Chronic administration of venlafaxine fails to attenuate 5-HT_{1A} receptor function at the level of receptor-G protein interaction

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Abstract

In this study venlafaxine was administered to rats at a low, moderate or high dose; for comparison, the selective serotonin reuptake inhibitor (SSRI) sertraline and the tricyclic antidepressant (TCA) amitriptyline were also included. We evaluated, using quantitative autoradiography, the effect of these antidepressant treatments on [\( ^{35} \)S]GTP\(^{\gamma}\)S binding stimulated by the 5-HT_{1A} receptor agonist 8-OH-DPAT, a measure of the capacity of 5-HT_{1A} receptors to activate G proteins. Chronic administration of amitriptyline resulted in a marked increase in 5-HT_{1A} receptor-stimulated [\( ^{35} \)S]GTP\(^{\gamma}\)S binding in the hippocampus which was accompanied by an increase in 5-HT_{1A} receptor number. 5-HT_{1A} receptor-stimulated [\( ^{35} \)S]GTP\(^{\gamma}\)S binding in the hippocampus was also increased by chronic treatment with the highest dose of venlafaxine; 5-HT_{1A} receptor number, however, was not significantly altered. In serotonergic cell body areas (i.e. dorsal and median raphe nuclei), 5-HT_{1A} receptor-stimulated [\( ^{35} \)S]GTP\(^{\gamma}\)S binding was not altered by chronic administration of amitriptyline, sertraline or venlafaxine. Chronic TCA treatment does not desensitize somatodendritic 5-HT_{1A} autoreceptor function. However, the lack of effect of chronic sertraline treatment on 5-HT_{1A} receptor-stimulated [\( ^{35} \)S]GTP\(^{\gamma}\)S binding is in contrast to what has been observed previously following chronic administration of the SSRI fluoxetine, and suggests that different SSRIs may regulate somatodendritic 5-HT_{1A} autoreceptor function differently depending on their pharmacology. Our data also suggest that the desensitization of somatodendritic 5-HT_{1A} autoreceptors observed in electrophysiological studies following chronic venlafaxine administration is not at the level of receptor-G protein interaction. The hypothermic response in vivo to acute injection of 8-OH-DPAT was significantly attenuated following chronic treatment with venlafaxine or sertraline, but not amitriptyline.

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Introduction

The distribution of the serotonin-1A (5-HT_{1A}) receptor in the brain is consistent with the proposal that this 5-HT receptor subtype may have a role in integrative functions, such as cognition or emotional states. The 5-HT_{1A} receptor is present in high density in serotonergic cell body areas, in particular the dorsal and median raphe nuclei, as well as in cortical and limbic areas (e.g. frontal cortex, entorhinal cortex, hippocampus, amygdala, septum) (Hensler et al., 1991; Kia et al., 1996; Vergé et al., 1986). 5-HT_{1A} receptors are also present in the hypothalamus where they play an important role in the regulation of neuroendocrine function and responses to stress (see Van de Kar, 1991). In the raphe nuclei, the 5-HT_{1A} receptor is located on serotonergic cell bodies and dendrites (Riad et al., 2000; Sotelo et al., 1990), and functions as the somatodendritic autoreceptor (de Montigny et al., 1984; see Aghajanian et al., 1990). In terminal field areas of serotonergic innervation, the 5-HT_{1A} receptor is located post-synaptically (Hensler et al., 1991; Riad et al., 2000; Vergé et al., 1986).

Adaptive changes in the serotonergic system are generally believed to underlie the therapeutic effectiveness of a variety of antidepressant drugs. By blocking the serotonin transporter (SERT) or inhibiting monoamine oxidase-A, these agents are expected to increase the synaptic concentration of the neurotransmitter.
5-HT. The sensitivity of behavioural, neurochemical and electrophysiological responses mediated by central 5-HT$_{1A}$ receptors is altered after repeated administration of antidepressant drugs, although in a drug- and region-specific manner (for review see Hensler, 2003). Thus, studies of the regulation of 5-HT$_{1A}$ receptor function may have important implications for our understanding the role of this receptor in the mechanism of action of these therapeutic agents.

Recently, a new class of antidepressant drug that blocks both 5-HT and norepinephrine (NE) reuptake has been developed. These 5-HT/NE reuptake inhibitors, such as venlafaxine and duloxetine, have relatively weak affinity for muscarinic, histaminergic, dopaminergic, serotonergic and $\alpha$-adrenergic receptors (Bymaster et al., 2001; Owens et al., 1997), which may account for the fewer side-effects than observed with the tricyclic antidepressants (TCAs) (e.g. amitriptyline). It has been proposed that these selective 5-HT/NE reuptake inhibitors are more effective than the selective serotonin reuptake inhibitors (SSRIs) for refractory or severely depressed patients, and have a more rapid onset of therapeutic effect (Deakin and Dursun, 2002; Mallick et al., 2003; Silverstone et al., 2002, but see also Shelton, 2004).

The goal of the current study was to examine the regulation of 5-HT$_{1A}$ receptor function at the level of receptor-G protein interaction following chronic administration of the selective 5-HT/NE reuptake inhibitor venlafaxine. In this study, venlafaxine was administered to rats at three doses, which produced steady-state serum levels corresponding to low, moderate and high levels within the therapeutic range of values for human patients. For comparison we included in this study the SSRI sertraline, and the TCA amitriptyline, a potent inhibitor of both 5-HT and NE reuptake (see Frazer, 1997). We evaluated, using quantitative autoradiography, the effect of these antidepressant treatments on $[^{35}S]$GTP$_{\gamma}$S binding stimulated by the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT, a measure of the capacity of 5-HT$_{1A}$ receptors to activate G proteins. Chronic administration of selective 5-HT/NE reuptake inhibitors or SSRIs has been shown to result in the desensitization of 5-HT$_{1A}$ somatodendritic autoreceptor function (Béique et al., 2000; Rueter et al., 1998; see Hensler et al., 2003). Following chronic administration of the SSRI fluoxetine, the desensitization of 5-HT$_{1A}$ somatodendritic autoreceptor function appears to be at the level of receptor-G protein interaction as 5-HT$_{1A}$ receptor-stimulated $[^{35}S]$GTP$_{\gamma}$S binding is attenuated in the dorsal raphe nucleus (Castro et al., 2003; Hensler 2002; Pejchal et al., 2002; Shen et al., 2002). We therefore hypothesized that chronic administration of venlafaxine or sertraline would result in the attenuation of 8-OH-DPAT-stimulated $[^{35}S]$GTP$_{\gamma}$S binding in the dorsal raphe nucleus. Total 5-HT$_{1A}$ receptor number ($R_1$), as measured by the binding of a single saturating concentration of the antagonist radioligand $[^{3}H]$MPPF, and the coupled, high-affinity agonist state of the receptor ($R_2$), as measured by the binding of the agonist radioligand $[^{3}H]$8-OH-DPAT, were also assessed by quantitative autoradiography. The hypothermic response in vivo to acute injection of 8-OH-DPAT was also measured. Portions of this work have been presented in abstract form (Hensler et al., 2003; Rossi et al., 2004).

