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α_{1B}-Adrenoceptor-mediated excitation of piriform cortical interneurons

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Abstract

Pharmacological techniques have defined the existence of two different α_1-adrenoceptors, the α_{1A}- and α_{1B}-adrenoceptor subtypes and both of these receptors have been cloned in addition to a cloned α_{1d}-adrenoceptor. A subpopulation of interneurons in layer III of the rat piriform cortex that are excited by 5-hydroxytryptamine (5-HT) via 5-HT_{2A} receptors are also excited by norepinephrine via α_1-adrenoceptors. In the present study we determined the pA_2 values against the norepinephrine-mediated excitation of piriform cortical interneurons for a number of antagonists that are (1) not selective for α_{1A}- or α_{1B}-adrenoceptors (prazosin), (2) selective for α_{1A}-adrenoceptors (5-methyl urapidil, 2-(2,6-dimethoxy-phenoxyethyl)-aminomethyl-1,4-benzodioxane hydrochloride (WB 4101), benoxathian, phentolamine) and (3) selective for α_{1B}-adrenoceptors (spiperone and risperidone). The pA_2 values for the antagonist blockade of norepinephrine-mediated interneuron excitation were significantly correlated to literature values for the pK_i values of antagonist binding to the α_{1B}-adrenoceptor ($r = 0.919$) and the cloned α_{1b}-adrenoceptor ($r = 0.849$) but were not correlated to the pK_i values of antagonist binding to the α_{1A}-adrenoceptor or the cloned α_{1a}- and α_{1d}-adrenoceptor. Thus, we conclude that this population of piriform cortical interneurons is excited by norepinephrine via α_{1B}-adrenoceptors.

Keywords: Norepinephrine; Risperidone; Primary olfactory cortex; Electrophysiology; Antipsychotic drug

1. Introduction

Electrophysiological studies have characterized a subpopulation of interneurons in layer III of piriform cortex that are excited by 5-hydroxytryptamine (5-HT) via the 5-HT_{2A} receptor (Sheldon and Aghajanian, 1990, 1991; Gellman and Aghajanian, 1993; Marek and Aghajanian, 1994, 1995). Many of the interneurons that are excited by 5-HT are also excited by norepinephrine. The excitation of these interneurons appears to be mediated by an α_1-adrenoceptor since 2 μM prazosin completely blocks the norepinephrine-mediated excitation (Sheldon and Aghajanian, 1988).

α_1-Adrenoceptors appear to have two distinct *pharmacological* subtypes that have been defined as α_{1A}- and α_{1B}-adrenoceptors (Morrow and Creese, 1986; see Minneman and Esbenshade, 1994). Prazosin has equal affinity for both pharmacologically defined subtypes (Morrow and Creese, 1986). The present studies were designed to test whether the norepinephrine-mediated excitation of interneurons is mediated by an α_{1A}- or an α_{1B}-adrenoceptor by quantifying pharmacologically the blockade of norepinephrine-mediated excitation by antagonists that are relatively selective for α_{1A}-adrenoceptors (5-methyl urapidil, WB 4101 (2-(2,6-dimethoxy-phenoxyethyl)-aminomethyl-1,4-benzodioxane hydrochloride), benoxathian, phentolamine) or α_{1B}-adrenoceptors (risperidone, spiperone; Ford et al., 1994). In addition, prazosin, which is not selective for α_{1A}- and α_{1B}-adrenoceptors, was tested.

2. Materials and methods

2.1. Brain slice preparation

Brain slices were prepared from 23 male Sprague-Dawley rats (100–200 g) as described previously (Aghajanian and Rasmussen, 1989). Briefly, rats were anaesthetized with chloral hydrate (400 mg/kg, i.p.), in adherence to

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protocols approved by the Yale University Animal Care and Use Committee. Following decapitation, the brain was removed rapidly and placed in an ice-cold modified artificial cerebrospinal fluid (ACSF) in which sucrose (252 mM) was substituted for NaCl. A block of tissue containing the anterior piriform cortex was dissected free. Coronal slices (500 μm) were cut with a vibrating-knife microtome (Vibraslice, WPI) at a level corresponding to approximately 2.2 mm anterior to bregma (Paxinos and Watson, 1986). A slice containing anterior piriform cortex was then transferred to the stage of a fluid-gas interface chamber which had a constant flow of humidified 95% O_2-5% CO_2. The slices were perfused with normal ACSF which consisted of (in mM) NaCl 126; KCl 3; $CaCl_2$ 2; $MgSO_4$ 2; $NaHCO_3$ 26; NaH_2PO_4 1.25; D-glucose 10. The chamber was heated slowly from room temperature to 34°C. The slices were perfused with ACSF for a 2 h recovery period prior to beginning experiments.

