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Evidence that 8-hydroxy-2-(n-dipropylamino)tetralin (8-OH-DPAT) is a selective α_2-adrenoceptor antagonist on guinea-pig submucous neurones

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1 Intracellular recordings were made from neurones of the submucous plexus and from submucosal arteriolar smooth muscle of the guinea-pig ileum for the purpose of examining the actions of 8-hydroxy-2-(n-dipropylamino)tetralin (8-OH-DPAT).

2 8-OH-DPAT (10 nM–20 μM) had no direct presynaptic or postsynaptic actions on submucous plexus neurones.

3 Membrane hyperpolarizations induced in neurones by noradrenaline or UK 14304 were competitively antagonized by 8-OH-DPAT. For dose-ratios up to 40, Schild plots were linear with slopes not significantly different from unity; pA_2 values for the 8-OH-DPAT antagonism of postsynaptic α_2-adrenoceptors were 6.9–7.2.

4 The inhibitory synaptic potential, which is due to activation of α_2-adrenoceptors located on submucous plexus neurones, was selectively inhibited by 8-OH-DPAT; the IC_{50} value for inhibition of the inhibitory synaptic potential was 250 nM.

5 Neuronal hyperpolarizations mediated through activation of δ-opioid receptors or somatostatin receptors were unaffected by 8-OH-DPAT (0.1–1 μM).

6 The ability of noradrenaline and UK 14304 to inhibit the release of acetylcholine at synapses in the submucous plexus, and to inhibit the release of the transmitter which mediates the excitatory junction potential in the submucosal arteriolar smooth muscle, was also blocked by 8-OH-DPAT.

7 These results suggest that some of the actions of 8-OH-DPAT previously ascribed to agonism at 5-hydroxytryptamine (5-HT)$_1$ receptors may actually result from blockade of the actions of endogenously released noradrenaline acting on α_2-adrenoceptors.

Introduction

The recent and still-emerging classifications of 5-hydroxytryptamine (5-HT) receptor subtypes in the central and autonomic nervous system have been based largely on results obtained with the growing arsenal of newer and more selective 5-HT receptor agonists and antagonists (Peroutka, 1984; Sills *et al.*, 1984; Richardson & Engel, 1986). One of these 5-HT receptor agonists, 8-hydroxy-2-(n-dipropylamino)tetralin (8-OH-DPAT), has played a significant role in attempts to classify subtypes of one class of 5-HT receptors, namely the 5-HT$_1$ receptor (Middlemiss & Fozard, 1983; Middlemiss, 1984). 8-OH-DPAT binds specifically to certain 5-HT recognition sites (Middlemiss & Fozard, 1983) and behavioural studies have revealed effects of 8-OH-DPAT that closely mimic those of 5-HT (Arvidsson *et al.*, 1981; Hjorth *et al.* 1982).

We have recently been engaged in a study of the actions of 5-HT and various 5-HT agonists on the membrane properties of neurones in the guinea-pig submucous plexus (Surprenant & Crist, 1986). Agonists with selectivity for 5-HT$_1$ receptors had no direct effects on the resting membrane properties of these neurones but were found to have actions suggesting a blockade of α_2-adrenoceptors. In this paper we present the experimental work which has characterized this α_2-receptor antagonism by 8-OH-DPAT.

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Methods

Preparations of the submucous plexus were obtained from the small intestine of young guinea-pigs (150–300 g); methods of dissection, intracellular recording from submucous plexus neurones or arterioles, perivascular or fibre tract nerve stimulation and drug applications were as described in detail previously (Surprenant, 1984; North & Surprenant, 1985; Surprenant & Williams, 1987). Physiological saline was of the following composition (mM): NaCl 126, NaH_2PO_4 1.2, $MgCl_2$ 1.2, $CaCl_2$ 2.5, KCl 5, $NaHCO_3$ 25, glucose 11; gassed with 95% O_2 and 5% CO_2. Temperature was maintained at 35–37°C. The submucous plexus was continuously superfused from tap-selectable reservoirs of normal and drug-containing solution; complete re-equilibration occurred within 60–90 s from turning the tap.

