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 monotonous 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...
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-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-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).