.2 \mu\text{g}$. Both groups of animals responded significantly to $1 \mu\text{g}$ 8-OH-DPAT.

Effects of haloperidol on feeding induced by buspirone, gepirone and ipsapirone

The effects of 0.1 mg kg^{-1} haloperidol on feeding elicited by 1 mg kg^{-1} buspirone, 2.5 mg kg^{-1} gepirone and 2.5 mg kg^{-1} ipsapirone are shown in Figure 4. Results were analysed by separate two-way analyses of variance with haloperidol and drug treatment as factors. Significant main effects of buspirone ($F(1,7) = 13.5$, $P < 0.01$), gepirone ($F(1,5) = 19.5$, $P < 0.01$) and ipsapirone ($F(1,5) = 19.7$, $P < 0.01$) showed that overall each drug increased food intake relative to the saline treatment. Significant interactions were observed between buspirone and haloperidol ($F(1,7) = 12.5$, $P < 0.01$) and gepirone and haloperidol ($F(1,5) = 27.2$, $P < 0.01$). Tests of simple main effects confirmed that buspirone ($F(1,7) = 22.9$, $P < 0.002$) and gepirone ($F(1,5) = 81.8$, $P < 0.001$) enhanced food intake relative to saline treatment under the vehicle pretreatment schedule. Haloperidol significantly reversed the effects of buspirone ($F(1,7) = 18.8$, $P < 0.01$) and gepirone ($F(1,5) = 40.7$, $P < 0.01$). The ipsapirone and haloperidol interaction narrowly failed to reach significance ($F(1,5) = 5.9$, $P < 0.06$), but *post-hoc* comparisons (Newman-Keuls, $\alpha = 0.05$) showed that haloperidol significantly attenuated the effect of ipsapirone. The dose of haloperidol used does not affect feeding elicited by injection of noradrenaline into the paraventricular nucleus of the hypothalamus (Davies & Fletcher, 1989; Fletcher & Davies, 1989). Therefore, the effects observed in these experi-

Figure 3 The effects of different doses of (a) buspirone, (b) gepirone, (c) ipsapirone and of saline (Sal) and $1 \mu\text{g}$ (8-hydroxy-2-(di-n-propyl-amino) tetralin (DPAT) on food intake. Columns represent mean intakes (g) over 1 h and bars show s.e.mean. * $P < 0.05$, ** $P < 0.01$ —significantly different from saline, Dunnett's test.

ments do not appear to result from an impairment of the motor responses required for eating.

Discussion

Subcutaneous injection of buspirone, gepirone and ipsapirone increased food intake in free feeding rats, consistent with previous findings (Dourish *et al.*, 1986b; Gilbert & Dourish, 1987; Gilbert *et al.*, 1988; Neill & Cooper, 1988). Examination of the dose-response relationships for each of these drugs suggests possible differences between the actions of buspirone on the one hand, and gepirone and ipsapirone on the other. Thus, both gepirone and ipsapirone were effective over a wider dose range than was buspirone, and both produced a larger eating response than buspirone. This greater effect of gepirone, at least in comparison to 8-OH-DPAT, was noted by Gilbert & Dourish (1987). In this case a possible explanation for the difference is that at high doses eating induced by 8-OH-DPAT is disrupted by the occurrence of the 5-HT syndrome (Tricklebank *et al.*, 1984), whereas eating induced by gepirone (and ipsapirone) is not, since these compounds are weaker elicitors of the 5-HT syndrome (Smith & Peroutka, 1987). The occurrence of symptoms of the 5-HT syndrome may also explain the weaker action of buspirone on food intake, but it is also clear that different neurochemical mechanisms underlie the eating induced by buspirone, and by gepirone and ipsapi-

Figure 4 The effects of haloperidol (Hal) treatment (0.1 mg kg^{-1} , 30 min) and its vehicle (Veh) on eating induced by (a) 1 mg kg^{-1} buspirone, (b) 2.5 mg kg^{-1} gepirone, (c) 2.5 mg kg^{-1} ipsapirone (hatched columns) and saline (open columns). Columns represent mean food intake (g) recorded over 1 h and bars show s.e.mean. * $P < 0.05$, ** $P < 0.01$ —significantly different from corresponding vehicle-pretreated condition.

rone, and this may also contribute to the differences in the magnitude of the eating responses.

