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Electrophysiological and neurochemical evidence that pindolol has agonist properties at the 5-HT_{1A} autoreceptor *in vivo*

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1 It has been hypothesized that 5-HT_{1A} autoreceptor antagonists may enhance the therapeutic efficacy of SSRIs and other antidepressants. Although early clinical trials with the β-adrenoceptor/5-HT_1 ligand, pindolol, were promising, the results of recent more extensive trials have been contradictory. Here we investigated the actions of pindolol at the 5-HT_{1A} autoreceptor by measuring its effect on 5-HT neuronal activity and release in the anaesthetized rat.

2 Pindolol inhibited the electrical activity of 5-HT neurones in the dorsal raphe nucleus (DRN). This effect was observed in the majority of neurones tested (10/16), was dose-related (0.2–1.0 mg kg^{-1}, i.v.), and was reversed by the 5-HT_{1A} receptor antagonist, WAY 100635 (0.1 mg kg^{-1}, i.v.), in 6/7 cases tested.

3 Pindolol also inhibited 5-HT neuronal activity when applied microiontophoretically into the DRN in 9/10 neurones tested. This effect of pindolol was current-dependent and blocked by co-application of WAY 100635 (3/3 neurones tested).

4 In microdialysis experiments, pindolol caused a dose-related (0.8 and 4 mg kg^{-1}, i.v.) fall in 5-HT levels in dialysates from the frontal cortex (under conditions where the perfusion medium contained 1 μM citalopram). In rats pretreated with WAY 100635 (0.1 mg kg^{-1}, i.v.), pindolol (4 mg kg^{-1}, i.v.) did not decrease, but rather increased 5-HT levels.

5 We conclude that, under the experimental conditions used in this study, pindolol displays agonist effects at the 5-HT_{1A} autoreceptor. These data are relevant to previous and ongoing clinical trials of pindolol in depression which are based on the rationale that the drug is an effective 5-HT_{1A} autoreceptor antagonist.

Keywords: Pindolol; 5-HT_{1A} receptor; antidepressants; DRN; microdialysis; electrophysiology

Introduction

Pindolol is currently the subject of much interest on the basis of recent clinical evidence that the drug potentiates the therapeutic effect of selective 5-hydroxytryptamine (5-HT; serotonin) reuptake inhibitors (SSRIs) and other drugs used in the treatment of major depressive illness (Artigas *et al*., 1994; Blier & Bergeron, 1995). Although pindolol is well known as a β-adrenoceptor antagonist, it is the ability of the drug to block 5-HT_{1A} autoreceptors that is believed to account for its antidepressant effects in these studies (Artigas *et al*., 1996).

5-HT_{1A} receptors are located on the soma and dendrites of 5-HT neurones where they function as autoreceptors to cause an inhibition of 5-HT cell firing and release (Aghajanian *et al*., 1987; Sharp & Hjorth, 1990; Miquel *et al*., 1991). The receptors are also located postsynaptically in specific regions of the forebrain (Miquel *et al*., 1991). There is much evidence indicative of pindolol behaving as an antagonist at both 5-HT_{1A} autoreceptors and postsynaptic 5-HT_{1A} receptors.

Thus, in microdialysis studies in the rat, pindolol has been shown to block the inhibition of hippocampal 5-HT release induced by 5-HT_{1A} receptor agonists acting on 5-HT_{1A} autoreceptors (Sharp *et al*., 1989; Sharp & Hjorth, 1990). Pindolol also blocks the 5-HT syndrome as well as other behavioural, and neuroendocrine, responses induced by 5-HT_{1A} receptor agonists acting on postsynaptic 5-HT_{1A} receptors (e.g. Tricklebank *et al*., 1985; Gilbert *et al*., 1988; Ahlenius & Larsson, 1989; Millan *et al*., 1991). Furthermore, pindolol inhibits 5-HT_{1A} receptor agonist-induced second messenger responses in rat hippocampal tissue (Oksenberg & Peroutka, 1988; Schoeffter & Hoyer, 1988) and transfected cells (Boddeke *et al*., 1992; Pauwels *et al*., 1993). In man, pindolol antagonizes neuroendocrine and temperature responses induced by 5-HT_{1A} receptor agonists (Lesch *et al*., 1990; Anderson & Cowen, 1992; Seletti *et al*., 1995).

