5-HT₁ agonists reduce 5-hydroxytryptamine release in rat hippocampus *in vivo* as determined by brain microdialysis

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1 An intracerebral perfusion method, brain microdialysis, was used to assess changes of 5-hydroxytryptamine (5-HT) release in the ventral hippocampus of the chloral hydrate-anaesthetized rat in response to systemic administration of a variety of 5-HT₁ receptor agonists.

2 A stable output of reliably detectable endogenous 5-HT was measured in dialysates collected from ventral hippocampus with the 5-HT reuptake inhibitor, citalopram, present in the perfusion medium.

3 Under these conditions the putative 5-HT_{1A} agonist 8-hydroxy-2-(di-n-propylamino)tetrinalin (8-OH-DPAT) caused a dose-dependent (5–250 µg kg⁻¹, s.c.) reduction of 5-HT in hippocampal dialysates.

4 Similarly, the putative 5-HT_{1A} agonists gepirone (5 mg kg⁻¹, s.c.), ipsapirone (5 mg kg⁻¹, s.c.) and buspirone (5 mg kg⁻¹, s.c.) markedly reduced levels of 5-HT in hippocampal perfusates whereas their common metabolite 1-(2-pyrimidinyl) piperazine (5 mg kg⁻¹, s.c.), which does not bind to central 5-HT_{1A} recognition sites, had no effect.

5 5-Methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (RU 24969), a drug with reported high affinity for brain 5-HT_{1B} binding sites, also produced a dose-dependent (0.25–5 mg kg⁻¹, s.c.) decrease of hippocampal 5-HT output.

6 These data are direct biochemical evidence that systemically administered putative 5-HT_{1A} and 5-HT_{1B} agonists markedly inhibit 5-HT release in rat ventral hippocampus *in vivo*.

Introduction

Radioligand binding studies have detected three pharmacologically distinct populations of 5-hydroxytryptamine (5-HT) recognition sites in rat brain tissue; 5-HT₁ sites bind [³H]-5-HT with high affinity (Peroutka & Snyder, 1979), 5-HT₂ sites are preferentially labelled by [³H]-spiperone (Leysen *et al.*, 1978; Peroutka & Snyder, 1979) and 5-HT₃ sites are recognised with high affinity by the ligand [³H]-GR65630 (Kilpatrick *et al.*, 1987). The 5-HT₁ binding site has been further subdivided on the basis of evidence that [³H]-5-HT binding sites display high and low affinity for spiperone, these being designated 5-HT_{1A} and 5-HT_{1B} recognition sites, respectively (Pedigo *et al.*, 1981). Additional 5-HT₁ subtypes, 5-HT_{1C} and 5-HT_{1D}, are also proposed (Pazos *et al.*, 1984; Heuring & Peroutka, 1987).

Currently, there are a number of ligands which show high selectivity for the 5-HT_{1A} binding site in

rat brain including 8-hydroxy-2-(di-n-propylamino)tetrinalin (8-OH-DPAT), buspirone, and its structurally related compounds, gepirone and ipsapirone (Middlemiss & Fozard, 1983; Hall *et al.*, 1985; Hamon *et al.*, 1986; McMillen *et al.*, 1987; Traber & Glaser, 1987). Further, these drugs behave as central 5-HT_{1A} agonists or partial agonists in both biochemical (De Vivo & Maayani, 1986; Bockaert *et al.*, 1987) and electrophysiological (Andrade & Nicoll, 1987; Rowen & Anwyl, 1987) experiments. On the other hand there are drugs such as 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (RU 24969) which have high affinity for the 5-HT_{1B} binding site (Sills *et al.*, 1984; Hoyer *et al.*, 1985; Peroutka, 1986).