Methods

Animals

Male Sprague–Dawley rats (200–275 g; Harlan, Indianapolis, IN, USA) were group-housed and maintained at 25.5 °C, on a 14/10 h day/night cycle with constant access to food and water. These studies were carried out in strict accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health. Every effort was made to minimize animal suffering and the number of animals used.

Drug treatments

Rats were treated for 21 d with amitriptyline (25 mg/kg . d), sertraline (7.5 mg/kg . d) or one of three doses of venlafaxine (15, 40, or 70 mg/kg . d). Control animals were administered either sterile water, the vehicle for amitriptyline and venlafaxine, or 40% ethanol:water solution, the vehicle for sertraline. Antidepressant drugs or vehicle were administered by subcutaneously implanted osmotic minipumps Model no. 2ML4 (Alza, Palo Alto, CA, USA). Rats were sacrificed on day 22 of treatment, and serum concentrations of antidepressant were determined from trunk blood (see Table 1). The selection of doses of amitriptyline or venlafaxine was based on an initial set of experiments in which serum drug levels at steady-state were determined from the Clinical Psychopharmacology Laboratories (University of Texas Health Science Center – San Antonio, TX, USA). The dose of sertraline was based on previous studies (Benmansour et al., 1999).

Hypothermia

Animals were acclimated to the behavioural testing room and the testing procedure for 3 d prior to behavioural measurement. Animals were habituated to the
Antidepressants were administered subcutaneously to rats by osmotic minipump. Serum concentrations of drugs were determined from trunk blood after 21 d of treatment. The values obtained are compared to therapeutic drug level guidelines for patients (Clinical Psychopharmacology Laboratories, University of Texas Health Science Center – San Antonio).

testing environment for at least 1 h prior to recording core body temperature. All experiments were performed between 09:00 and 13:00 hours, at ambient room temperature. Measurement of core body temperature was performed as previously described (Hensler et al., 1991; Hensler and Truett, 1998) on day 14 of treatment using a digital thermometer (Fisher Scientific, Pittsburgh, PA, USA) and rectal probe (YSI, Yellow Springs, OH, USA). With the animal unrestrained, the probe was lubricated with petroleum jelly and inserted to a depth of 5 cm. Core body temperature was taken for 2 min at 5- or 10-min intervals. The temperature at the end of the 2-min period was recorded. Three temperature measurements were taken 10 min, 5 min and immediately prior to subcutaneous injection of the 5-HT1A receptor agonist 8-OH-DPAT (0.05 mg/kg). Core body temperature immediately prior to 8-OH-DPAT injection was used as baseline. Temperature measurements were obtained 20, 30, and 40 min after injection of 8-OH-DPAT. In previous experiments we have characterized the dose–response relationship for 8-OH-DPAT-induced hypothermia and found that subcutaneous injection of 0.05 mg/kg 8-OH-DPAT produces a reproducible and statistically significant drop in core body temperature of 1.5 °C (Frazer and Hensler, 1990; Hensler and Truett, 1998).

Tissue preparation

Rat brains were rapidly removed and frozen on powdered dry ice. Brains were stored at −80 °C until sectioning. Coronal sections of 20-μm thickness were cut at −17 °C in a cryostat microtome at the level of the lateral septum (plates 11–13), dorsal hippocampus (plates 30–32) or dorsal raphe (plates 48–50) according to the atlas of the rat brain of Paxinos and Watson (1986). Sections were thaw-mounted onto gelatin-coated glass slides, desiccated at 4 °C for 18 h under vacuum and then stored at −80 °C until required.

[35S]GTPγS autoradiography

Autoradiography of (+)8-OH-DPAT-stimulated [35S]-GTPγS binding in brain sections was performed as previously described (Hensler and Durgam, 2001; Hensler, 2002). Slide-mounted sections were thawed and desiccated at 4 °C for 1 h, and then equilibrated in Heps buffer (50 mM; pH 7.4), supplemented with 3 mM MgCl2, 0.2 mM EGTA, 100 mM NaCl, and 0.2 mM dithiothreitol for 10 min at 30 °C. Sections were pre-incubated in Heps buffer containing GDP (2 mM) for 10 min at 30 °C, and then incubated in Heps buffer containing GTP (2 mM) and 80 μM [35S]GTPγS, either in the absence or in the presence of (+)8-OH-DPAT (1 μM), for 45 min at 30 °C. Basal [35S]GTPγS binding was defined in the absence of (+)8-OH-DPAT. Non-specific [35S]GTPγS binding was defined in the absence of (+)8-OH-DPAT and in the presence of 10 μM GTPγS. The incubation was stopped by two washes for 5 min each in ice-cold 50 mM Tris–HCl buffer (pH 7.4), followed by a brief immersion in ice-cold de-ionized water. Sections were dried on a slide-warmer and exposed to Kodak BioMax MR film (Amersham, Piscataway, NJ, USA) for 24 h.