Drugs used were (−)-noradrenaline bitartrate (Sigma), idazoxan (Reckitt and Colman); cocaine hydrochloride (Sigma); prazosin hydrochloride (Pfizer) UK 14304 (5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline, gift from Pfizer) (±)-8-hydroxy-2-(n-dipropylamino) tetralin (8-OH-DPAT) (Research Biochemicals Inc.); [D-Pen,[2] D-Pen[5]] enkephalin (DPDPE) (Peninsula) and somatostatin (Sigma).

Results are expressed as means ± s.e.mean; *n* refers to number of individual neurones tested.

Results

Superfusion of the submucous plexus with 8-OH-DPAT (0.5–20 μM) produced no changes in the membrane potential recorded from submucous neurones ($n = 35$) (Figure 1a) or submucous arteriolar smooth muscle (total of 25 impalements carried out on four arteriolar preparations).

Antagonism at postsynaptic α_2-adrenoceptors by 8-OH-DPAT

8-OH-DPAT inhibited (Figure 1a) or reversed (Figure 1b) the hyperpolarization produced by noradrenaline or the α_2-adrenoceptor agonist, UK 14304. As is apparent from Figure 1, this action of 8-OH-DPAT was observed within 1–2 min of its introduction into the bathing fluid. The inhibition of the α_2-receptor mediated hyperpolarization by 8-OH-DPAT was fully reversible within 30–60 min of washing (Figure 1a). This recovery was much slower than that required for the α_2-adrenoceptor antagonist idazoxan. For exam-

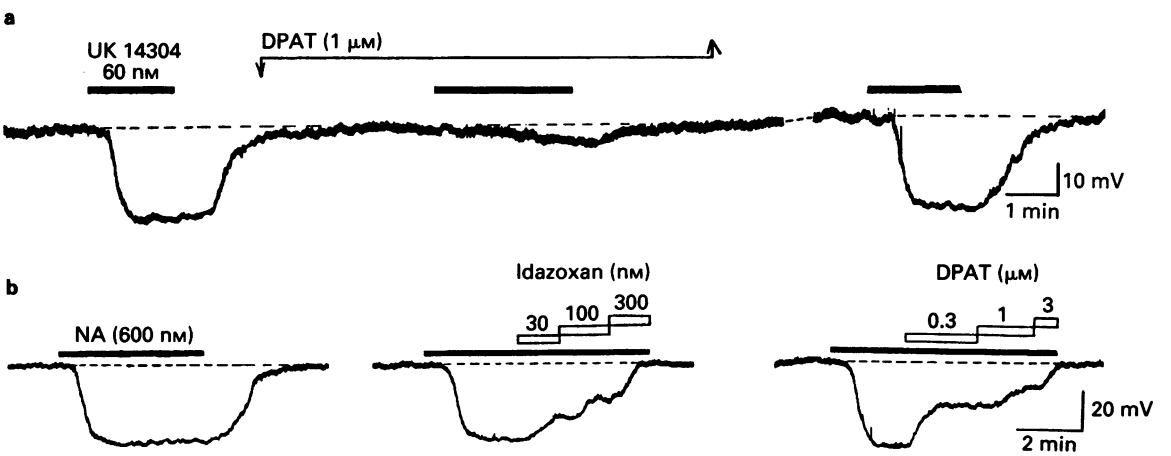

Figure 1 8-Hydroxy-2-(n-dipropylamino)tetralin (DPAT) prevents (a) or reverses (b) the hyperpolarizations produced by α_2-adrenoceptor agonists. (a) Superfusion with 60 nM UK 14304, which is an agonist at α_2-adrenoceptors, produced a 27 mV hyperpolarization in this neurone; 5 min after the addition of 1 μM 8-OH-DPAT the same concentration of UK 14304 produced a 5 mV hyperpolarization. Thirty min after washout of 8-OH-DPAT the UK 14304-induced hyperpolarization was again 27 mV (right trace). Note that 8-OH-DPAT itself had no significant effect on the resting membrane potential. (b) Hyperpolarizations recorded from one submucous neurone in response to repeated applications of 600 nM noradrenaline (NA); left hand recording shows that the hyperpolarization is maintained throughout the duration of agonist application. The α_2-adrenoceptor antagonist, idazoxan, readily reversed the response (middle recording) as did 8-OH-DPAT (right hand recording; this trace was obtained 30 min after discontinuing exposure to idazoxan). In this and subsequent figures, solid bars represent duration of superfusion with the agonist; open bars represent duration of superfusion with antagonists.