Despite the findings outlined above, there is also some indirect evidence that pindolol may have some agonist activity at 5-HT_{1A} receptors. Thus, Hjorth and Carlsson (1986) showed that pindolol (but not selective β-adrenoceptor antagonists) reduced brain 5-HT synthesis and metabolism. Also, in certain behavioural tests (anti-conflict, exploration, lower-lip-retraction, drug-discrimination) pindolol shows activity consistent with it being a 5-HT_{1A} receptor agonist (Moore *et al*., 1993; Sánchez, 1993; Przegalinski *et al*., 1994; 1995; Sánchez *et al*., 1996). Furthermore, in the latter tests the effect of pindolol was blocked by 5-HT_{1A} receptor antagonists (Sánchez, 1993; Przegalinski *et al*., 1994; 1995; Sánchez *et al*., 1996). Finally, in volunteer studies Meltzer and Maes (1996) found that pindolol induces hypothermia and elevates plasma cortisol, and concluded that pindolol has 5-HT_{1A} receptor agonist properties in man.

The utility of pindolol as an adjunct to antidepressant treatments was predicted on the basis of it being an antagonist at 5-HT_{1A} autoreceptors. Should pindolol have efficacy at 5-HT_{1A} receptors, then this would need to be taken into account when interpreting the results of the recent antidepressant trials

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using the drug. For instance, a partial agonist might be expected to have a small and/or inconsistent therapeutic benefit compared to a silent antagonist. Indeed, despite the promising positive results in early antidepressant trials with pindolol (Artigas *et al*., 1994; Blier & Bergeron, 1995), results have been contradictory in recent more extensive trials (Berman *et al*., 1997; Perez *et al*., 1997).

In recent electrophysiological studies we unexpectedly found that pindolol inhibited the activity of 5-HT neurones in the dorsal raphe nucleus (DRN). Here we describe our investigation of this effect in which we used a combination of *in vivo* electrophysiological and neurochemical methods.

Methods

Animals

Male Sprague-Dawley rats (270–310 g, Harlan-Olac, Bicester, U.K.) were housed in groups of up to 6 under conditions of constant temperature (21°C) and humidity (50%), in a 12 h light/dark cycle (lights on 8 h 00 min). Food and water were available *ad libitum*.

General surgical procedures

Rats were initially anaesthetized with 400–500 mg kg^{-1}, i.p., chloral hydrate and supplementary doses were given as required to maintain full general anaesthesia. Animals were mounted in a stereotaxic frame (Kopf; with the incisor bar set at −3.3 mm) for implantation of a recording electrode or microdialysis probe. A lateral tail vein was cannulated for administration of drugs. Core temperature was maintained at 35–36°C throughout the experiment by use of a thermo-regulated blanket connected to a rectal thermometer.

Electrophysiological studies

Spontaneously active 5-HT neurones in the DRN were monitored by means of extracellular recording techniques. Single or multi-barrelled glass microelectrodes filled with 2 M NaCl containing 2% Pontamine Sky Blue (3–8 MΩ impedance *in vitro*), were implanted above the DRN (AP −7.8 mm; ML 0 mm; DV −4.5 mm) and then lowered under the control of a microdriver. Signals were amplified (×1000), filtered (300–3000 Hz band-pass) and fed to an audio speaker, an oscilloscope, and a chart recorder. The signal was also recorded on digital audio tape for off-line analysis.

5-HT neurones were identified on the basis of their electrophysiological characteristics (broad action potentials with positive-negative or positive-negative-positive deflections, regular firing pattern, 0.5–3 Hz firing rate). Burst-firing 5-HT neurones (Hajós *et al*., 1995) were not included in this study.

When drugs were administered systemically, baseline firing activity was recorded for at least 3 min, before vehicle or drugs were administered. Drugs were injected i.v. in doubling doses (initial volume 0.1 ml) at 2 min intervals. Only one neurone per animal was studied.

Prefabricated 5-barrelled electrodes (R & D Scientific Glass Company) coupled to an iontophoretic unit (IP-X5, Neuro Data) were used for iontophoresis. The central barrel (impedance of 2–8 MΩ) was used for extracellular recordings, one side barrel (filled with 2 M NaCl solution was used for automatic current balancing, and other side barrels (impedance of 30–50 MΩ) were used for application of drugs. The drug solutions were; 8-OH-DPAT (5 mM in 0.2 M NaCl, 5 nA negative retaining current), pindolol (20 mM in 0.2 M NaCl, 5 nA negative retaining current) or WAY 100635 (5 mM in 0.2 M NaCl, 5 nA negative retaining current). Drugs were applied for 30–60 s (pindolol and 8-OH-DPAT), or 90 s (WAY 100635) at regular intervals. Multiple applications of the same drug were made in a random order.