There is increasing evidence that 5-HT_{1A} and 5-HT_{1B} binding sites function as autoreceptors on rat 5-HTergic neurones ascending from the mid-brain raphe nuclei into regions such as hippocampus

and cortex. For instance, putative 5-HT_{1A} agonists, both when systemically administered and micro-iontophoretically applied into the dorsal raphe nucleus, cause a marked reduction of the rate of firing of 5-HTergic neurones in the dorsal raphe nucleus (De Montigny *et al.*, 1984; Vander Maelen *et al.*, 1986; Blier & De Montigny, 1987; Sprouse & Aghajanian, 1987). These findings together with the observation that 5-HT_{1A} binding sites in the dorsal raphe nucleus are diminished by the neurotoxic lesion of brain 5-HT-containing neurones (Verge *et al.*, 1985; Weissmann-Nanopoulos *et al.*, 1985) indicate that the somatodendritic 5-HT autoreceptor is of the 5-HT_{1A} subtype. Conversely, data showing that the potency of 5-HT agonists in inhibiting the release of preloaded [³H]-5-HT from cortical slices *in vitro* correlates better with their affinity for the 5-HT_{1B} than 5-HT_{1A} recognition sites, suggest that the nerve terminal 5-HT autoreceptor is of the 5-HT_{1B} subtype (Middlemiss, 1984a,b; Engel *et al.*, 1986).

Consistent with the idea of a 5-HT₁ autoreceptor are data showing that putative 5-HT_{1A} and 5-HT_{1B} agonists reduce regional rat brain 5-HT turnover and metabolism measured *ex vivo* (Hjorth & Carlsson, 1982; Hjorth *et al.*, 1982; Anderson *et al.*, 1987; McMillen *et al.*, 1987) and *in vivo* (Brazell *et al.*, 1985; Marsden & Martin, 1986). Additionally, Brazell *et al.* (1985) reported that RU 24969 reduced cortical 5-HT release measured in the intact rat using brain microdialysis (Ungerstedt *et al.*, 1982; Zetterström *et al.*, 1983), but studies on the effect of 5-HT₁ agonists on this more direct *in vivo* measure of brain 5-HT release are currently lacking. The aim of the present study was to determine whether putative 5-HT_{1A} agonists inhibit brain 5-HT release as assessed by the microdialysis technique, with the view that this method may prove to be a useful tool to probe the pharmacology of the central 5-HT autoreceptor *in vivo*. This work has been presented in a preliminary form to the British Pharmacological Society (Sharp *et al.*, 1988).

Methods

Dialysis probe preparation and implantation

Male Sprague Dawley rats (280–320 g) were anaesthetized with a bolus injection of chloral hydrate (360 mg kg⁻¹) and supplementary doses were given as the experiment progressed (approximately 60 mg kg⁻¹ h⁻¹). A dialysis probe of the loop type (3 mm length, 270 µm diameter membrane, Cordis Dow Medical Inc., Brussels, Belgium) was prepared as previously described (Sharp *et al.*, 1986) and stereotactically implanted into either ventral hippocampus (co-ordinates for probe tip; rostral-caudal

–4.8 mm, lateral –4.6 mm, ventral –8.5 mm, from bregma and dura surface according to Paxinos & Watson, 1982) or medial frontal cortex (rostral-caudal +2.5 mm, lateral –0.6 mm, ventral –2.8 mm) and secured in place with dental cement and skull screws. The probe was continuously perfused (1 µl min⁻¹) with artificial CSF composition, mM: (NaCl 140, KCl 3, CaCl₂ 2.5, MgCl 1.0, Na₂HPO₄ 1.2, NaH₂PO₄ 0.27, glucose 7.2, pH 7.4) with or without the selective 5-HT reuptake inhibitor citalopram (1 µM). At the end of most experiments, brains were removed and frozen for examination of the cannula track in razor blade-cut fine sections. In all cases the track was correctly localized, terminating within the confines of either ventral hippocampus or medial frontal cortex.

Perfusate analysis

Perfusates were collected every 20 min and analysed directly for 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) using h.p.l.c. with electrochemical detection as described by Sharp *et al.* (1987). Separation was achieved by reversed-phase ion-pair chromatography conditions comprising a mobile phase of 0.15 M NaH₂PO₄, 0.1 mM EDTA, 12% (v/v) methanol, 0.01 mM sodium octane sulphonate, pH 4.0 with an Ultrasphere ODS column (150 × 4.6 mm). Detection was by a carbon paste or glassy carbon working electrode coupled to a BAS-4A electrochemical detector.

Experimental design

It was found that perfusion of the ventral hippocampus with artificial CSF containing citalopram 10⁻⁶ M provided dialysates with readily detectable and constant amounts of 5-HT (see Results) which enabled reliable determination of drug-induced decreases in 5-HT output. Under these conditions, 20 min dialysates were taken until similar amounts of 5-HT were detected in 2–3 consecutive samples (typically 120–160 min post probe implantation). Drug or saline vehicle was then administered subcutaneously, and dialysates were collected for a further 2 h.