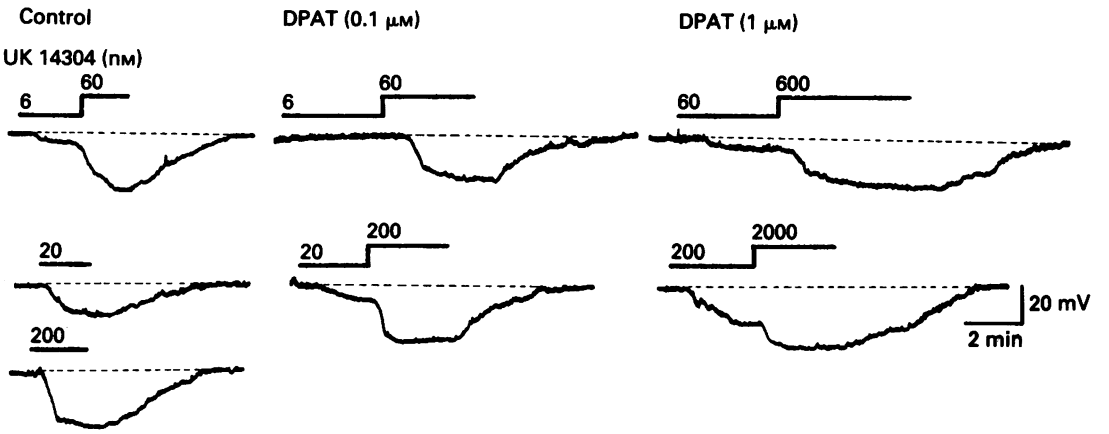

Figure 2 Hyperpolarizations recorded from a single neurone in response to superfusions with several concentrations of UK 14304 in the absence (control) and presence of increasing concentrations of 8-hydroxy-2-(n-dipropylamino) tetralin (DPAT). Numbers indicate UK 14304 concentration in nM.

ple, the noradrenaline or UK 14304-induced hyperpolarizations returned to control levels within 15–20 min of washing a supramaximal concentration of idazoxan (10 μM) from the bath, whereas a washout period of approximately 60–75 min was necessary after application of 1 or 3 μM 8-OH-DPAT.

Determination of dissociation equilibrium constant

Membrane hyperpolarizations produced by superfusion with several concentrations of noradrenaline or UK 14304 were recorded in the absence and then the presence of increasing concentrations of 8-OH-DPAT while recording from a single submucous plexus neurone. Figure 2 shows the types of recordings obtained during the protocol used in these experiments; agonists (UK 14304 or noradrenaline) were applied for 2–6 min periods either in a non-cumulative or semi-cumulative fashion (see Figure 2) and 8-OH-DPAT was present in the bathing fluid for 7 min before and then throughout the agonist applications. Four or five different concentrations of the α_2-adrenoceptor agonist were applied in control solution and then again in the presence of 3–4 concentrations of 8-OH-DPAT (0.1–3 μM); at each concentration of 8-OH-DPAT the agonist concentration was increased until a maximum response was attained.

Figure 3a shows all of the data points obtained from the experiment carried out on the neurone from which the recordings of Figure 2 were made. 8-OH-DPAT, in concentrations up to 1 μM, produced a parallel rightward shift in the UK 14304 concentration-hyperpolarization response curve. The maximum hyperpolarization produced by UK 14304 was slightly reduced in the presence of 3 μM 8-OH-DPAT, being 90% of the control response in this cell. In four other neurones examined this concentration (3 μM) of 8-OH-DPAT also depressed the maximum response to noradrenaline or UK 14304 by 5–15%, lower concentrations did not alter the maximum hyperpolarization ($n = 7$).