At the end of each experiment a small amount of Pontamine Sky Blue was iontophoretically ejected from the tip of the recording electrode. The brain was removed, post-fixed in 4% paraformaldehyde, and the position of the electrode tip was subsequently determined by microscopic inspection of slide-mounted sections.

Microdialysis studies

We selected the frontal cortex for our microdialysis studies since this region receives its 5-HT input predominantly from the DRN (cf. McQuade *et al*., 1997) where the 5-HT neuronal recordings were made. Single cannula microdialysis probes (with 4 mm window) were stereotaxically implanted into the frontal cortex (AP +3.2 mm; ML +3.0 mm; DV −4.5 mm; from bregma and dura surface, Paxinos & Watson, 1986) and constantly perfused (2 μl min^{-1}) with artificial cerebrospinal fluid containing citalopram (1 μM). Dialysates were collected every 20 min and assayed immediately for 5-HT by high performance liquid chromatography with electrochemical detection (Gartside *et al*., 1995). Basal levels of 5-HT in dialysates from the frontal cortex were typically 40–60 fmol (see figure legends for individual group means).

After baseline levels of 5-HT had stabilized (typically 3–4 h post probe implantation), drugs were administered i.v. as a single bolus injection of 1 ml kg^{-1}. The response was followed for a further 2 h. At the end of each experiment, the brain was removed, post-fixed in 4% paraformaldehyde and the location of the microdialysis probe was subsequently verified in brain sections.

Data analysis

For the electrophysiological studies, the firing rate was determined during 6×10 s periods before, and for 3×10 s sample periods during (iontophoresis) or after (systemic administration) drugs. From these data, a percentage inhibition induced by each total dose (or current) of drug was calculated. For the microdialysis experiments, data are expressed as a % of the amount of 5-HT in the 20 min sample collected immediately before the pindolol/vehicle injection. For the 2 h following pindolol/vehicle injection, an area under the curve (% AUC) was calculated relative to no change (100%). Drug-treated groups were compared to the vehicle-treated group by analysis of the % AUC by 1-way ANOVA with *post-hoc* Dunnett's test. Significance at the 95% level and above is shown. Data are presented as mean±s.e.mean values.

Drugs and chemicals

The drugs used (with suppliers) were as follows: (±)-pindolol (Sigma), WAY 100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl) cyclo-hexane carboxamide 3HCl; Wyeth Research, Maidenhead, U.K.), paroxetine HCl (SmithKline Beecham, Harlow, U.K.), and 8-OH-DPAT (8-hydroxy-di(2-n-dipropylamino)tetralin HBr; RBI). Pindolol was dissolved in a few drops of glacial acetic acid, made up to volume with 5% glucose and then adjusted to approximately pH 4.5 with sodium hydroxide. WAY100635 and paroxetine were dissolved in water.

Results

Effect of pindolol on 5-HT neuronal firing: systemic administration

The effect of i.v. pindolol administration was tested on 16 5-HT neurones in the DRN of the anaesthetized rat. With respect to their response to pindolol, the neurones could be divided into 2 groups.

Pindolol-sensitive neurones The first group comprised 10 neurones which were 'pindolol-sensitive'. In these neurones pindolol caused a dose-dependent inhibition of firing (see Figure 1). The response of individual 'pindolol-sensitive' neurones ranged from complete inhibition at 0.5 mg kg^{-1} pindolol, to only 30% inhibition after 2.0 mg kg^{-1} pindolol. The 5-HT$_{1A}$ receptor antagonist WAY 100635 (0.1 mg kg^{-1}, i.v.) reversed the effect of pindolol in the majority of neurones tested (7/8). Figure 2a and b shows the effect of pindolol and WAY 100635 on the activity of individual pindolol-sensitive neurones.

Pindolol-insensitive neurones The remaining 6 neurones were 'pindolol-insensitive' (see Figure 2c for an example). In these neurones, administration of pindolol at doses from 0.25–2.0 mg kg^{-1} had no consistent effect on firing rate. Small variations in firing rate were observed, but they showed no apparent dose-response relationship. In 4 of the 6 pindolol-insensitive neurones the 5-HT uptake inhibitor, paroxetine (0.1–1.6 mg kg^{-1}, i.v.), was administered after pindolol. In each case (4/4), the firing activity of the neurone was inhibited by paroxetine (data not shown).