[3H]MPPF autoradiography

Autoradiography of the binding of [3H]MPPF to 5-HT1A receptors in brain sections was performed as described (Hensler and Durgam, 2001; Hensler, 2002). Briefly, slide-mounted sections were thawed and desiccated at 4 °C for 1 h. Sections were pre-incubated for 30 min at 30 °C in assay buffer (170 mM Tris–HCl; pH 7.6), and then incubated in assay buffer containing 10 nM [3H]MPPF for 90 min at 30 °C. Non-specific binding was defined by incubating adjacent sections in the presence of 10 μM WAY 100635. Incubation was terminated by two washes for 5 min each in ice-cold 170 mM Tris–HCl buffer (pH 7.6), followed by a dip in ice-cold de-ionized water. Sections were dried on a slide warmer and exposed to Kodak BioMax MR Film (Amersham) for a period of 5 wk to generate autoradiograms. We have compared the quantitation of [3H]MPPF binding obtained with Kodak BioMax MR film with that obtained using tritium-sensitive film, which has not been available. We are satisfied that the

Table 1. Serum concentrations of antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg·d)</th>
<th>Steady-state (ng/ml)</th>
<th>Therapeutic (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>25 (n = 14)</td>
<td>220 ± 10</td>
<td>100–600</td>
</tr>
<tr>
<td>Sertraline</td>
<td>7.5 (n = 8)</td>
<td>59 ± 13</td>
<td>30–150</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>15 (n = 6)</td>
<td>138 ± 7</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>40 (n = 8)</td>
<td>308 ± 47</td>
<td>100–800</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>70 (n = 6)</td>
<td>712 ± 51</td>
<td></td>
</tr>
</tbody>
</table>
binding data are comparable using these two types of film, although the time the film is exposed to the sections to generate autoradiograms is somewhat longer when using BioMax MR film (~1.5 times). Our data in the present study using BioMax MR film are very much in agreement with previous data from our laboratory using tritium-sensitive film (Hensler and Durgam, 2001; Hensler, 2002).

$[^3]H$8-OH-DPAT autoradiography

Autoradiography of the binding of $[^3]H$8-OH-DPAT to 5-HT$_{1A}$ receptors in brain sections was performed as described (Hensler et al., 1991). Briefly, slide-mounted sections were thawed and desiccated at 4°C for 1 h. Sections were pre-incubated for 30 min at 30°C in assay buffer (170 mM Tris–HCl; pH 7.6), and then incubated in assay buffer containing 2 nM $[^3]H$8-OH-DPAT for 60 min at room temperature. Non-specific binding was defined by incubating adjacent sections in the presence of 10 μM WAY 100635. Incubation was terminated by two washes for 5 min each in ice-cold 170 mM Tris–HCl buffer (pH 7.6), followed by a dip in ice-cold de-ionized water. Sections were dried on a slide warmer and exposed to Kodak BioMax MR Film (Amersham) for a period of 9 wk to generate autoradiograms.

Image analysis

Analysis of the digitized autoradiograms was performed using the image analysis program NIH Image, version 1.47 (NIH, Bethesda, MD, USA). Tissue sections were stained with thionin and the brain areas identified using the atlas of the rat brain of Paxinos and Watson (1986). Autoradiograms of $[^3]H$MPPF or $[^3]H$8-OH-DPAT binding were quantified by the use of simultaneously exposed $[^3]H$ standards (ART-123, American Radiochemicals, St. Louis, MO, USA) which had been calibrated using brain-mash sections according to the method of Geary and colleagues (Geary and Wooten, 1983; Geary et al., 1985). The amount of ligand bound was determined by converting optical density measurements to femtomoles per milligram of protein. Specific binding was calculated by subtracting non-specific binding from total binding on adjacent sections. Autoradiograms of (±)-8-OH-DPAT-stimulated $[^3]H$GTP$\gamma$S binding were quantified by the use of simultaneously exposed $[^3]C$ standards (ARC-146, American Radiochemicals). Standard curves were fitted to pixel data obtained from $[^3]C$ standards and tissue equivalent values (nCi/g) provided by American Radiochemicals, and were used to transform the actual regional densitometric values into relative radioactivity measures. Non-specific binding of $[^8]S$GTP$\gamma$S was subtracted from basal binding and from binding in the presence of (±)-8-OH-DPAT. Specific (±)-8-OH-DPAT-stimulated binding was expressed as % above basal.

Data analysis

Statistical comparisons were made by one-way ANOVA. F values reaching significance ($p<0.05$) were evaluated further by post-hoc analysis using Fisher’s Protected Least Significant Difference test. Statistical tests were performed using Statistica software (version 4.1, StatSoft, Tulsa, OK, USA).

Materials

$[^8]S$GTP$\gamma$S (1250 Ci/mmol) and $[^3]H$MPPF (70.5 Ci/mmol) were purchased from Dupont/NEN (Boston, MA, USA). $[^3]H$8-OH-DPAT (210 Ci/mmol) was purchased from Amersham Biosciences (Piscataway, NJ, USA). Amitriptyline HCl, WAY 100635 maleate and GDP (disodium salt) were purchased from Sigma/RBI (St. Louis, MO, USA). GTP$\gamma$S (tetralithium salt) was purchased from Roche/Boehringer–Mannheim (Indianapolis, IN, USA). (±)-8-OH-DPAT hydrobromide was purchased from Tocris Cookson (Ballwin, MO, USA). Sertraline hydrochloride was obtained from Pfizer (Groton, CT, USA). Venlafaxine hydrochloride was obtained from Wyeth Research (Princeton, NJ, USA).