Figure 3b shows the Schild analysis (Arunlakshana & Schild, 1959) of the data in Figure 3a; the relationship was linear with a slope of 0.98 and pA_2 of 7.0. Similar experiments were carried out in two other neurones where concentration-effect curves were obtained before and in the presence of three concentrations (0.1, 0.3, 1 μM) of 8-OH-DPAT. These Schild plots were also linear with slopes of 0.97 and 0.95 and pA_2 values of 6.9 and 7.2; the dissociation equilibrium constants (K_D values) then were 60–125 nM. K_D values were also estimated in six other experiments in which approximately equal noradrenaline-induced hyperpolarizations were recorded before and after the addition of 0.3 or 1 μM 8-OH-DPAT; K_D values estimated in this manner were 40–170 nM ($n = 6$).

Selectivity of action of 8-OH-DPAT at other postsynaptic receptors

Somatostatin and opioids both hyperpolarize submucous plexus neurones by increasing the same potassium conductance as do α_2-adrenoceptor agonists; the opioid-induced hyperpolarization is mediated through δ-opioid receptor activation while the somatostatin response is unaffected by either naloxone or idazoxan (Mihara & North, 1986; Mihara *et al.*, 1987). It was therefore of interest to examine the

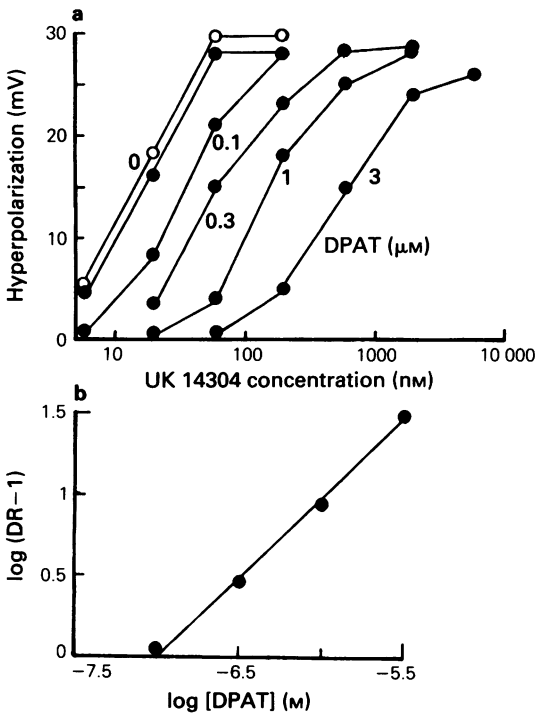

Figure 3 (a) Concentration-hyperpolarization response curves for the effect of UK 14304 in presence of increasing concentrations of 8-OH-DPAT and (b) Schild plot of these data, obtained from the experiment illustrated in Figure 2. (a) 8-Hydroxy-2-(n-dipropylamino) tetralin (DPAT) produced a parallel concentration-dependent shift to the right in the UK 14304 response (b) The Schild plot forms a straight line with slope of 0.98 and pA_2 (x-intercept) value of 7.0.

effects of 8-OH-DPAT on the hyperpolarizations produced by activation of these separate sets of receptors. We found that concentrations of 8-OH-DPAT less than 1 μM had no effect on the concentration-hyperpolarization response curves produced by either somatostatin or the δ-opioid receptor agonist, DPDPE ($n = 3$); higher concentrations (1–10 μM) also did not alter the opioid-induced hyperpolarization ($n = 4$) (Figure 4). However 1–10 μM 8-OH-DPAT slightly (10–20%) reduced the maximum response to somatostatin (Figure 4). This reduction in the maximum stomatostatin response was not dose-dependent, being 14 ± 1% ($n = 7$), 13 ± 2% ($n = 6$) and 15 ± 3% ($n = 5$) in the presence of 1, 3 and 10 μM 8-OH-DPAT, respectively.

Blockade of adrenergic inhibitory synaptic potential by 8-OH-DPAT

Stimulation of the nerve supply to submucous neurones can evoke three distinct synaptic potentials: the nicotinic fast excitatory synaptic potential (fast e.p.s.p.), the adrenergic inhibitory synaptic potential (i.p.s.p.), and the slow excitatory synaptic potential (slow e.p.s.p.) (Hirst & McKirdy, 1975; Surprenant, 1984; Mihara *et al.*, 1985). The i.p.s.p. has been shown to be due to activation of α_2-adrenoceptors (North & Surprenant, 1985). Superfusion with 8-OH-DPAT (20 nM) inhibited the i.p.s.p. in a concentration-dependent manner without decreasing the amplitudes of the fast or slow e.p.s.ps (Figure 5). The concentration of 8-OH-DPAT which produced 50% inhibition of the 'maximum-amplitude' i.p.s.p. (i.e. i.p.s.p. evoked by 4–6 nerve stimuli at 20 Hz, see North & Surprenant, 1985) was 250 ± 25 nM ($n = 10$).