Depletion of 5-HT with the tryptophan hydroxylase inhibitor PCPA abolished the eating induced by equi-effective doses of gepirone and ipsapirone, but did not modify buspirone-induced eating. These results demonstrate that gepirone and ipsapirone elicit eating by interacting with 5-hydroxytryptaminergic neural systems, but that buspirone does not. Treatment with PCPA abolishes 8-OH-DPAT-induced eating (Dourish *et al.*, 1986a), and an important brain 5-hydroxytryptaminergic site in mediating the effect of 8-OH-DPAT is the DRN (Bendotti & Samanin, 1986; Hutson *et al.*, 1986; Fletcher & Davies, 1989). This site is also important in the actions of gepirone and ipsapirone, since both drugs elicited eating when injected into the DRN. The magnitude of the effects induced by both drugs appeared lower following DRN injection, compared to subcutaneous injection. This may indicate that subcutaneously injected gepirone and ipsapirone act at sites in addition to the DRN to elicit feeding. One such site may be the median raphe nucleus (MRN) since 8-OH-DPAT increases eating following injection into the MRN (Bendotti & Samanin, 1986; Hutson *et al.*, 1986).

Iontophoretic application of 8-OH-DPAT, ipsapirone (Sprouse & Aghajanian, 1987) and gepirone (McMillen *et al.*, 1987) inhibits DRN neural activity, and local injection of 8-OH-DPAT (Hjorth & Magnusson, 1988) and ipsapirone (Hamon *et al.*, 1988) into the DRN reduces 5-HT turnover in forebrain regions. On the basis of these results, together with

the observations that DRN injection of 8-OH-DPAT, gepirone and ipsapirone elicits eating, it is reasonable, at this stage, to postulate that reduced 5-HT function arising from the DRN contributes to the increased food intake observed with 8-OH-DPAT, gepirone and ipsapirone. Buspirone also inhibits the activity of DRN neurones (VanderMaelen *et al.*, 1986) and decreases 5-HT turnover when administered peripherally (Hjorth & Carlsson, 1982; Fuller & Perry, 1988). It is perhaps surprising then that buspirone failed to induce eating when injected into the DRN, even though it has been shown previously that 0.04 and $0.2 \mu\text{g}$ of buspirone alter behaviour in tests of anxiolytic activity (Higgins *et al.*, 1988). However, this lack of effect of buspirone on feeding is consistent with the finding that the effect of peripherally injected buspirone is not affected by 5-HT depletion with PCPA. Higgins *et al.* (1988) found that buspirone did not affect 5-HT turnover when injected into the DRN at behaviourally active doses, and did so only marginally at a dose of $5 \mu\text{g}$. This relatively small effect of buspirone on 5-HT turnover may explain the lack of effectiveness of buspirone in eliciting feeding following DRN injection. These results may also imply that buspirone is not as effective at inhibiting 5-HT neural activity in conscious, behaving animals, as it is in electrophysiological studies involving anaesthetized animals. It is known that anaesthesia can affect markedly the responsiveness of DRN neurones to psychoactive drugs (Trulsson & Trulsson, 1983). Of particular relevance here is the finding that the α_1 -antagonist WB-4101, which like buspirone, gepirone, ipsapirone and 8-OH-DPAT has a high affinity for the 5-HT_{1A} binding site (Peroutka, 1986), totally suppresses DRN activity in anaesthetized cats, but is considerably less effective in conscious cats (Heym *et al.*, 1984). Since the behavioural effects of this class of compounds are often interpreted with reference to their actions on neuronal activity in anaesthetized animals, this issue of drug activity in anaesthetized versus unanaesthetized animals deserves further investigation.

