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5-HT_{1A} agonists and dopamine: the effects of 8-OH-DPAT and buspirone on brain-stimulation reward

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Summary. Two specific 5-HT_{1A} agonists, 8-OH-DPAT (0–300 μg/kg), and buspirone (0–3.0 mg/kg), were tested on variable-interval, threshold-current self-stimulation of rat lateral hypothalamus. Buspirone produced a prolonged monotonic depression of responding, whereas the effects of 8-OH-DPAT were biphasic: 3.0 μg/kg produced a sustained enhancement of responding while higher doses (100–300 μg/kg) produced a relatively short-lasting depression. This biphasic pattern parallels previously reported effects of 8-OH-DPAT on food intake and on various other behaviours. Threshold-current self-stimulation is highly sensitive to alterations in dopaminergic transmission but relatively insensitive to changes in 5-HT. Thus the facilitatory effect of low-dose 8-OH-DPAT seems most plausibly interpreted in terms of enhanced dopaminergic transmission. This could be brought about by $5HT_{1A}$ autoreceptor-mediated inhibition of 5-HT release and consequent disinhibition of dopaminergic transmission. Depression of self-stimulation by higher doses of 8-OH-DPAT may reflect the activity of 8-OH-DPAT at postsynaptic 5-HT receptors, with consequent inhibition of DA transmission. Suppression of responding after buspirone at all doses tested may reflect the action of this compound as a partial agonist at postsynaptic 5-HT receptors, and/or its effects on other systems.

Keywords: Buspirone, dopamine, feeding, presynaptic receptor, self-stimulation, $5HT_{1A}$ receptor, 8-OH-DPAT.

Introduction

8-OH-DPAT, the prototype agonist binding to the 5-HT_{1A} receptor (Middlemiss and Fozard, 1983), shows a distinctive biphasic pattern of effects on spontaneous

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feeding behaviour: low doses are stimulant, whereas higher doses depress intake (Ahlenius et al., 1981; Dourish et al., 1985). The anorexia seen with high doses is in keeping with the well-known inhibitory actions of 5-HT, and with the supposed role of 5-HT in mediating satiation (Blundell, 1984), but the stimulant effect of small doses remains puzzling. One explanation rests on the finding that low concentrations of 8-OH-DPAT bind selectively to somatic $5HT_{1A}$ autoreceptors (Hjorth and Magnusson, 1988), and thereby inhibit 5-HT cell firing in the dorsal raphé (Dourish et al., 1986 b). 8-OH-DPAT could therefore stimulate appetite, in a specific manner, counteracting a tonic serotonergic inhibition of feeding (Dourish et al., 1988). But the feeding patterns actually elicited by 8-OH-DPAT are qualitatively unusual (Fletcher, 1987; Montgomery et al., 1988), and seem to bear the hallmarks of feeding induced by dopamine (DA) – as typically seen after tailpinch (Antelman and Szechtman, 1975) or after very low doses of amphetamine (Blundell and Latham, 1978; Winn et al., 1982). Some investigators have accordingly proposed that 8-OH-DPAT stimulates food intake in a less direct manner, by facilitating DA transmission and promoting nonspecific motivational arousal. Facilitation of dopaminergic transmission might be brought about either by a direct action on DA receptors (where 8-OH-DPAT may in some cases act as a weak direct agonist (Simonovic et al., 1984; Ahlenius et al., 1989; Smith and Cutts, 1989; Bull et al., 1990) or transynaptically, via inhibitory $5\text{-}HT_{1A}$ autoreceptors sited on DA-inhibitory serotonergic cells (see below).