Results

The effectiveness of chronic antidepressant administration in altering serotonergic function was assessed in the whole animal on day 14 of treatment by measuring hypothermia induced by acute injection of the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT (0.05 mg/kg s.c.). In rats, the hypothermic response to 8-OH-DPAT is mediated by both the 5-HT$_{1A}$ and 5-HT$_{7}$ receptor (Hedlund et al., 2004). Because the hypothermic response to 8-OH-DPAT (temperature decrease, °C) was not statistically different in control animals treated with either sterile water vehicle (1.33±0.19, n=8) or 40% ethanol:water solution (1.54±0.28, n=8) ($p=0.536$), the data from these two vehicle groups were combined. As shown in Figure 1, 8-OH-DPAT-induced hypothermia was significantly attenuated in rats treated for 14 d with sertraline or any dose of venlafaxine (15, 40 and 70 mg/kg, d). By contrast, administration of amitriptyline for 14 d did not alter 8-OH-DPAT-induced hypothermia (Figure 1). To address the question as to whether a longer treatment...
with amitriptyline would result in significant attenuation of this 5-HT$_{1A}$ receptor-mediated response, hypothermia induced by acute injection of 8-OH-DPAT (0.05 mg/kg s.c.) was assessed in a separate group of animals after 21 d of treatment. In this experiment, hypothermia was not significantly altered as a result of this longer treatment period (temperature decrease, °C) [vehicle-treated: 1.26 ± 0.25 (n = 6); amitriptyline-treated: 0.9 ± 0.23 (n = 6), p = 0.29].

Quantitative autoradiographic studies were performed following 21 d of amitriptyline, sertraline or venlafaxine administration using animals in which 8-OH-DPAT-mediated hypothermia had been assessed on day 14 of drug treatment. To address the concern that acute injection of 8-OH-DPAT on day 14 may alter 5-HT$_{1A}$ receptor-stimulated [35S]GTP$_{y}$S binding or the binding of [3H]8-OH-DPAT to 5-HT$_{1A}$ receptor sites in animals killed 7 d later, a separate group of animals was administered saline by osmotic minipump and we determined the effect of 8-OH-DPAT injection (on day 14) on 5-HT$_{1A}$ receptor quantitative autoradiography after 21 d of saline administration. Injection of rats with 8-OH-DPAT (0.05 mg/kg s.c.) on day 14 did not alter the binding of [35S]GTP$_{y}$S stimulated by 1 μM 8-OH-DPAT in the dorsal raphe nucleus or dorsal hippocampus, assessed after 21 d of saline administration [dorsal raphe: saline-treated/saline-injected = 40 ± 4.7% above basal (n = 6); saline-treated/8-OH-DPAT-injected = 48 ± 6.3% above basal (n = 6); dentate gyrus region of hippocampus: saline/saline-injected = 146 ± 24.5% above basal (n = 6); saline/8-OH-DPAT-injected = 145 ± 13.7% above basal (n = 6)]. The binding of [3H]8-OH-DPAT (2 nM) to 5-HT$_{1A}$ receptor sites in these brain regions was also not altered (data not shown). Taken together, these data indicate that acute injection of 8-OH-DPAT (0.05 mg/kg s.c.) does not alter 5-HT$_{1A}$ receptor binding or function at the level of receptor-G protein interaction in brain sections taken from animals sacrificed 7 d later.

The effect of chronic administration of amitriptyline, sertraline or venlafaxine on post-synaptic 5-HT$_{1A}$ receptor function in cortical and limbic structures was determined using quantitative autoradiography to measure [35S]GTP$_{y}$S binding stimulated by 8-OH-DPAT (1 μM). In all areas of the brain examined, 8-OH-DPAT-stimulated [35S]GTP$_{y}$S binding was not statistically different in control animals treated with either water or 40% ethanol:water vehicle. For this reason, data from these two vehicle groups were combined for each brain region. As shown in Figure 2, 8-OH-DPAT-stimulated [35S]GTP$_{y}$S binding was increased in the CA$_3$ region and dentate gyrus of the hippocampus following chronic administration of amitriptyline or the highest dose of venlafaxine (70 mg/kg, d) (Figure 2). By contrast, treatment of rats with sertraline or with the low or moderate dose of venlafaxine (15 or 40 mg/kg, d) did not alter 8-OH-DPAT-stimulated [35S]GTP$_{y}$S binding in the hippocampus (Figure 2). 8-OH-DPAT-stimulated [35S]GTP$_{y}$S binding was not altered by any of the antidepressant treatments in the entorhinal cortex (Figure 2), or in other forebrain regions examined (i.e. lateral septum, anterior cingulate cortex) (data not shown).

In order to determine the effect of chronic administration of amitriptyline, sertraline or venlafaxine on 5-HT$_{1A}$ receptor function in serotonergic cell body areas, [3H]8-OH-DPAT binding stimulated by the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT (1 μM) was measured by quantitative autoradiography in the dorsal and median raphe nuclei. In these brain regions 8-OH-DPAT-stimulated [3H]8-OH-DPAT binding was not statistically
different in control animals treated with either vehicle and, therefore, data from the two vehicle groups were combined. As shown in Figure 3, treatment of rats with amitriptyline for 21 d did not alter 8-OH-DPAT-stimulated \[^{35}\text{S}]\text{GTP}^\gamma\text{S} \text{ binding in serotonergic cell body areas measured. These findings are in agreement with our previous study in which amitriptyline (10 mg/kg) was administered i.p. once daily for 14 d (Hensler, 2002). In addition, treatment of rats for 21 d with venlafaxine, at either the low, moderate or high dose, did not alter 8-OH-DPAT-stimulated \[^{35}\text{S}]\text{GTP}^\gamma\text{S} \text{ binding in the dorsal or median raphe (Figure 3). These data are in contrast to what has been observed following chronic administration of the SSRI fluoxetine (Castro et al., 2003; Hensler, 2002; Pejchal et al., 2002; Shen et al., 2002), and suggest that chronic administration of drugs that block both 5-HT and NE reuptake do not alter 5-HT\textsubscript{1A} receptor-stimulated \[^{35}\text{S}]\text{GTP}^\gamma\text{S} \text{ binding in serotonergic cell body areas. However, we also failed to observe an attenuation of 8-OH-DPAT-stimulated \[^{35}\text{S}]\text{GTP}^\gamma\text{S} \text{ binding in the dorsal or median raphe following chronic administration of the SSRI sertraline. This was unexpected and as discussed below, suggests that additional mechanisms may be involved in the regulation of 5-HT\textsubscript{1A} receptor-stimulated \[^{35}\text{S}]\text{GTP}^\gamma\text{S} \text{ binding in the raphe nuclei.}\n
The effect of chronic administration of amitriptyline, sertraline or venlafaxine on 5-HT\textsubscript{1A} receptor binding in cortical and limbic structures, as well as in serotonergic cell body areas, was also determined using quantitative autoradiography. Total 5-HT\textsubscript{1A} receptor number (\(R_T\)) was measured by the binding of a single saturating concentration of the antagonist radioligand \[^{3}\text{H} \] \text{MPPF} (10 \text{ nM}). There was a statistically significant difference in \[^{3}\text{H} \] \text{MPPF} binding between control animals treated with either sterile water or 40% ethanol:water vehicle in the dorsal raphe nucleus \[(F(1,14)=11.68, p=0.0046)\] and in the CA\textsubscript{1} region of the hippocampus \[(F(1,14)=9.781, p=0.0074)\]. For this reason, data from animals treated with the antidepressant agents are presented with their respective vehicle controls (Figure 4a), and sertraline-treated rats (Figure 4b), are presented with their respective vehicle control groups.