Data analysis

5-HT in dialysates from rats treated with drug or saline is expressed as a percentage of the absolute amount of 5-HT contained in the dialysates collected immediately before drug or saline injection. Areas under the curve for the 2 h post injection period were calculated and statistical comparisons are made between the drug-treated groups and the saline-treated control group using Student's unpaired *t* test (two tailed) following analysis of variance where

appropriate. The approximate dose producing half the maximal observed effect was determined by extrapolation from plots of drug dose versus area under the curve data.

Drugs

Drugs with the following sources were used: 8-hydroxy-2-(di-n-propylamino)tetralin. HBr. (8-OH-DPAT, Research Biochemicals Inc., SEMAT, St. Albans), gepirone.HCl, buspirone.HCl and 1-(2-pyrimidinyl)-piperazine.HCl (1-PP; all from Bristol-Myers Co., Evansville, IN, U.S.A.), ipsapirone.HCl (TVX Q 7821, Troponwerke, Cologne, W. Germany) and 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-IH-indole (RU 24969, ICI). All drugs were soluble in normal or slightly acidified (ipsapirone) saline and injected in a volume of 1 ml kg⁻¹ (except RU 24969; 2 ml kg⁻¹).

Results

Basal levels of 5-HT and 5-HIAA in rat hippocampal and cortical dialysates

Endogenous 5-HT in dialysates collected from frontal cortex of the chloral hydrate-anaesthetized rat, in which artificial CSF was used as the perfusion medium, declined from high amounts detected 20–40 min following probe implantation (0.94 ± 0.1 (7) pmol 20 μ l⁻¹, mean value $\pm$ s.e.mean (n)) to considerably lower amounts 5 h later (0.1 ± 0.04 (7) pmol 20 μ l⁻¹) without reaching a constant level of output. In comparison, 5-HT in hippocampal dialysates declined from initially high amounts to a more constant output during the 2–4 h post implantation period (Figure 1) although levels of 5-HT during this time interval were considered to be too close to the limit of detection to assess accurately drug-induced reductions. Addition of citalopram (1 μ M) to the perfusion medium raised 5-HT levels in hippocampal dialysates by about 3 fold with output being relatively constant 100–120 min after implantation (Figure 1). All experiments were subsequently carried out with citalopram present and in the hippocampus.

In contrast to 5-HT, basal levels of 5-HIAA in both cortical (12.07 ± 1.63 (7) pmol 20 μ l⁻¹ perfusate, 3 h post implantation) and hippocampal (17.7 ± 5.1 (7) pmol 20 μ l⁻¹ perfusate, 3 h post implantation) dialysates were constant over the initial 4 h of perfusion. Addition of citalopram (1 μ M) to the perfusion medium tended to increase 5-HIAA in dialysates from hippocampus although this effect was not statistically significant (Figure 1). Introduction of citalopram to the perfusion medium following a 2 h control period also produced about a 4 fold rise of 5-HT with no consistent change in 5-HIAA in the dialysates (data not shown).

Figure 1 Basal amounts of 5-hydroxytryptamine (5-HT) (a) and 5-hydroxyindoleacetic acid (5-HIAA) (b) in 20 min dialysates collected from ventral hippocampus of the chloral hydrate-anaesthetized rat. Perfusion medium was artificial CSF with (●, 6 rats) or without (○, 5 rats) 1 μ M citalopram. Dotted line represents limit of detection for 5-HT. Mean values are shown with s.e.mean indicated by vertical bars.