A simple way to assess the role of DA in the stimulant action of 8-OH-DPAT would be to examine the effect of 8-OH-DPAT on electrical self-stimulation. Self-stimulation is very sensitive to drugs affecting DA transmission, more sensitive than other behavioural indices of DA activity (Gallistel et al., 1982; Rolls et al., 1974); on the other hand, self-stimulation has usually been found to be much less sensitive, or completely insensitive, to quite severe decrements in 5-HT transmission, whether brought about by lesions (Lorens, 1971; Deakin, 1980) or by drugs such as p-chlorophenylalanine, metergoline, cyproheptadine, or methysergide (Crow, 1969; Margules, 1969; Deakin, 1980). Thus there would be no reason to expect appreciable improvement in self-stimulation performance in response to 8-OH-DPAT if the stimulant effect of this compound were mediated simply by dampening of central 5-HT release; on the other hand, stimulant effects produced by facilitation of DA transmission would presumably be reflected by clear enhancement of self-stimulation. In the present study we have examined the effects on self-stimulation of 8-OH-DPAT administered in a wide range of doses, including low doses thought to act in a specific manner on presynaptic $5\text{-}HT_{1A}$ autoreceptors (Dourish et al., 1988). We also examined the effects of buspirone, because buspirone is thought to act on the $5HT_{1A}$ receptor in a similar manner to 8-OH-DPAT (Peroutka, 1985; Dourish et al., 1986 a) (although it also has other important effects, to be considered below).

Method

Subjects

Male Lister hooded rats (National Institute of Medical Research, London) weighing 200–250 g were implanted with twisted bipolar stainless steel electrodes of 0.25 mm nominal diameter (Plastic Products Co, Roanoke VA), aimed at the mid-lateral hypothalamus. Electrode coordinates relative to bregma (Pellegrino et al., 1979) were A − 1.0, ± 1.4, 8.5. Electrode placements were verified on 50-μm unstained frozen sections at the end of the experiment.

Self-stimulation

On recovery from surgery, the rats were trained to operate a lever to obtain a 0.5-s 50-Hz sinewave constant-current reinforcing stimulus available at randomly varied intervals of 10 s mean duration (VI 10 s). Stimulus intensities were fixed at the lowest value that would just maintain uninterrupted responding, as determined in preliminary trials with intensities descending in 1-decilog steps. Variable-interval responding at this threshold intensity occurs at approximately half the maximal response rate as determined in rate-intensity studies (Rose et al., 1988), and is maximally sensitive to small changes in central dopaminergic activity implicated in motivational processes (Rose et al., 1988; Wise, 1978). The relatively slow rate of responding is also well within the rat's physical capacity, and is minimally sensitive to performance-related variables (Liebman, 1983). Response rates were printed out automatically at 5-min intervals.

Drugs

8-OH-DPAT [(±)8-hydroxy-2-(di-*n*-propylamino)tetralin] (Research Biochemicals Inc, Natick, Mass), and buspirone (Bristol Myers Co, Evansville, Ind) were dissolved in isotonic saline and injected intraperitoneally in volumes of 1.0 ml/kg. Control injections contained the corresponding vehicle.

Procedure

For dose-response studies, different doses of either 8-OH-DPAT (0, 3.0, 10, 100 and 300 μg/kg) or buspirone (0, 0.1, 0.3, 1.0 and 3.0 mg/kg, as the HCl salt) were tested in random order at intervals of not less than 48 hr, each rat receiving each dose once. At each test, the rat was allowed to self-stimulate for approximately 45 min, the last 30 min before injection providing a pre-drug baseline. The response rate after each injection was scored as a percentage of the preceding predrug rate, and group scores were submitted to analysis of variance, supplemented by tests of simple main effects and planned comparisons.

Results

8-OH-DPAT gave a biphasic dose-response curve (Fig. 1 A), with facilitation occurring at a low dose-level (3.0 μg/kg), and depression at higher doses. Analysis of variance in the first and second 30-min periods after injection showed a significant effect of dose [$F(6,36) = 5.23$, $p < 0.001$] that altered with time [Dose-Interval interaction $F(6,36) = 2.79$, $p < 0.025$]. Facilitation by the 3.0-μg/kg dose persisted throughout the first and second 30 min of the 1-hr test period [$F(1,72) \geq 4.7$, $p < 0.05$], but depression of responding produced by higher doses in the first 30 min [($F(1,72) = 5.48$, $p < 0.05$, and $F(1,72) = 12.28$, $p < 0.001$ for 100 and 300 μg/kg respectively] was no longer significant in the