Post-hoc examination of the data, revealed that the mean basal firing rate of pindolol-insensitive neurones was twice that of the pindolol-sensitive group (19.81 ± 0.7 (6) spikes 10 s^{-1} and 8.95 ± 1.33 (10) spikes 10 s^{-1}, respectively). In other respects (e.g. regularity of firing, location within the DRN) the two groups were indistinguishable.

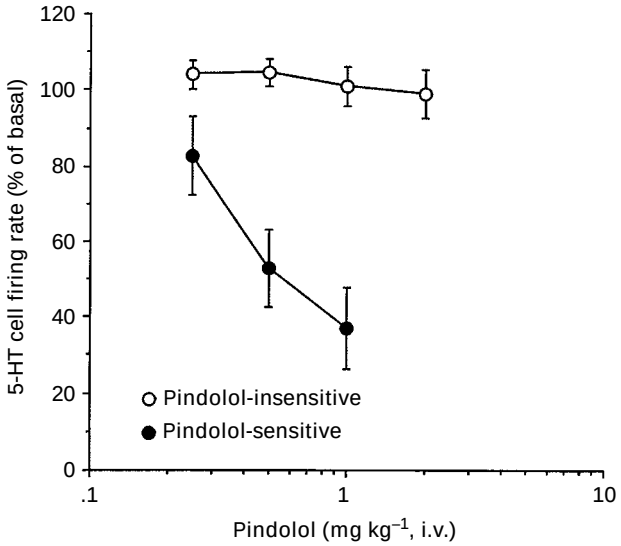

Figure 1 Dose-response curve showing the effect of i.v. administration of pindolol on the firing rate of 5-HT neurones in the DRN of the anaesthetized rat. Cells were grouped into pindolol-sensitive ($n=10$) and pindolol-insensitive ($n=6$) as described in the text. Each point is a mean and vertical lines show s.e.mean.

Effect of pindolol on 5-HT neuronal firing: iontophoretic application

Pindolol was iontophoretically applied to 10 5-HT neurones in the DRN (2 rats). In 9/10 neurones, pindolol inhibited firing activity in a current-dependent (5–30 nA) manner, with near complete cessation of firing being achieved at the higher currents (Figures 3 and 4). The inhibitory effect of iontophoretically applied pindolol was achieved regardless of the baseline firing rate. When pindolol was iontophoretically applied during administration of WAY 100635, the inhibitory effect of pindolol (30 nA) was abolished in each of the 3 neurones tested (see Figure 4b, for an example).

