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

A. M. J. Montgomery*, I. C. Rose, and L. J. Herberg

Institute of Neurology, National Hospital, London, United Kingdom

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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
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 5HT1A 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-HT1A 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-HT1A autoreceptors (Dourish et al., 1988). We also examined the effects of buspirone, because buspirone is thought to act on the 5HT1A 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).