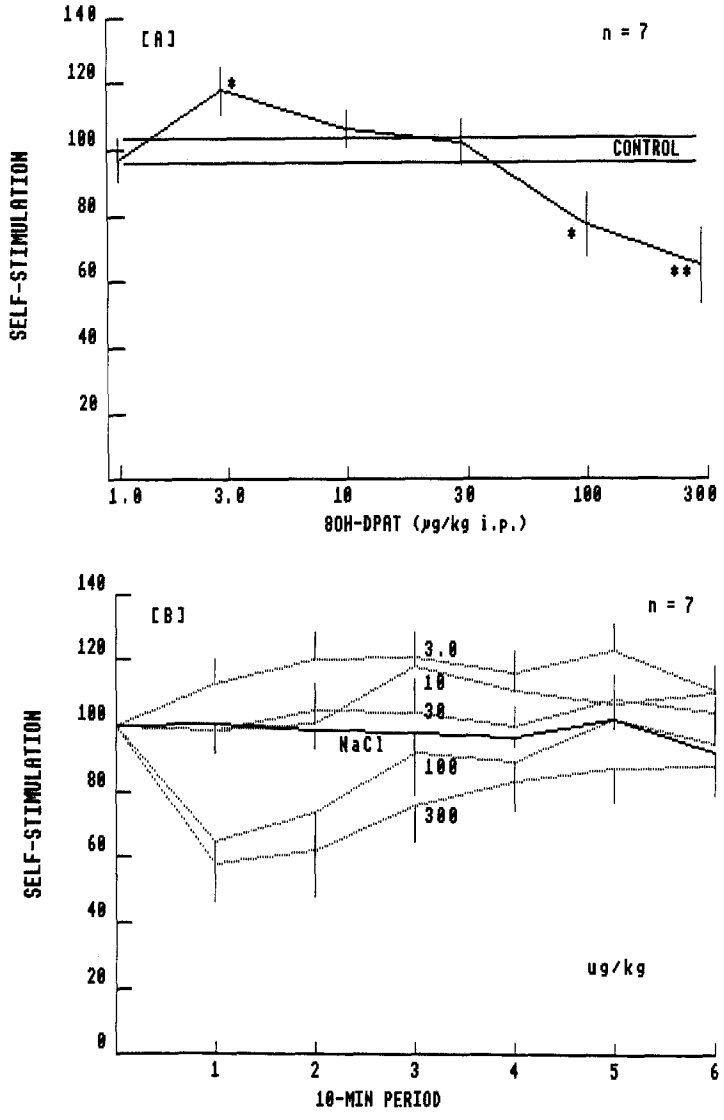

Fig. 1. A Dose-response curve for variable-interval self-stimulation at threshold current in the 30 min after i.p. injection of 8-OH-DPAT. Response rates are expressed as percentages of the respective pre-injection rates. Vertical bars indicate standard errors. Paired horizontal lines indicate response rates (± SE) during corresponding periods after injection of isotonic saline. * Significantly different from vehicle, ($p < 0.05$). ** Significantly different from vehicle, ($p < 0.01$). **B** Time course of responding recorded at 10-min intervals after injection of different doses of 8-OH-DPAT or vehicle. Other details as in Fig. 1 A

second 30 min (Fig. 1 B). Inspection of the rat during self-stimulation, and during periods of interrupted responding, revealed no signs of tremor, wet-dog shakes or other symptoms of the 5-HT motor syndrome (Grahame-Smith, 1971), a condition previously shown to be associated with impaired self-stimulation (Herberg and Franklin, 1976).