2.2. Electrophysiological recordings

Extracellular recordings were conducted using an Axoclamp-2A (Axon Inst., Burlingame, CA, USA). Placement of the recording electrodes was facilitated by visualizing the three layers of the piriform cortex at low magnification under reflected light. Extracellular recordings from interneurons located in layer III of the piriform cortex were made using glass microelectrodes filled with 2 M NaCl (5–10 MΩ) as described previously (Sheldon and Aghajanian, 1990). Cells were found by searching while the slice was perfused with 30 μM 5-HT in order to activate quiescent cells. Cells were identified as interneurons if they had short duration (0.1–0.5 ms) and low amplitude (0.25–1 mV) extracellular action potentials. Unlike interneurons, pyramidal cells in layer II are not brought to threshold for firing by bath application of 5-HT (Sheldon and Aghajanian, 1990). Cells identified as interneurons had the ability to sustain rapid firing rates as characterized previously by both intracellular and extracellular recording (Sheldon and Aghajanian, 1990, 1991). Once an interneuron was located, the solution was switched from 30 μM 5-HT back to control ACSF and the 5-HT activated cells gradually slowed and, in most cases, ceased firing. Then, the effects of 5-HT creatinine sulfate, (−)-norepinephrine bitartrate (Sigma Chemical Co., St. Louis, MO, USA) and α-amino-3-hydroxy-5-methyl-iso-