Following chronic administration of amitriptyline, the binding of \[^{3}\text{H} \] \text{MPPF} to 5-HT\textsubscript{1A} receptor sites was unchanged in the entorhinal cortex, or in the dorsal or
5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding

Figure 3. Effect of chronic administration of antidepressants on 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding in serotonergic cell body areas. Rats were administered vehicle, amitriptyline, sertraline or venlafaxine for 21 d. Coronal brain sections were incubated with [\textsuperscript{35}S]GTP\textgamma{}S (80 pm). Non-specific binding was defined in the presence of 10 \textmu{}M GTP\textgamma{}S. [\textsuperscript{35}S]GTP\textgamma{}S binding was stimulated by (10\textmu{}M) 8-OH-DPAT (1 \textmu{}M). Specific binding of [\textsuperscript{35}S]GTP\textgamma{}S is expressed as % above basal. Shown are the mean \pm{} S.E.M. Vehicle (n = 16); amitriptyline (n = 8); venlafaxine (15 mg/kg . d) (n = 6); venlafaxine (40 mg/kg . d) (n = 8); venlafaxine (70 mg/kg . d) (n = 6); sertraline (n = 8).

Discussion

In the current study we have examined the regulation of 5-HT\textsubscript{1A} receptor sensitivity at the level of receptor-G protein interaction following chronic administration of the selective 5-HT/NE reuptake inhibitor venlafaxine, given at a low, moderate and high dose. For comparison, we included in this study the SSRI sertraline and the TCA amitriptyline. Chronic administration of amitriptyline resulted in a marked increase in 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding in the hippocampus which was accompanied by an increase in 5-HT\textsubscript{1A} receptor number. 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding in the hippocampus was also increased by chronic treatment with the highest dose of venlafaxine (70 mg/kg . d); 5-HT\textsubscript{1A} receptor number, however, was not significantly altered. In contrast to what has been observed following chronic administration of the SSRI fluoxetine (Castro et al., 2003; Hensler, 2002; Pejchal et al., 2002; Shen et al., 2002), 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]-GTP\textgamma{}S binding in serotonergic cell body areas (i.e. dorsal and median raphe nuclei) was not altered by chronic administration of amitriptyline, venlafaxine or sertraline.

In the current study, the 5-HT\textsubscript{1A} receptor agonist 8-OH-DPAT (1 \textmu{}M) was used to stimulate [\textsuperscript{35}S]GTP\textgamma{}S binding in our autoradiographic assays. Concern has been recently raised about the non-selective nature of 8-OH-DPAT. 8-OH-DPAT, which has high affinity for median raphe nuclei, but significantly increased in the CA\textsubscript{3} region and dentate gyrus of the hippocampus (Figure 4a). These data suggest that the increase in 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding in the hippocampus following chronic amitriptyline treatment may be due to an up-regulation of 5-HT\textsubscript{1A} receptors. Chronic administration of venlafaxine at any dose did not significantly alter [\textsuperscript{3}H]MPPF binding in any area examined. Interestingly, following chronic administration of the highest dose of venlafaxine (70 mg/kg . d), [\textsuperscript{3}H]8-OH-DPAT binding was not increased in the hippocampus (Figure 4a), suggesting that the increase in 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding following chronic treatment with this dose of venlafaxine is not due to an increase in the number of receptors coupled to G proteins. [\textsuperscript{3}H]8-OH-DPAT binding to 5-HT\textsubscript{1A} receptor sites was unchanged in the areas of brain examined by chronic sertraline administration (Table 2).

Discussion

In the current study we have examined the regulation of 5-HT\textsubscript{1A} receptor sensitivity at the level of receptor-G protein interaction following chronic administration of the selective 5-HT/NE reuptake inhibitor venlafaxine, given at a low, moderate and high dose. For comparison, we included in this study the SSRI sertraline and the TCA amitriptyline. Chronic administration of amitriptyline resulted in a marked increase in 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding in the hippocampus which was accompanied by an increase in 5-HT\textsubscript{1A} receptor number. 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding in the hippocampus was also increased by chronic treatment with the highest dose of venlafaxine (70 mg/kg . d); 5-HT\textsubscript{1A} receptor number, however, was not significantly altered. In contrast to what has been observed following chronic administration of the SSRI fluoxetine (Castro et al., 2003; Hensler, 2002; Pejchal et al., 2002; Shen et al., 2002), 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]-GTP\textgamma{}S binding in serotonergic cell body areas (i.e. dorsal and median raphe nuclei) was not altered by chronic administration of amitriptyline, venlafaxine or sertraline.

In the current study, the 5-HT\textsubscript{1A} receptor agonist 8-OH-DPAT (1 \textmu{}M) was used to stimulate [\textsuperscript{35}S]GTP\textgamma{}S binding in our autoradiographic assays. Concern has been recently raised about the non-selective nature of 8-OH-DPAT. 8-OH-DPAT, which has high affinity for median raphe nuclei, but significantly increased in the CA\textsubscript{3} region and dentate gyrus of the hippocampus (Figure 4a). These data suggest that the increase in 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding in the hippocampus following chronic amitriptyline treatment may be due to an up-regulation of 5-HT\textsubscript{1A} receptors. Chronic administration of venlafaxine at any dose did not significantly alter [\textsuperscript{3}H]MPPF binding in any area examined. Interestingly, following chronic administration of the highest dose of venlafaxine (70 mg/kg . d), [\textsuperscript{3}H]MPPF binding was not increased in the hippocampus (Figure 4a), suggesting that the increase in 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding following chronic treatment with this dose of venlafaxine is not due to an increase in receptor number. By contrast, [\textsuperscript{3}H]MPPF binding to 5-HT\textsubscript{1A} receptor sites was unchanged in the areas of brain examined by chronic sertraline administration (Figure 4b).