Buspirone caused a dose-dependent depression of responding in the 60 min

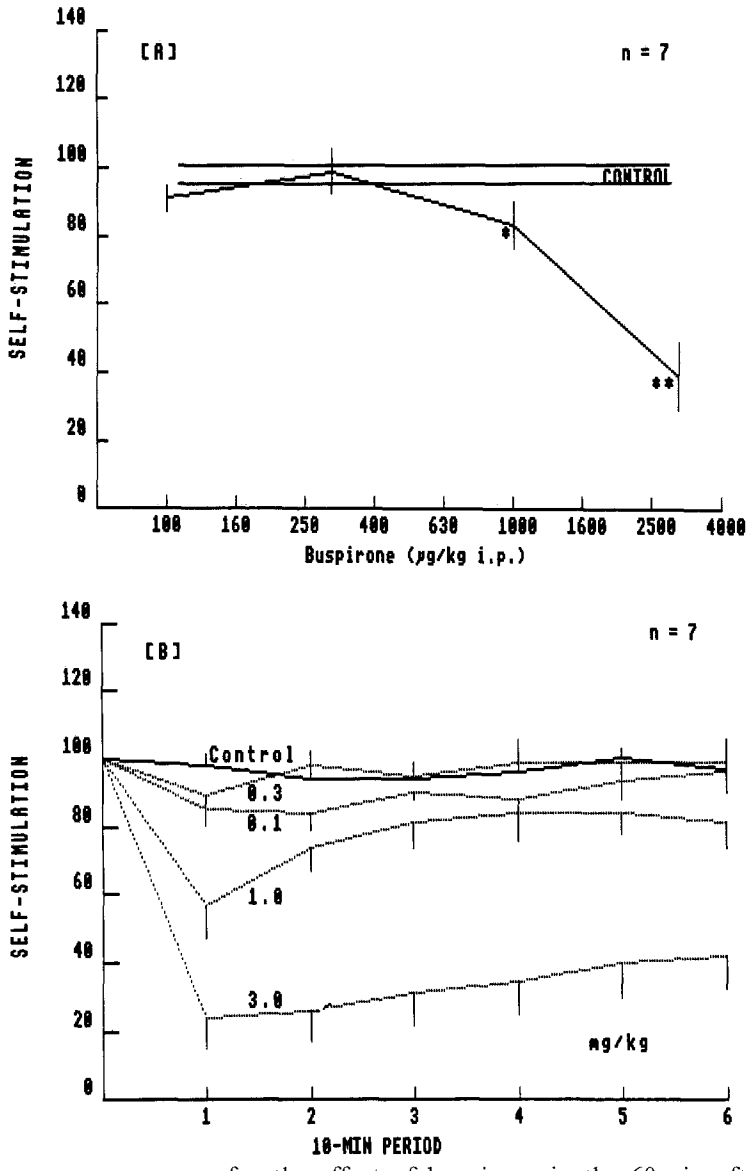

Fig. 2. **A** Dose-response curve for the effect of buspirone in the 60 min after injection. Other details as in Fig. 1. **B** Time course of responding after injection of different doses of buspirone or vehicle. Details as in Fig. 1

after injection [$F(4,24) = 19.3, p < 0.001$], without significant stimulant effects at any dose (Fig. 2 A). The depression of responding after the highest dose of buspirone (3.0 mg/kg), unlike depression after 8-OH-DPAT, was still present in the second 30 min after injection [$F(1,48) = 43.4, p < 0.001$] (Fig. 2 B). No evidence of the 5-HT motor syndrome was seen.

Discussion

The biphasic effect of 8-OH-DPAT on self-stimulation in this study resembles its reported effect in other behavioural models, including male sexual behav-

ioural (Ahlenius et al., 1981), conflict behaviour (Engel et al., 1984), place-preference (Papp and Willner, 1989), and feeding (Dourish et al., 1985). This wide range of effects, involving an assortment of consummatory and non-consummatory activities with little in common, suggests that the tendency of 8-OH-DPAT to promote feeding is not a specific action by 8-OH-DPAT on hunger mechanisms, but rather a consequence of non-specific motivational arousal, as seen typically with agents causing dopaminergic stimulation.

The high potency of 8-OH-DPAT in the self-stimulation model lends further support to the proposed role of dopamine. The maximally effective stimulant dose of 8-OH-DAPT in the present study (3.0 μg/kg) corresponds to the lowest effective dose in previous feeding studies (Dourish et al., 1988), and the small size of this dose is consistent with the especial sensitivity of self-stimulation to a rise or fall in dopaminergic transmission (Gallistel et al., 1982; Rolls et al., 1974; Rose et al., 1988).