Effect of 8-OH-DPAT on 5-HT in hippocampal dialysates

In comparison to saline-treated controls, the 5HT_{1A} agonist 8-OH-DPAT (5–250 μ g kg⁻¹, s.c.) caused an immediate and dose-dependent decrease in 5-HT in dialysates of the ventral hippocampus (Figure 2). The doses 100 and 250 μ g kg⁻¹ reduced 5-HT output to about 75% of preinjection values within 40 min of administration and 5-HT output remained at this level for the following 80 min. The approximate dose

Figure 2 Effect of the 5-HT_{1A} agonist 8-hydroxy-2-(di-n-propylamino)tetralin HBr (8-OH-DPAT) on 5-hydroxytryptamine (5-HT) in rat ventral hippocampus dialysates. Saline (○) or 8-OH-DPAT, at doses 5 (●), 10 (□), 100 (△) and 250 (▲) $\mu\text{g kg}^{-1}$, were injected subcutaneously at time zero. 5-HT in dialysates is expressed as a percentage of the absolute amount of 5-HT in the dialysate collected immediately before injection. Each curve is constructed from mean time point values obtained from the number of rats shown in parentheses; s.e.mean shown by vertical bars.

of 8-OH-DPAT producing half the maximal observed effect was 10 $\mu\text{g kg}^{-1}$.

Effect of gepirone, buspirone, ipsapirone and 1-PP on 5-HT in hippocampal dialysates

Each of the putative 5-HT_{1A} agonists gepirone, buspirone and ipsapirone, at a dose of 5 mg kg^{-1} s.c., markedly reduced 5-HT output in ventral hippocampus (Figure 3). A major metabolite of these compounds, 1-PP, which does not have significant affinity for 5-HT_{1A} binding sites (see Discussion), had no effect on 5-HT in hippocampal dialysates at the dose (5 mg kg^{-1} , s.c.) and over the time (120 min) tested when compared to saline-injected controls (Figure 3, Table 1).

Effect of RU 24969 on 5-HT in hippocampal dialysates

RU 24969, a drug with high affinity for the 5-HT_{1B} binding site, dose-dependently (0.25–5 mg kg^{-1}) decreased the amount of 5-HT in hippocampal dialysates (Figure 4). Note the slower onset of RU 24969 effect compared to the 5-HT_{1A} agonists. The highest dose tested (5 mg kg^{-1}) reduced 5-HT levels to 78% of preinjection values 120 min postdrug. The approximate dose of RU 24969 producing half the maximal observed effect was 0.5 mg kg^{-1} .

Figure 3 Effect of putative 5-HT_{1A} agonists on 5-hydroxytryptamine (5-HT) in rat ventral hippocampus dialysates. Saline (○) or gepirone (●), ipsapirone (□) and buspirone (△) and their common metabolite 1-(2-pyrimidinyl)-piperazine HCl (1-PP, x), all at 5 mg kg^{-1} , were injected subcutaneously at time zero. See legend to Figure 1 for further details.

Effect of 5-HT agonists on 5-HIAA in hippocampal dialysates

Both 8-OH-DPAT and RU 24969 caused a decrease of 5-HIAA in hippocampal dialysates although these responses were considerably smaller (Table 1) and slower in onset (time course data not shown) than the change in 5-HT. In contrast to their effects on 5-HT output, neither gepirone, nor buspirone, nor ipsapirone reduced 5-HIAA output at the doses and over the time tested (Table 1). Similarly 1-PP had no effect on 5-HIAA in hippocampal dialysates.

Figure 4 Effect of the putative 5-HT_{1B} agonist RU 24969 on 5-hydroxytryptamine (5-HT) in rat ventral hippocampus dialysates. Saline (○) or RU 24969, at doses 0.25 (●), 1.0 (□), 2.5 (△) and 5.0 (▲) mg kg^{-1} , were injected subcutaneously at time zero. See legend to Figure 1 for further details.

Table 1 Summary of effect of 5-hydroxytryptamine (5-HT) agonists on 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in ventral hippocampus dialysates of the rat

Treatment	5-HT (AUC)	5-HIAA (AUC)
Saline	100.0 ± 4.8 (6)	100.0 ± 3.3 (6)
8-OH-DPAT ($\mu\text{g kg}^{-1}$)		
5	83.0 ± 7.6 (4)	87.7 ± 1.2 (4)*
10	71.6 ± 9.2 (10)*	88.9 ± 3.4 (10)*
100	32.1 ± 5.6 (4)**	77.4 ± 2.2 (4)**
250	34.2 ± 10.6 (5)**	82.9 ± 3.1 (5)**
RU 24969 (mg kg^{-1})		
0.25	82.3 ± 3.6 (4)*	87.7 ± 3.1 (4)*
1	69.1 ± 2.1 (3)**	79.7 ± 5.3 (3)*
2.5	55.5 ± 17.3 (4)*	77.9 ± 1.4 (4)*
5	44.8 ± 8.9 (3)**	42.7 ± 1.8 (3)**
Gepirone 5 mg kg^{-1}	59.8 ± 9.7 (4)**	93.9 ± 4.2 (4)
Ipsapirone 5 mg kg^{-1}	48.8 ± 4.7 (3)**	89.5 ± 8.9 (3)
Buspirone 5 mg kg^{-1}	43.5 ± 16.3 (4)**	90.6 ± 9.6 (4)
1-PP 5 mg kg^{-1}	94.4 ± 7.7 (4)	95.6 ± 5.9 (4)