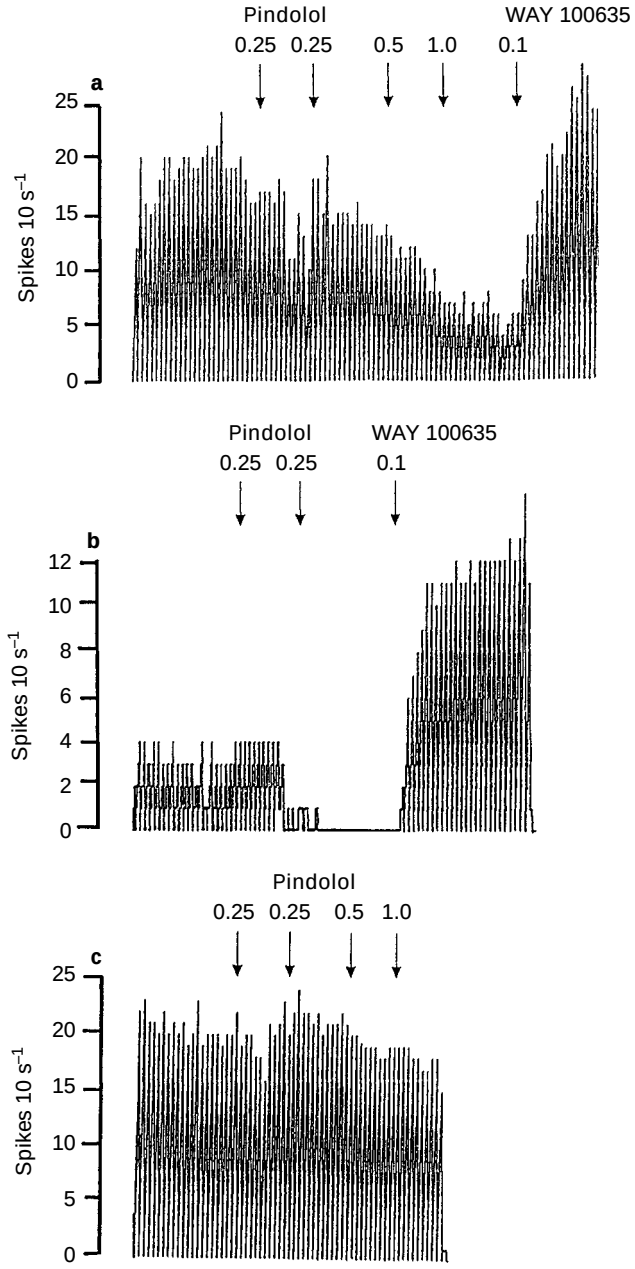

Figure 2 The effect of i.v. pindolol on the electrical activity of individual 5-HT neurones in the DRN. (a) and (b) Show pindolol-sensitive neurones while (c) shows a pindolol-insensitive neurone. Note the reversal of the inhibitory effect of pindolol by WAY 100635. Drugs were administered at the time points and doses (mg kg^{-1}, i.v.) indicated.

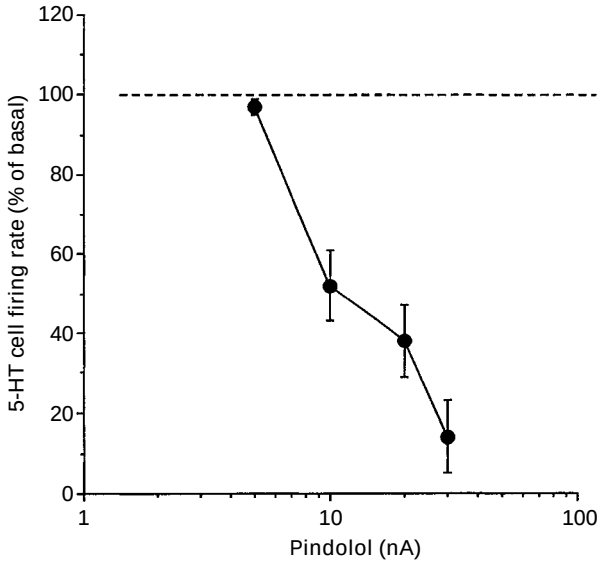

Figure 3 Current-response curve showing the effect of microiontophoretically applied pindolol on 5-HT neurones in the DRN. The cells shown ($n=9$) were pindolol-sensitive; one pindolol-insensitive neurone was also noted in these experiments (see text). Each point is a mean and vertical lines show s.e.mean.

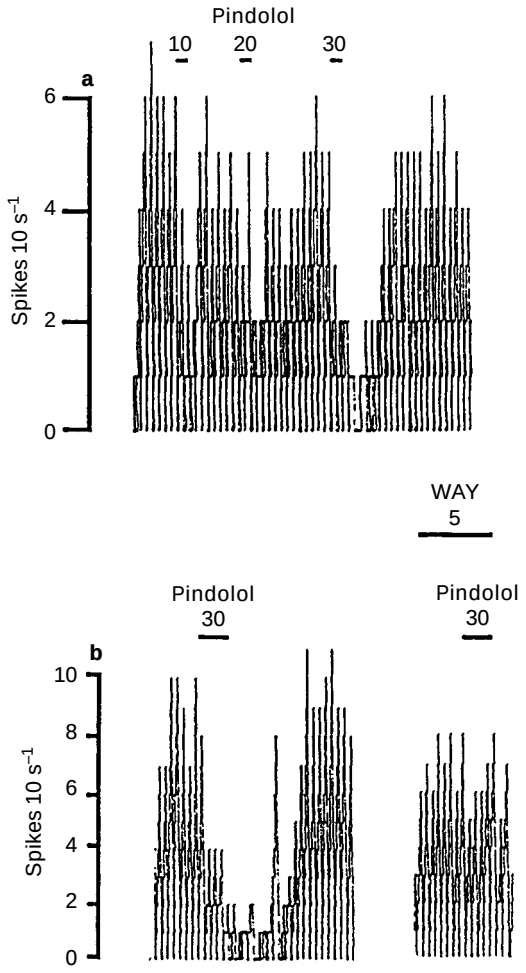

Figure 4 Examples of individual 5-HT neurones in the DRN and their response to (a) iontophoretic application of increasing currents of pindolol, and (b) iontophoretic application of pindolol in the absence and presence of WAY 100635. Bars represent the duration of drug application at the current (nA) indicated.