How might 8-OH-DPAT enhance dopaminergic transmission? 8-OH-DPAT has been reported to act directly on the DA receptor, but only in much higher concentrations (0.3–1.0 μM) (Smith and Cutts, 1989) than the low nanomolar concentrations typically effective at the 5-HT_{1A} receptor (e.g. Hamon et al., 1988). Moreover, the direct action of 8-OH-DPAT on DA receptors may be selective for D 2 receptors (Ahlenius et al., 1989; Bull et al., 1990), whereas self-stimulation requires both D 1 and D 2 activity (Nakajima, 1989). Thus direct stimulation of the DA receptor does not seem a likely explanation for the enhancement of self-stimulation by low doses of 8-OH-DPAT.

Enhancement of dopaminergic transmission by 8-OH-DPAT may also be brought about indirectly, via the well-documented inhibitory link between serotonergic activity and dopaminergic function (e.g. Weiner et al., 1973; Hollister et al., 1976; Costall et al., 1976; Waldmeier and Delini-Stula, 1979). Low doses of 8-OH-DPAT, inhibiting 5-HT cells in the raphé nuclei, would thereby reduce the inhibitory influence of 5-HT on the dopaminergic substrates of self-stimulation. Projections from raphé nuclei to the substantia nigra, ventral tegmental area, nucleus accumbens and striatum provide anatomical, biochemical, electrophysiological and behavioural evidence for this disinhibitory process (Conrad et al., 1974; Saavedra et al., 1974; Dray et al., 1978; but cf. Hjorth et al., 1982; Dourish et al., 1986).

The effects of 8-OH-DPAT on self-stimulation are unlikely to have been mediated by other systems. Moderate facilitation of self-stimulation does occur with certain other classes of drug, particularly benzodiazepines, phencyclidine-like agonists, opiates and cannabinoids, but the distinctive behavioural features of these agents have not to date been associated with 8-OH-DPAT. Maximal facilitation of responding by 8-OH-DPAT (ca. 25%) was only modest compared to the 200 or 300% enhancement of variable-interval responding commonly seen with dopaminergic stimulants such as *d*-amphetamine (Herberg et al., 1976); this suggests that any effect on dopaminergic transmission by 8-OH-DPAT was quite limited. Thus it does not seem plausible to explain the *depression* of self-

stimulation by higher doses of 8-OH-DPAT, in terms of *over*stimulation of dopaminergic transmission. At these doses, however, 8-OH-DPAT is no longer selective for presynaptic 5-HT_{1A} autoreceptors, and postsynaptic serotonergic activity predominates (Dourish et al., 1986 b). This transition offers a likely explanation for the biphasic dose-response curve, since there is ample evidence of impaired self-stimulation responding if 5-HT transmission is abnormally increased (Bose et al., 1974; Herberg and Franklin, 1976; Katz and Carroll, 1977), even though 5-HT *depletion* may have little effect (Lorens, 1971; Margules, 1969). Heightened postsynaptic activity may thus have been the cause of depressed responding after the higher doses of 8-OH-DPAT, especially in the first 20 min or so after injection, and also throughout the session after buspirone.

At first sight, the absence of facilitation after buspirone might seem to contradict the 8-OH-DPAT findings, since buspirone, like 8-OH-DPAT, inhibits serotonergic firing by acting on presynaptic 5-HT_{1A} receptors (Peroutka, 1985). However, buspirone has been shown also to act as a partial agonist at postsynaptic 5-HT receptors (Andrade and Nicoll, 1987). The combined effect of these actions of buspirone is likely to be a sustained low level of activity in 5-HT-sensitive neurones, dissociated from serotonergic firing (Andrade and Nicoll, 1987). The behavioural consequences of this are difficult to predict, but could account for differences from 8-OH-DPAT, and for the failure of buspirone to facilitate self-stimulation.

Buspirone also acts directly on a number of other systems, including the DA receptor (McMillen and Mattiace, 1983), but neuroleptic activity (capable of supressing food intake and self-stimulation) is unlikely to be seen with doses of buspirone as low as those used here (McMillen et al., 1983). A capacity to facilitate self-stimulation is a consistent feature of virtually all drugs of abuse (Gardner et al., 1988); thus the absence of such facilitation by buspirone is consistent with clinical evidence that buspirone differs from other anxiolytics (e.g. the benzodiazepines) in lacking apparent abuse potential (Goa and Ward, 1986).

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