Areas under the curves (AUC) are the accumulated amounts of 5-HT or 5-HIAA in dialysates collected over the 2 h post injection period and are expressed as a percentage of the saline-injected control group. Mean values $\pm$ s.e.mean (n = number of rats) are shown. * P < 0.05, ** P < 0.01 versus saline treated group (unpaired t test on raw data following 1-way ANOVA). 1-PP = 1-(2-pyrimidinyl)-piperazine HCl.

Discussion

The present study demonstrates that systemic administration of the putative 5-HT_{1A} agonists 8-OH-DPAT, gepirone, buspirone and ipsapirone markedly reduces 5-HT in dialysates of the ventral hippocampus of the chloral hydrate-anaesthetized rat. This finding is direct biochemical evidence that 5-HT_{1A} agonists decrease hippocampal 5-HT release *in vivo*, and it is probable that this is due to activation of somatodendritic 5-HT_{1A} autoreceptors causing a reduction of 5-HTergic impulse flow. Thus, electrophysiological studies have shown that micro-iontophoretic application of 8-OH-DPAT, gepirone, buspirone or ipsapirone into the rat dorsal raphe nucleus, which is rich in 5-HT_{1A} binding sites

localized on 5-HTergic neurones (Verge *et al.*, 1985; Weismann-Nanopoulos *et al.*, 1985), causes a reduction in the rate of 5-HTergic cell firing similar to that seen when these drugs are administered systemically (Sprouse & Aghajanian, 1986; Vander-Maelen *et al.*, 1986; Blier & De Montigny, 1987). It seems less likely that nerve terminal 5-HT autoreceptors mediate the effects of 5-HT_{1A} agonists on 5-HT release since 8-OH-DPAT, gepirone and ipsapirone are reported to have weak or little effect on the release of [³H]-5-HT from rat hippocampus and cortex *in vitro* (Middlemiss, 1984a; Engel *et al.*, 1986; this laboratory, unpublished observations).

Although our data show that four drugs, which have high selectivity for the 5-HT_{1A} versus 5-HT_{1B}, 5-HT₂ and other neurotransmitter binding sites (see Introduction), reduce 5-HT in ventral hippocampal dialysates, the pharmacological identity of the receptor mediating these effects awaits further characterization. A recent study reported that the α_2 -adrenoceptor antagonist, idazoxan, prevents the decrease of 5-HT metabolism in the rat supra-chiasmatic nucleus induced by 8-OH-DPAT (Marsden & Martin, 1986). Also, buspirone, gepirone and ipsapirone, as well as their common metabolite 1-PP, have some affinity for the α_2 -adrenoceptor binding site in rat cortex (Rimele *et al.*, 1987). Our finding that 1-PP, which has little affinity for the 5-HT_{1A} binding site (Traber & Glaser, 1987), had no effect on 5-HT output in ventral hippocampus, strengthens the idea that the decrease in 5-HT output produced by its parent compounds and 8-OH-DPAT is mediated through 5-HT_{1A} receptors and not α_2 -adrenoceptors.

Various effects of 8-OH-DPAT and the buspirone-related compounds in rats are thought to relate to reduced central 5-HTergic neurotransmission following activation of somatodendritic 5-HT_{1A} autoreceptors; increased feeding (Dourish *et al.*, 1986), hypothermia (Goodwin *et al.*, 1987 but see Hutson *et al.*, 1987), anxiolysis (Traber & Glaser, 1987) and possibly increased sexual activity (Ahlenius *et al.*, 1981). Interestingly, the functional effects of 8-OH-DPAT which are believed to correlate with decreased brain 5-HT function, as well as the 8-OH-DPAT-induced decrease of hippocampal 5-HT output (present study), occur at doses of 8-OH-DPAT well below those that induce the postsynaptically-mediated 5-HT behavioural syndrome.