Iontophoretic application of 8-OH-DPAT also inhibited firing in a current-dependent (1 – 10 nA) manner (6/6 neurones tested). The inhibition by 8-OH-DPAT was seen in 5 of the neurones inhibited by pindolol as well as in the single neurone in which pindolol had no effect (data not shown).

Effect of pindolol on extracellular 5-HT in frontal cortex: systemic administration

The effect of pindolol on extracellular 5-HT in the frontal cortex was examined by use of *in vivo* microdialysis. Pindolol (0.8 and 4.0 mg kg^{-1}, i.v.) induced a modest, dose-related decrease in 5-HT levels in dialysates which lasted over the 2 h of the experiment (Figure 5). When WAY 100635 (0.1 mg kg^{-1}, i.v.) was administered 10 min before pindolol (4.0 mg kg^{-1}), pindolol no longer induced a decrease in 5-HT levels, but rather 5-HT levels rose to approximately 150% of the pre-drug value. Analysis of variance of the % AUC revealed a highly significant effect of treatment ($F=8.5$, $P<0.0001$) with both the pindolol (4 mg kg^{-1}, i.v.) and the pindolol (4 mg kg^{-1}) plus WAY 100635 (0.1 mg kg^{-1}, i.v.) groups being significantly different from the vehicle-treated group.

Discussion

In the present study we investigated the activity of pindolol at 5-HT$_{1A}$ autoreceptors as assessed by its ability, firstly, to inhibit 5-HT neuronal firing in the DRN and, secondly, to decrease 5-HT release in frontal cortex as measured by microdialysis. In more than 50% of the 5-HT neurones tested, i.v. administration of pindolol caused a clear-cut and dose-related inhibition of firing. An even higher proportion of 5-HT neurones was inhibited when pindolol was applied directly into the DRN by microiontophoresis. These electrophysiological data were supported by the findings in the microdialysis study

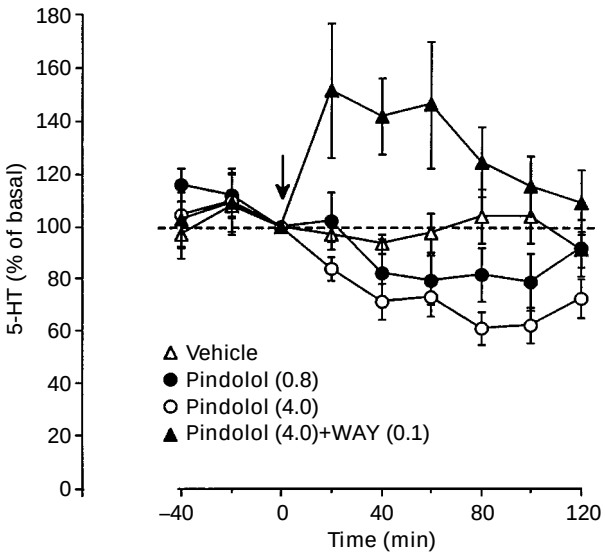

Figure 5 Effect of pindolol and WAY 100635 on extracellular 5-HT in frontal cortex of the anaesthetized rat. 5-HT in dialysates is expressed a % of the absolute amount of 5-HT in the sample collected immediately before injection of pindolol/vehicle (arrowed). Rats were treated with pindolol and WAY 100635 (10 min before pindolol) at the doses (mg kg^{-1}, i.v.) shown in the figure. Basal levels (fmol 20 min^{-1}) of 5-HT (mean$\pm$s.e.mean (n)) in the 4 treatment groups were as follows: vehicle, 47$\pm$6 (6); 0.8 mg kg^{-1} pindolol, 50$\pm$3 (5); 4 mg kg^{-1} pindolol, 42$\pm$7 (6); WAY 100635 + pindolol, 57$\pm$3 (6).

that i.v. pindolol also induced a fall in 5-HT efflux in the frontal cortex. Both the inhibition of 5-HT cell firing and 5-HT efflux were blocked by the selective 5-HT$_{1A}$ receptor antagonist, WAY 100635. It has previously been shown that blockade of β-adrenoceptors *per se* does not decrease either 5-HT neuronal firing or release (Lanfumey & Adrien, 1988; Sharp *et al*., 1989). Taken together, our findings suggest that under the present experimental conditions, pindolol has an agonist action at the somatodendritic 5-HT$_{1A}$ autoreceptor.