The coupled, high-affinity agonist state of the 5-HT\textsubscript{1A} receptor (R\textsubscript{H}) was measured by the binding of the agonist radioligand [\textsuperscript{3}H]8-OH-DPAT at a concentration equivalent to the K\textsubscript{d} value of [\textsuperscript{3}H]8-OH-DPAT at the 5-HT\textsubscript{1A} receptor (Table 2). In all areas of the brain examined, [\textsuperscript{3}H]8-OH-DPAT binding was not statistically different in control animals treated with either sterile water or 40% ethanol:water vehicle. For this reason, data from these two vehicle groups were combined for each brain region.

Following chronic administration of amitriptyline, the binding of [\textsuperscript{3}H]8-OH-DPAT (2 \textmu{}M) to 5-HT\textsubscript{1A} receptor sites was unchanged in the hippocampus, entorhinal cortex, or in the dorsal or median raphe nuclei. Chronic administration of venlafaxine at any dose did not alter [\textsuperscript{3}H]8-OH-DPAT binding in any area examined. Interestingly, following chronic administration of the highest dose of venlafaxine (70 mg/kg . d), [\textsuperscript{3}H]8-OH-DPAT binding was not increased in the hippocampus (Table 2), suggesting that the increase in 5-HT\textsubscript{1A} receptor-stimulated [\textsuperscript{35}S]GTP\textgamma{}S binding following chronic treatment with this dose of venlafaxine is not due to an increase in the number of receptors coupled to G proteins. [\textsuperscript{3}H]8-OH-DPAT binding to 5-HT\textsubscript{1A} receptor sites was unchanged in the areas of brain examined by chronic sertraline administration (Table 2).
the 5-HT
1
A receptor (K
i
= 1 nM) (e.g. Sprouse et al., 2004), also has moderate affinity for the 5-HT
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receptor (K
i
= 250 nM) (Hagan et al., 2000). 8-OH-DPAT has agonist activity at the 5-HT
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receptor expressed in recombinant systems (Krobert et al., 2001), and responses in vivo elicited by acute injection of 8-OH-DPAT are attenuated by SB 269970 (Duncan et al., 2004; Hedlund et al., 2004; Sprouse et al., 2004), a selective antagonist at the 5-HT
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receptor (Hagan et al., 2000). However, the stimulation of [35S]GTPγS binding by (1 μM) 8-OH-DPAT, although completely blocked by the 5-HT
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A receptor antagonist WAY 100635

Figure 4. Effect of chronic administration of antidepressants on the binding of [3H]MPPF to 5-HT
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A receptor sites. Rats were treated for 21 d with (a) sterile water vehicle, amitriptyline or venlafaxine, or (b) 40% ethanol:water vehicle or sertraline. Coronal brain sections were incubated with [3H]MPPF (10 nM). Non-specific binding was defined in the presence of 10 μM WAY 100635. Specific binding of [3H]MPPF is expressed as fmol/mg protein. Shown are the mean ± SEM. Sterile water vehicle (n = 8); amitriptyline (n = 8); venlafaxine (15 mg/kg . d) (n = 6); venlafaxine (40 mg/kg . d) (n = 8); venlafaxine (70 mg/kg . d) (n = 6); 40% ethanol: water vehicle (n = 8); sertraline (n = 8). Analysis of data by one-way ANOVA revealed a significant effect of antidepressant treatment in the CA
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region of hippocampus [F(4, 31) = 11.85, p < 0.0001] and in dentate gyrus [F(4, 31) = 4.863, p = 0.0037]; * p < 0.05, Fisher’s Protected Least Significant Difference test.
thermia is attenuated by both 5-HT
7
post-synaptic 5-HT
1A
agonists and radioligands.

5-HT
1A
receptor-stimulated [35S]GTPγS binding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vehicle</th>
<th>Amitriptyline</th>
<th>Venlafaxine (15 mg/kg . d)</th>
<th>Venlafaxine (40 mg/kg . d)</th>
<th>Venlafaxine (70 mg/kg . d)</th>
<th>Sertraline</th>
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<td>Entorhinal cortex</td>
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<td>993 ± 14</td>
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<tr>
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<td>Median raphe nucleus</td>
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<td>179 ± 28</td>
<td>193 ± 9</td>
<td>215 ± 16</td>
<td>238 ± 14</td>
<td>179 ± 24</td>
</tr>
</tbody>
</table>

Shown are the mean ± S.E.M. Vehicle (n = 16); amitriptyline (n = 8); venlafaxine (15 mg/kg . d) (n = 6); venlafaxine (40 mg/kg . d) (n = 8); venlafaxine (70 mg/kg . d) (n = 6); sertraline (n = 8).

(100 nm) in all areas of brain examined (Hensler and Durgam, 2001), is not altered by the selective 5-HT
7
receptor antagonist SB 269970 (100 nm) (Rossi and Hensler, unpublished observations).

In the current study, the hypothermic response in vivo to acute injection of the agonist 8-OH-DPAT was used as an indication of the effectiveness of these antidepressant treatments in altering serotonergic neurotransmission. In rats, the hypothermic response to acute injection of the 5-HT
1A
receptor agonist 8-OH-DPAT has been used in the past as an indication of post-synaptic 5-HT
1A
receptor function (Bill et al., 1991; Hutson et al., 1987; Millan et al., 1993; O’Connell et al., 1992), and as a measure of post-synaptic 5-HT
1A
receptor sensitivity following a variety of antidepressant treatments (e.g. Goodwin et al., 1987; Hensler et al., 1991; Wozniak et al., 1988). However, recent evidence indicates that in rats the hypothermic response to 8-OH-DPAT is mediated by 5-HT
1A
and 5-HT
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receptors. In rats 8-OH-DPAT-induced hypothermia is attenuated by both 5-HT
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receptor antagonists (Hedlund et al., 2004), as well as by 5-HT
1A
receptor antagonists (Allen et al., 1997; Hedlund et al., 2004; Millan et al., 1993). Both 5-HT
1A
and 5-HT
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receptor-mediated responses are desensitized by a variety of antidepressant treatments (Mullins et al., 1999; see Hensler, 2003).