The putative 5-HT_{1B} selective agonist, RU 24969, also dose-dependently reduced 5-HT levels in hippocampal dialysates. This finding is consistent with a previous report that RU 24969 decreases 5-HT in rat cortical dialysates (Brazell *et al.*, 1985). On the basis of biochemical evidence that the nerve terminal 5-HT autoreceptor is of the 5-HT_{1B} subtype

(Middlemiss, 1984a,b; Engel *et al.*, 1986) and electrophysiological data showing that systemic and intraraphé injection of the putative 5-HT_{1B} agonists mCPP and TFMPP has little effect on the firing of 5-HTergic neurones in the rat dorsal raphé nucleus (Sprouse & Aghajanian, 1987), it would seem reasonable to assume that the effect of RU 24969 on hippocampal 5-HT output relates to activation of the nerve terminal 5-HT_{1B} autoreceptor in hippocampus. Indeed, local administration of RU 24969 (10^{-5} M) into hippocampus via the perfusion medium markedly reduces 5-HT in the dialysates (unpublished data). However, while there is little evidence from functional studies that RU 24969 activates central 5-HT_{1A} receptors (e.g. Goodwin & Green, 1985; Dourish *et al.*, 1986; Tricklebank *et al.*, 1987) this drug has significant affinity for the 5-HT_{1A} binding site (Peroutka, 1986; Hamon *et al.*, 1986). Therefore, whether RU 24969 reduces 5-HT released from the hippocampus *in vivo* through stimulation of 5-HT autoreceptors on the 5-HT nerve terminals without involving those on the 5-HT cell body, remains an open question.

In the present study it was found necessary to add the selective 5-HT uptake blocker, citalopram, to the perfusion medium to provide readily measurable, constant amounts of 5-HT in the hippocampal dialysates. It has recently been reported that 5-HT in rat striatal dialysates collected on the day of probe implantation, but without a 5-HT reuptake inhibitor in the perfusion medium, predominantly originates from the blood (Kalén *et al.*, 1988). However, in view of our finding of a marked decrease of 5-HT in hippocampal dialysates in response to the 5-HT_{1A} agonists, and the known potent inhibitory actions of these drugs on 5-HTergic cell firing, it seems highly likely that a major component of extracellular 5-HT measured under our conditions arises from central 5-HT neurones. Furthermore, we recently observed

that local infusion of tetrodotoxin, a drug that inhibits action potentials, causes a marked decrease of 5-HT in the hippocampal dialysates (Sharp *et al.*, unpublished).

Both 8-OH-DPAT and RU 24969 reduced extracellular 5-HIAA in rat hippocampus, which is consistent with previous experiments on the effect of these drugs on brain 5-HT metabolism (Hjorth *et al.*, 1982; Brazell *et al.*, 1985; Marsden & Martin, 1986). It is notable that the responses of 5-HIAA to 8-OH-DPAT and RU 24969 were small compared to those of 5-HT. Furthermore, while gepirone, ipsapirone and buspirone markedly reduced 5-HT output, they had no significant effect on 5-HIAA output at the doses and over the time-course tested. Given that the basal amounts of 5-HIAA in the hippocampal dialysates are much higher than 5-HT, the proportionate reductions in 5-HIAA in response to the 5-HT agonists are likely to be much smaller. Also, extracellular 5-HIAA need not necessarily change in close accordance with extracellular 5-HT if, as previously proposed (Grahame-Smith, 1974; Kuhn *et al.*, 1985), a significant part of 5-HIAA is derived from the catabolism of unreleased 5-HT. Our finding that the presence of a 5-HT reuptake inhibitor, while increasing 5-HT overflow, did not reduce 5-HIAA, is consistent with the latter hypothesis.

In conclusion, brain microdialysis was used to provide direct biochemical evidence that putative 5-HT_{1A} and 5-HT_{1B} agonists reduce 5-HT release in the rat ventral hippocampus *in vivo*. Whilst further characterization of the drug responses is necessary, it seems likely that the microdialysis method will be a useful approach to probe 5-HT autoreceptor function *in vivo*.

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