Surprisingly few studies have described the effect of pindolol on 5-HT neuronal firing in the DRN. In a recent study, Romero and colleagues (1996) showed that pindolol had no effect on the baseline firing activity of 5-HT neurones in the DRN. However, major differences between the latter study and our own in terms of the duration and route of administration of pindolol (2 days at 10–15 mg kg^{-1}, day^{-1} s.c. infusion via minipumps, versus 0.25–2.0 mg kg^{-1}, i.v. bolus injection), make comparison of the findings very difficult. Nevertheless, it is of note that in the present study we did find neurones in the DRN which were insensitive to the inhibitory effects of pindolol. Since these neurones were inhibited by the 5-HT uptake blocker, paroxetine, they are likely to be 5-HT neurones.

Interestingly, we noted that those 5-HT neurones inhibited by pindolol (given i.v.) had a mean basal firing rate which was approximately half that of the pindolol-insensitive neurones. In this respect the pindolol-sensitive and -insensitive groups of 5-HT neurones were distinct, with only one pindolol-sensitive neurone (shown in Figure 2b) having a basal firing rate in the range of the pindolol-insensitive neurones. A negative correlation between basal firing rate and susceptibility to inhibition by autoreceptor agonists (given i.v.) has been noted previously for both 5-HT neurones (Jacobs *et al*., 1983) and dopaminergic neurones (Shepherd & German, 1982; White & Wang, 1983). It has been suggested that slow firing 5-HT neurones are more sensitive to 5-HT agonists because they have higher autoreceptor density than fast firing neurones (Jacobs *et al*., 1983). Therefore, since the inhibition of 5-HT neurones by pindolol is likely to be mediated via activation of 5-HT$_{1A}$ autoreceptors (see above), the pindolol-sensitive neurones may have higher 5-HT$_{1A}$ autoreceptor densities than the pindolol-insensitive neurones.

We did not test whether pindolol-insensitive 5-HT neurones would be inhibited by higher doses of pindolol. However, this may well be the case since almost all 5-HT neurones tested were inhibited by iontophoretically applied pindolol, regardless of baseline firing rate. It is likely that the local concentration of pindolol achieved following iontophoretic application is much higher than that achieved following systemic administration.

In our microdialysis experiments we found that pindolol decreased dialysate 5-HT levels, and that this effect was blocked by WAY 100635. This finding is consistent with our electrophysiological data, and also directly supports our conclusion that pindolol has a 5-HT$_{1A}$ receptor agonist action. In contrast to these results, previous microdialysis studies from this laboratory (Sharp *et al*., 1989; Hjorth & Sharp, 1990) and elsewhere (Bosker *et al*., 1994; Assié & Koek, 1996) have failed to detect a decrease in extracellular 5-HT following administration of pindolol. In this respect, two points are worthy of note.

Firstly, previous studies were carried out in the hippocampus, whilst here we studied the frontal cortex. There is recent evidence that 5-HT efflux in the frontal cortex is more sensitive to inhibition by 5-HT$_{1A}$ receptor agonists than in the hippocampus (Casanova & Artigas, 1996; McQuade *et al*., 1996). In addition, there is *in vitro* evidence that pindolol has antagonist properties at the rat 5-HT$_{1B}$ autoreceptor in frontal cortex (Middlemiss, 1985; Engel *et al*., 1986), an action which would tend to increase 5-HT release and offset the effect of 5-HT$_{1A}$ autoreceptor activation. It is conceivable that, under the experimental conditions used, the tone on 5-HT$_{1B}$ autoreceptors in the frontal cortex is less than in the hippocampus.

Secondly, in the present study pindolol was administered i.v. and could therefore reach the brain in higher concentrations than achieved in the previous studies in which the drug was administered s.c. Both ourselves (Sharp *et al*., 1989) and others (Assié & Koek, 1996) have found that the 5-HT$_{1A}$ antagonist properties of pindolol are poorer at higher doses. This latter result could reflect a 5-HT$_{1A}$ receptor agonist action at higher doses of pindolol.