In the current study, 8-OH-DPAT-induced hypothermia was markedly attenuated following chronic administration of sertraline, consistent with previous studies using a variety of SSRIs (Goodwin et al., 1987; Hensler et al., 1991). By contrast, as has been observed previously (Yamada et al., 1994), chronic administration of amitriptyline did not alter the hypothermic response to 8-OH-DPAT. Chronic treatment of rats with the low, moderate or high dose of venlafaxine resulted in attenuation of 8-OH-DPAT-induced hypothermia. This effect of venlafaxine treatment was dose-dependent as a greater attenuation of this response was observed following administration of higher doses of venlafaxine.

The attenuation of 8-OH-DPAT-induced hypothermia following chronic administration of sertraline or venlafaxine may very well be due to desensitization of both 5-HT
1A
and 5-HT
7
receptors. Both serotonin receptor subtypes have been shown to be regulated by chronic antidepressant treatments. Chronic administration of venlafaxine or the SSRIs fluoxetine or paroxetine results in the desensitization of hypothalamic 5-HT
1A
receptor-mediated neuroendocrine responses (Gur et al., 2002; Li et al., 1993, 1996, 1997). The number of 5-HT
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receptor-binding sites in hypothalamic homogenates is down-regulated following chronic administration of a variety of antidepressants, including the SSRIs fluoxetine or the TCAs desipramine and imipramine (Mullins et al., 1999). Further evaluation of the effect of chronic antidepressant treatments on the regulation of 5-HT
7
receptor function and number awaits the development and availability of selective agonists and radioligands.

As mentioned above, chronic administration of the selective 5-HT/NE re-uptake inhibitor venlafaxine results in the desensitization of 5-HT
1A
receptor-mediated neuroendocrine responses in the hypothalamus (Gur et al., 2002). We are unable to examine 5-HT
1A
receptor-stimulated [35S]GTPγS binding in the...
hypothalamus due to the high basal binding of $[^1]S\text{GTPyS}$. However, our data following chronic administration of the low and moderate dose of venlafaxine are in agreement with electrophysiological studies which indicate that in the hippocampus the sensitivity of 5-HT$_{1A}$ receptors is unchanged (Ruetter et al., 1998; Béique et al., 2000). In the current study we observed no change in 5-HT$_{1A}$ receptor-stimulated $[^3]S\text{GTPyS}$ binding in the hippocampus following chronic treatment of rats with venlafaxine at comparable doses (i.e. 15 or 40 mg/kg d).

Electrophysiological studies indicate that chronic treatment with TCAs results in the sensitization of neurons in the hippocampus to 5-HT$_{1A}$ receptor agonists (Chaput et al., 1991; de Montigny and Aghajanian, 1978). In the present study, 5-HT$_{1A}$ receptor-stimulated $[^3]S\text{GTPyS}$ binding was increased in the CA$_1$ region and dentate gyrus of the hippocampus following chronic administration of amitriptyline. The binding of $[^3]\text{H}\text{MPFF}$, an indication of total 5-HT$_{1A}$ receptor number ($R_T$), was also increased in these regions following chronic administration of amitriptyline. However, the binding of $[^3]\text{H}8\text{-OH-DPAT}$, an indication of the number of 5-HT$_{1A}$ receptors in the coupled high-affinity agonist state ($R_{AI}$), was not altered. These data suggest that in the absence of an increase in the binding of $[^3]\text{H}8\text{-OH-DPAT}$, the increased capacity of 5-HT$_{1A}$ receptors to activate G proteins in CA$_1$ and dentate gyrus of the hippocampus may be due to regulatory changes at the level of the G protein, e.g. phosphorylation. This may be the mechanism underlying the sensitization of hippocampal 5-HT$_{1A}$ receptor-mediated responses observed in electrophysiological studies following chronic TCA administration (Chaput et al., 1991; de Montigny and Aghajanian, 1978).

We have previously shown that administration of amitriptyline (10 mg/kg i.p.) once a day for 14 d results in an increase in total 5-HT$_{1A}$ receptor number, as measured by the binding of $[^3]\text{H}\text{MPFF}$, in dentate gyrus and CA$_1$ regions of the hippocampus (Hensler, 2002). We did not observe an increase in 5-HT$_{1A}$ receptor-stimulated $[^3]S\text{GTPyS}$ binding in these hippocampal regions following this dose of amitriptyline and treatment regimen (Hensler, 2002). The discrepant observations from the current study and our previous work may be related to dose and duration of treatment with amitriptyline.

We also observed an increase in 5-HT$_{1A}$ receptor-stimulated $[^3]S\text{GTPyS}$ binding in dentate gyrus and CA$_1$ regions of the hippocampus following the highest dose of venlafaxine (70 mg/kg, d); an effect not seen after chronic administration of the low and moderate doses of venlafaxine. It is tempting to speculate that the up-regulation of 5-HT$_{1A}$ receptor-stimulated $[^3]S\text{GTPyS}$ binding following chronic treatment with amitriptyline or the highest dose of venlafaxine may somehow be due to involvement of the noradrenergic system. Although venlafaxine and amitriptyline have similar affinities for the SERT ($K_i = 16–19 \text{nM}$), amitriptyline has much higher affinity for the NE transporter (NET) ($K_i = 8 \text{nM}$) than venlafaxine ($K_i = 1067 \text{nM}$) (Owen et al., 1997). The idea that venlafaxine does not block NE reuptake unless given at higher doses, however, is not supported by the finding that $\beta$-adrenergic receptors are down-regulated after chronic administration of venlafaxine at a dose of 15 mg/kg d s.c. (Gould et al., 2004), an indication that venlafaxine is blocking the NET even at this low dose. Interestingly, the increase in the capacity of 5-HT$_{1A}$ receptors to activate G proteins observed following chronic treatment of rats with the highest dose of venlafaxine was not accompanied by an increase in total 5-HT$_{1A}$ receptor number, or in the number of 5-HT$_{1A}$ receptors in the coupled high-affinity agonist state. Taken together these data suggest that the increase in 5-HT$_{1A}$ receptor-stimulated $[^3]S\text{GTPyS}$ binding may be due to regulatory changes at the level of the G protein, e.g. phosphorylation.