Antagonism of presynaptic α_2-adrenoceptors

Activation of presynaptic α_2-adrenoceptors leads to a reduced amount of transmitter release at many central and peripheral synapses (e.g. Starke, 1977; Langer, 1981). In the submucous plexus preparation α_2-adrenoceptor-mediated presynaptic inhibition of transmitter release can be examined by recording the depression of the amplitude of the nicotinic fast e.p.s.p. in the submucous neurones (Mihara *et al.*, 1985), as well as by recording the reduction of the amplitude of the excitatory junction potential (e.j.p.) in the smooth muscle of the arterioles (Holman & Surprenant, 1980).

In two separate series of experiments, nicotinic fast e.p.s.ps were recorded from the submucous neurones or e.j.ps were recorded from the submucous plexus arteriolar smooth muscle; superfusion with UK 14304 depressed the amplitudes of the fast e.p.s.ps and e.j.ps in a concentration-dependent manner. The concentrations of UK 14304 which reduced these responses by 50% were similar, being 55 ± 6 nM ($n = 8$) and 62 ± 12 nM ($n = 4$) for the fast e.p.s.p. and e.j.p., respectively. In the presence of 300 nM 8-OH-DPAT, the fast e.p.s.p. was reduced by only 6 ± 2% ($n = 4$) by 50 nM UK 14304 and the e.j.p. was not significantly altered by this concentration of UK 14304 ($n = 3$). An example of the reversal of the α_2-adrenoceptor-mediated inhibition of the fast e.p.s.p. and the e.j.p. by 8-OH-DPAT is shown in Figure 6.

Discussion

Results of this study show that 8-OH-DPAT can act as a competitive α_2-adrenoceptor antagonist with a K_D value of approximately 100 nM at the postsynaptic α_2-adrenoceptors on submucous plexus neurones. 8-OH-