Injection of gepirone and ipsapirone into the DRN induced feeding only at low doses; higher doses failed to increase feeding. Similar biphasic effects related to dose have been observed in tests of anxiolytic activity following DRN injection of 5-HT_{1A} agonists (Higgins *et al.*, 1988). These authors suggest that possible effects of these drugs on hypoactivity, cardiovascular function and/or thermoregulation may be responsible for the disappearance of behavioural effects at high doses (Higgins *et al.*, 1988). Such effects may also adversely affect the expression of eating at higher doses of gepirone and ipsapirone.

Haloperidol pretreatment attenuated the eating induced by peripherally administered buspirone, gepirone and ipsapirone. This dose of haloperidol has been shown previously to attenuate eating induced by DRN injection of 8-OH-DPAT, without affecting the ability of the animals to perform the eating response (Davies & Fletcher, 1989; Fletcher & Davies, 1989). These results suggest the involvement of dopaminergic mechanisms in mediating the increased feeding induced by these compounds. This possibility is supported further by the findings that peripheral injection of buspirone (Wood *et al.*, 1983; Fuller & Perry, 1988), gepirone (McMillen *et al.*, 1987) and both peripheral and DRN injection of ipsapirone (Hamon *et al.*, 1988) increase striatal dopamine turnover. 5-Hydroxytryptaminergic systems exert an inhibitory influence over nigrostriatal dopamine neurones, and a reduction in 5-HT activity increases the functional activity of these nigrostriatal neurones (Dray *et al.*, 1978). Given that 5-HT_{1A} agonists inhibit the activity of 5-hydroxytryptaminergic DRN neurones (VanderMaelen *et al.*, 1986; McMillen *et al.*, 1987; Sprouse & Aghajanian, 1987), it is likely that the effects of gepirone and ipsapirone on dopamine turnover, and on feeding, result from a removal of the inhibitory influence of DRN efferents on nigrostriatal dopamine activity. This 5-HT-dopamine interactive mechanism cannot account for the effects of peripherally injected buspirone on feeding, since PCPA failed to block this response, and buspirone did not

elicit eating following DRN injection. However, low doses of buspirone increase dopamine turnover in the striatum via a direct blockade of presynaptic dopamine autoreceptors (McMillen & Mattiace, 1983; McMillen *et al.*, 1987), which may be sufficient to induce feeding. The diminution of the feeding response at higher doses of buspirone may then arise because of increased postsynaptic receptor blockade, which will tend to normalize or reduce the net functional activity of striatal dopamine synapses (Wood *et al.*, 1983).

Feeding can be elicited by several other manipulations which increase dopaminergic activity, including tail-pinch (Antelman & Szechtman, 1975), low doses of D-amphetamine injected peripherally or into the striatum (Winn *et al.*, 1982) and a selective dopamine D₂ agonist (Martin-Iverson & Dourish, 1988). These manipulations also increase chewing and oral motor activities. It is thought that these effects result from a dopamine-mediated behavioural activation or arousal which is expressed as eating when food is the most salient stimulus in the animal's environment. Eating thus appears to be stimulus bound. Previously 8-OH-DPAT has been shown to elicit chewing and oral motor activities, effects which are

attenuated by haloperidol (Fletcher, 1987), although these effects are not necessarily observed when palatable foods are available (Dourish *et al.*, 1988). Thus, the effects of 8-OH-DPAT may be stimulus bound, and this may apply also to the effects of buspirone, gepirone and ipsapirone. Future experiments should therefore be concerned with the behavioural specificity of the eating responses induced by these compounds. To date many of the reported changes in behaviour induced by 5-HT_{1A} agonists involve increases rather than decreases in behavioural output (see Introduction). Given the importance of the nigrostriatal dopamine pathway in general behavioural arousal and activation (Robbins & Everitt, 1982; White, 1986) together with the present results, the possibility that these behavioural effects reflect task-specific behavioural activation warrants investigation.

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