We found no change in 5-HT$_{1A}$ receptor number or 5-HT$_{1A}$ receptor-stimulated $[^3]S\text{GTPyS}$ binding in dentate gyrus or CA$_1$ regions of the hippocampus following chronic sertraline treatment. These data are consistent with previous studies in which we and others found no change in 5-HT$_{1A}$ receptor-stimulated $[^3]S\text{GTPyS}$ binding in the hippocampus following chronic administration of the SSRI fluoxetine (Hensler, 2002; Pejchal et al., 2002). However, an increase in 5-HT$_{1A}$ receptor-stimulated $[^3]S\text{GTPyS}$ binding in the hippocampus following chronic fluoxetine treatment has also been observed (Castro et al., 2003; Shen et al., 2002). The reasons for these discrepant observations may be related to dose, manner of administration (e.g. repeated i.p injection vs. osmotic minipump implanted s.c.), and duration of treatment. Electrophysiological responses mediated by postsynaptic 5-HT$_{1A}$ receptors appear to be regulated differentially within subregions of the hippocampus, i.e. enhanced in the CA$_1$ region of the hippocampus (Beck et al., 1997), but unchanged in the CA$_1$ region of the hippocampus (Blier and de Montigny, 1983; Chaput et al., 1986; Le Poul et al., 2000) following chronic administration of SSRIs.

Neurochemical and electrophysiological studies have shown that chronic administration of TCAs does not result in the desensitization of the 5-HT$_{1A}$
somatodendritic autoreceptor (Blier and de Montigny, 1980; Kreiss and Lucki, 1995). Our findings in the current study are consistent with this in that we observed no change in 5-HT1A receptor-stimulated [35S]GTPγS binding in the dorsal and median raphe nuclei following chronic administration of amitriptyline.

We and others have shown that following chronic administration of the SSRI fluoxetine, 5-HT1A receptor-stimulated [35S]GTPγS binding in the dorsal and median raphe nuclei is attenuated (Castro et al., 2003; Hensler, 2002; Pejchal et al., 2002; Shen et al., 2002). These data indicate that the desensitization of 5-HT1A somatodendritic autoreceptors observed in neurochemical and electrophysiological studies following chronic fluoxetine administration (Czachura and Rasmussen, 2000; Kreiss and Lucki, 1995; Le Poul et al., 2000) may be due to a reduction in the capacity of 5-HT1A receptors to activate G proteins. Somewhat surprisingly, in light of these previous studies, is the lack of effect of chronic sertraline administration on 5-HT1A receptor-stimulated [35S]GTPγS binding in the dorsal and median raphe nuclei in the current study. Unlike fluoxetine, sertraline has high affinity for α1-adrenergic receptors (36 nM) (Owens et al., 1997). It is tempting to speculate that lack of effect of chronic sertraline administration on the capacity of 5-HT1A receptors to activate G proteins in serotonergic cell body areas may be due to the blockade of α1-adrenergic receptors.

Electrophysiological studies indicate that somatodendritic 5-HT1A autoreceptors are desensitized following chronic administration of the selective 5-HT1A NE re-uptake inhibitors venlafaxine or duloxetine (Béique et al., 2000; Rueter et al., 1998). However, we observed no change in 5-HT1A receptor-stimulated [35S]GTPγS binding in the dorsal and median raphe nuclei following chronic administration of venlafaxine at any dose. Thus, the desensitization of somatodendritic 5-HT1A autoreceptor function observed in electrophysiological studies appears not to be due to a reduction in the capacity of the receptor to activate G protein, but may occur at the level of effector, e.g. ion channel.

In conclusion, there is abundant evidence in the literature of functional interactions between the noradrenergic and serotonergic systems, including neuroanatomical evidence of reciprocal innervation between noradrenergic and serotonergic cell body groups (Baraban and Aghajanian, 1981; Kaehler et al., 1999; Kim et al., 2004; Loizou, 1969; Peyron et al., 1996). Serotonergic neuronal firing in the raphe nuclei is increased via excitatory α1-adrenergic receptors, and decreased by activation of α2-adrenergic receptors (Adell and Artigas, 1999; Baraban and Aghajanian, 1980; Freedman and Aghajanian, 1984). The interaction between NE and 5-HT neurons might not only serve as an important site of action for drugs used to treat anxiety and depression, but could also impact on the regulation of 5-HT1A receptors in brain.

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Statement of Interest

None.

References


Gould GG, Benmansour S, Frazer A (2004). Interactions between serotoninergic and noradrenergic systems are not responsible for venlafaxine’s lack of effect on serotonin (5-HT) and norepinephrine (NE) transporter density. Society for Neuroscience, Program no. 54.9.


Hensler JG (2003). Regulation of 5-HT_{1A} receptor function in brain following agonist or antidepressant administration. Life Science 72, 1665–1682.


Hensler JG, Gould GG, Rossi DV, Valdez M (2003). Regulation of 5-HT_{1A} receptor function following administration of the antidepressant venlafaxine. Society for Neuroscience, Program no. 362.8.


Rossi DV, Valdez M, Gould GG, Hensler JG (2004). Mechanism of sensitization of postsynaptic 5-HT1A receptors in hippocampus following chronic tricyclic antidepressant (TCA) administration. *Society for Neuroscience, Program no. 394.16*


Shen C, Li H, Meller E (2002). Repeated treatment with antidepressants differentially alters 5-HT1A receptors.