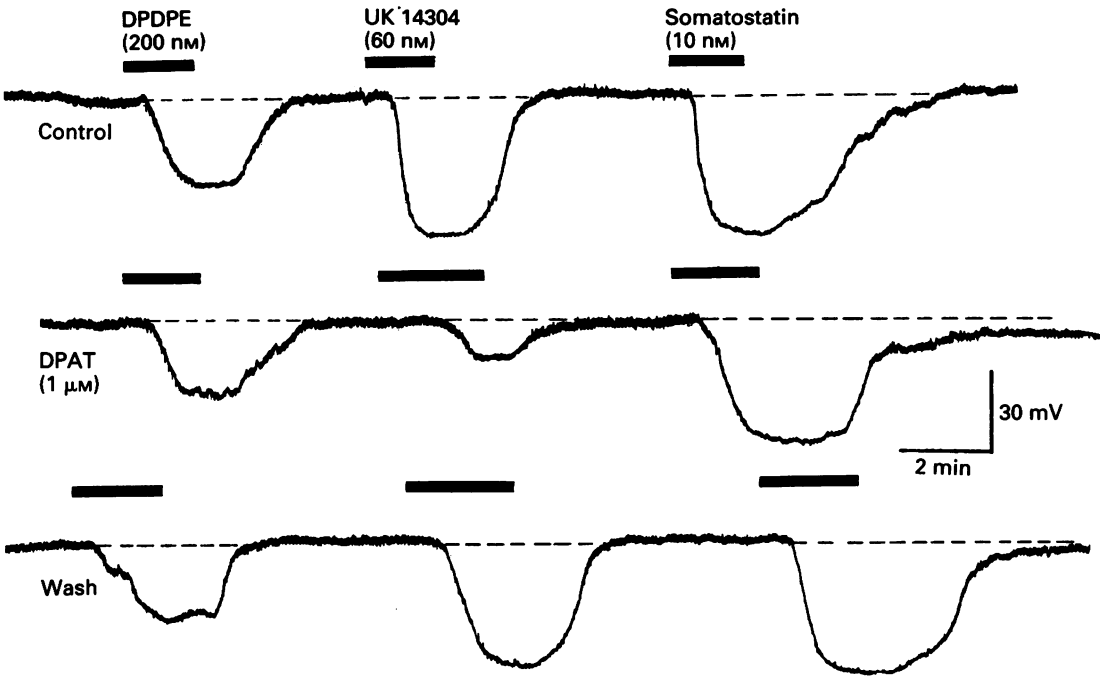

Figure 4 Selectivity of action of 8-hydroxy-2-(n-dipropylamino)tetralin (DPAT) in blocking α_2-adrenoceptor-mediated hyperpolarizations. Recordings obtained from a single neurone. The δ-opioid receptor agonist [D-Pen^2, D-Pen^5] enkephalin (DPDPE), UK 14304 and somatostatin each produced membrane hyperpolarizations; concentrations of each agonist are those which produced maximum responses. In the presence of 1 μM 8-OH-DPAT (middle trace) the UK 14304 response was decreased by 75%, the somatostatin response was decreased by 12% and the opioid response was not altered when compared to the opioid response obtained 35 min after washout of 8-OH-DPAT.

DPAT was also effective in blocking the presynaptic α_2-adrenoceptors on cholinergic fibres of submucous neurones and on noradrenergic fibres innervating the submucous arterioles; in fact, the hyperpolarization of locus coeruleus neurones in slices of the rat brain, which results from activation of α_2-adrenoceptors (Williams *et al.*, 1985), is similarly inhibited by 8-OH-DPAT (J.T. Williams & M.J. Christie, personal communication). Thus, it would appear that 8-OH-DPAT is an effective α_2-receptor blocker centrally, as well as in the periphery.

The study of the actions of 8-OH-DPAT on sub-

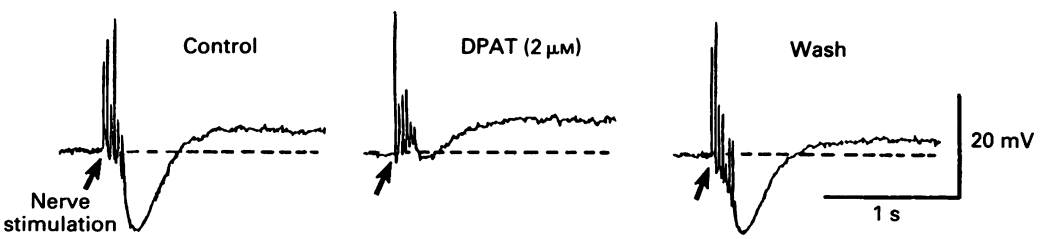

Figure 5 8-Hydroxy-2-(n-dipropylamino)tetralin (DPAT) blocks the α_2-receptor-mediated inhibitory synaptic potential in submucous plexus neurones. Shown are synaptic potentials recorded from one neurone in response to a train of 6 stimuli delivered at a frequency of 20 Hz before adding 8-OH-DPAT, 5 min after the addition of 2 μM 8-OH-DPAT and 30 min after washout of 8-OH-DPAT.