In the present dialysis experiments, the combination of WAY 100635 and pindolol, caused an increase in extracellular 5-HT in the frontal cortex. We did note an increase above baseline in the firing rate of some (but not all) 5-HT neurones when WAY 100635 and pindolol were combined, which could possibly account for the increase in 5-HT. However, it seems more probable that the increase in 5-HT reflects the 5-HT$_{1B}$ receptor antagonist action of pindolol which becomes apparent when the 5-HT$_{1A}$ receptor agonist action of the drug is blocked (by WAY 100635). We have recently shown that the selective 5-HT$_{1B/1D}$ receptor antagonist, GR 127935, increases cortical extracellular 5-HT under conditions of high 5-HT tone (Sharp *et al*., 1997).

Although pindolol is generally considered to be a 5-HT$_{1A}$ receptor antagonist (see Introduction), our conclusion that the drug has 5-HT$_{1A}$ receptor agonist activity is supported by data in the literature. Thus, Hjorth and Carlsson (1986) found that (−)-pindolol decreased 5-HT synthesis and metabolism in various brain regions including cortex. In addition, in *in vivo* models of 5-HT$_{1A}$ receptor function, including antianxiety tests, drug discrimination paradigms, and measures of hypothermia and orofacial responses, pindolol has been found to have effects similar to established 5-HT$_{1A}$ receptor agonists (Meller *et al*., 1992; Sánchez, 1993; Moore *et al*., 1993; Przegalinski *et al*., 1994; 1995; Sánchez *et al*., 1996; Meltzer & Maes, 1996). Furthermore, when tested these effects were blocked by 5-HT$_{1A}$ receptor antagonists (Moore *et al*., 1993; Przegalinski *et al*., 1994; 1995). Indeed, although these models are indirect, a number of authors have concluded that pindolol may be a partial 5-HT$_{1A}$ receptor agonist (Meller *et al*., 1992; Moore *et al*., 1993; Przegalinski *et al*., 1994; Meltzer & Maes, 1996; Sánchez *et al*., 1996).

In *in vitro* assays of second messenger responses, pindolol invariably behaves as a silent 5-HT$_{1A}$ receptor antagonist at native 5-HT$_{1A}$ receptors (hippocampal membranes) and transfected 5-HT$_{1A}$ receptors (eg. HeLa cells), (Oskenberg & Peroutka, 1988; Schoeffter & Hoyer, 1988; Boddeke *et al*., 1992; Pauwels *et al*., 1993). Whilst such assays are generally regarded as providing a direct measure of drug efficacy, it is not without precedent that compounds behave as silent 5-HT$_{1A}$ receptor antagonists in these assays, but show agonist activity at the 5-HT$_{1A}$ autoreceptor. Thus, many 5-HT$_{1A}$ ligands with little or no apparent efficacy in *in vitro* second messenger assays (e.g. BMY 7378, MDL 73005EF, NAN-190, SDZ 216-525), and at first regarded as silent antagonists, have been shown *in vivo* to cause 5-HT$_{1A}$ receptor-mediated decreases in 5-HT neuronal firing and release (Gartside *et al*., 1990; Hjorth & Sharp, 1990; Sharp *et al*., 1990; 1996). Such compounds are now widely regarded as partial 5-HT$_{1A}$ receptor agonists. The present findings suggest that pindolol also belongs in this category.

Pindolol has recently been used as an adjunct to SSRIs in the treatment of depression. Although, initial open trials found that pindolol improved the efficacy of SSRIs (Artigas *et al*., 1994; Blier & Bergeron, 1995), more recent double blind trials have been less conclusive (Berman *et al*., 1997; Perez *et al*., 1997). The rationale for these studies is that pindolol facilitates the effect of SSRIs on 5-HT function by blocking somatodendritic 5-HT$_{1A}$ autoreceptors (for review see Artigas *et al*., 1996). It is possible that an agonist activity of pindolol at 5-HT$_{1A}$ autoreceptors makes the drug less effective in these trials than might be the case with a silent antagonist. Alternatively, it may be that in the presence of an SSRI, pindolol would act as an antagonist. This issue is a feature of our ongoing investigations.

In summary, although pindolol has 5-HT$_{1A}$ receptor antagonist properties (see Introduction), in the present experiments the drug clearly demonstrates an agonist action at the 5-HT$_{1A}$ autoreceptor. Whilst further investigation of the actions of pindolol is needed, trials into the potential of 5-HT$_{1A}$ receptor antagonists for the adjunctive treatment of depression might benefit from the investigation of 5-HT$_{1A}$ ligands with lower efficacy (and greater selectivity) than pindolol.

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