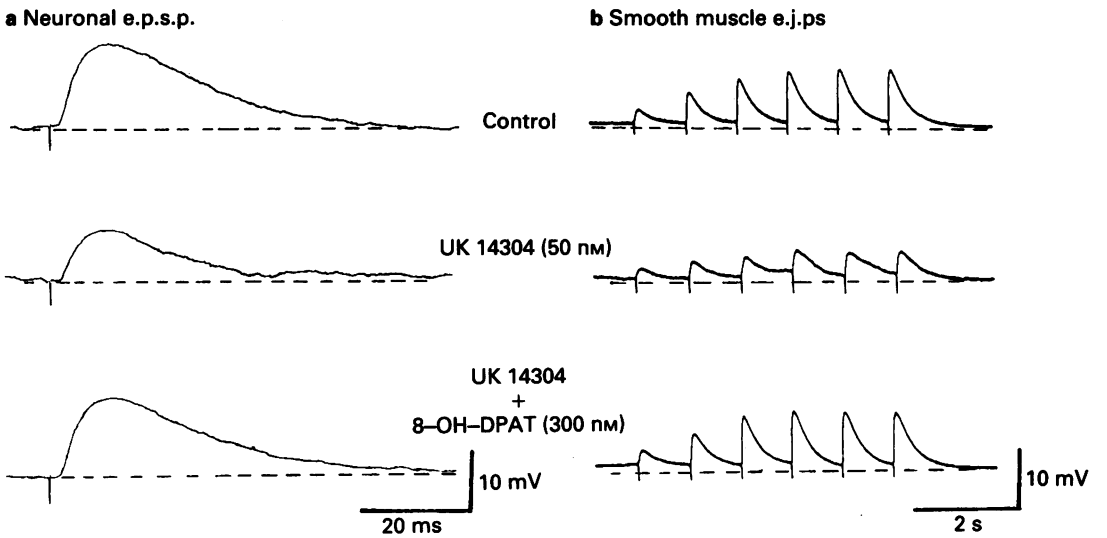

Figure 6 (a) Fast excitatory synaptic potentials (e.p.s.ps) recorded from a submucous plexus neurone and (b) (e.j.ps) recorded from submucous plexus arteriolar smooth muscle in control solution (upper traces), in the presence of 50 nM UK 14304 (middle traces) and in the presence of UK 14304 (50 nM) plus 300 nM 8-hydroxy-2-(n-dipropylamino) tetralin (8-OH-DPAT) (lower traces). 8-OH-DPAT prevented the presynaptic (a) and prejunctional (b) inhibition of transmitter release by this α_2-adrenoceptor agonist. All recordings of e.j.ps were obtained in the presence of 200 nM prazosin in order to prevent any possible postsynaptic α_1-adrenoceptor-mediated effects. Perivascular nerve stimulation (6 pulses at 1 Hz) was used to evoke the train of e.j.ps.

mucous neurones was made easier by the absence of any direct effect of this substance on the membrane potential of these neurones. Although 5-HT itself has both direct (membrane depolarization) and indirect (presynaptic inhibition of transmitter release) actions on submucous neurones (Hirst & Silinsky, 1975; Surprenant & Crist, 1986), none of these actions was mimicked by 8-OH-DPAT. In contrast, direct hyperpolarizing actions of 8-OH-DPAT and other 5-HT_1 agonists have been observed in 5-HT-containing neurones of the rat dorsal raphe nucleus (Sprouse & Aghajanian, 1987; J.T. Williams, personal communication) and hippocampus (Andrade *et al.*, 1986). These 5-HT_1 receptor-activated membrane hyperpolarizations, like the α_2-adrenoceptor-mediated hyperpolarization in submucous neurones, are due to an increased potassium conductance of the membrane (Segal, 1980; Aghajanian & Lakoski, 1984; Yoshimura & Higashi, 1985). Thus, the intriguing situation exists whereby two distinct receptors (α_2 and 5-HT_1) which mediate the same effect are acted upon in exactly the opposite manner by the same molecule. In other words, activation of 5-HT_1 receptors on dorsal raphe and hippocampal neurones leads to an increased membrane potassium conductance and 8-OH-DPAT is an agonist. Activation of α_2-adrenoceptors in submucous plexus (and a variety of other neurones) leads to an increased potassium conductance but 8-OH-DPAT is an antagonist. Furthermore, this α_2-antagonist/5-HT_1-agonist capacity does not appear to be unique to 8-OH-DPAT but may be a common feature of other 5-HT_1 agonists; we have observed qualitatively similar (though less potent) actions by trifluoromethyl (phenyl) piperazine (TFMPP), another often used 5-HT_1 agonist (e.g. Sills *et al.*, 1984; Peroutka, 1984). These findings might suggest that significant homology exists between the molecular structure of the α_2-adrenoceptor and the 5-HT_1 receptor.

Results from recent behavioural and *in vivo* voltammetry studies have indicated that α_2-adrenoceptors may be involved in the actions of intravenously or intrathecally administered 8-OH-DPAT and other 5-HT receptor agonists (Marsden & Martin, 1986; Archer *et al.*, 1986). In view of the present findings, it seems likely that some of the actions of 8-OH-DPAT observed in *in vivo* experiments may have resulted from blockade of α_2-adrenoceptors.

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