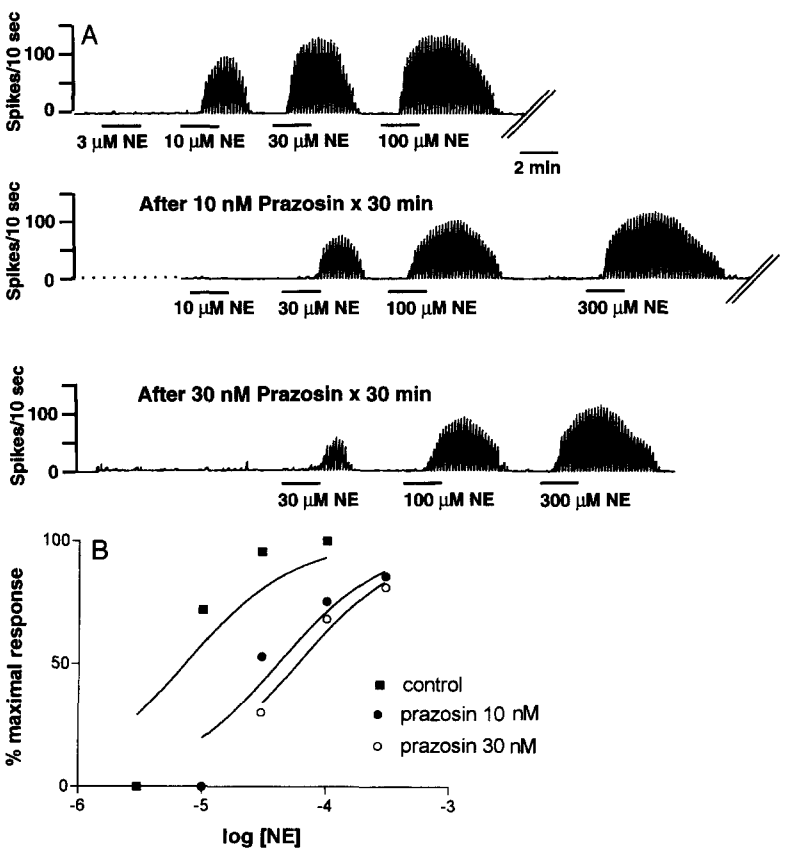

Fig. 1. Firing rate histogram (A) of a piriform cortical interneuron before (top panel) and after a 30 min perfusion with 10 nM prazosin (middle panel) and 30 nM prazosin (bottom panel). Norepinephrine (NE; 3, 10, 30, 100 and 300 μM) was bath applied in ACSF for 2 min at the times indicated. The concentration-response relationship from this experiment is also shown (B). The lack of response for the 3 μM norepinephrine concentration under control conditions may reflect absence of equilibrium conditions for the lowest norepinephrine concentration compared to the other concentrations. The pA_2 for blockade of excitation by norepinephrine in this interneuron was 8.66 and 8.44 for 10 nM and 30 nM prazosin, respectively.

xazoleproprionate (AMPA; RBI, Natick, MA, USA) were tested. Concentration-response determinations for norepinephrine alone were made by perfusing increasing concentrations of norepinephrine ranging from near threshold (3–10 μM) through near maximal (30–100 μM) for 2 min and then testing the next higher dose after the previous response returned to baseline. In preliminary experiments, it had been shown that repeated applications of norepinephrine produced replicable responses. Even continuous application of 100 μM norepinephrine for 15–18 min did not reveal any decrease in the excitation of the interneurons by norepinephrine ($n = 3$; not shown). The response for each drug concentration was defined as the total number of counts during the 1 min period of maximal activation for a given cell. Following determination of the norepinephrine concentration-response relationship, prazosin (10 nM; Sigma, St. Louis, MO, USA), spiperone (30 nM, RBI), WB 4101 (1 μM, RBI), 5-methyl urapidil (1 μM, RBI), benoxathian HCl (1 μM, RBI), phentolamine mesylate (1 μM, Ciba-Geigy, Summit, NJ, USA) and risperidone (3 and 30 nM; Janssen, Beerse, Belgium) were applied for 30 min prior to the redetermination of the norepineprhine concentration-response relationship. Since spiperone, unlike the other antagonists, did reach equilibrium during this time, the norepinephrine concentration-response determination was not performed until at least 30–60 min passed and it could be demonstrated that the blockade of norepinephrine was no longer progressing.

2.3. Data analysis

The response for each drug was defined as the total number of spikes during the one min period of maximal activation for a given cell. The EC_{50}'s for the norepinephrine concentration-response curves was calculated by non-linear regression using Prism. The pA_2 was calculated from the formula as derived by Arunlakshana and Schild, 1959; $pA_2 = \log [\text{Antagonist}] - \log (dr - 1)$, where dose ratio (dr) was the EC_{50} for norepinephrine in the presence of the antagonist divided by the EC_{50} for norepinephrine in the absence of the antagonist.

3. Results

A low concentration of the potent and selective α_1-adrenoceptor antagonist prazosin (10 nM) reduced the norepinephrine-mediated excitation of piriform cortical interneurons and also increased the latency of the response to norepinephrine (Fig. 1A), consistent with the actions of an antagonist (Kenakin, 1993). The excitation of these interneurons by 5-HT, carbachol, and AMPA (data not shown) was not affected by prazosin. The reduction in the norepinephrine-mediated excitation was mediated primarily by shifting the dose-response curve to the right (Fig. 1B). The pA_2 value from six similar experiments for the blockade of norepinephrine-mediated excitation by prazosin (10 nM) was 8.92. Note that the pA_2 values from the experiment shown in Fig. 1 were 8.66 and 8.44 for the 10 nM and 30 nM prazsoin concentrations, respectively. The selective α_{1B}-adrenoceptor antagonist risperidone (30 nM; Sleight et al., 1993; however, see Giardina et al., 1995) also potently blocked the norepinephrine-mediated excitation of cortical interneurons and delayed the onset of the norepinephrine-mediated excitation without affecting the AMPA-mediated excitation; this antagonism of norepinephrine-mediated excitation was surmountable by higher concentrations of norepinephrine (Fig. 2). The pA_2 value for the blockade of norepinephrine-mediated excitation by risperidone (30 nM) was 8.23 ($n = 3$, Table 1). Again, the pA_2 value obtained appeared to be independent of the antagonist concentration as the pA_2 value obtained

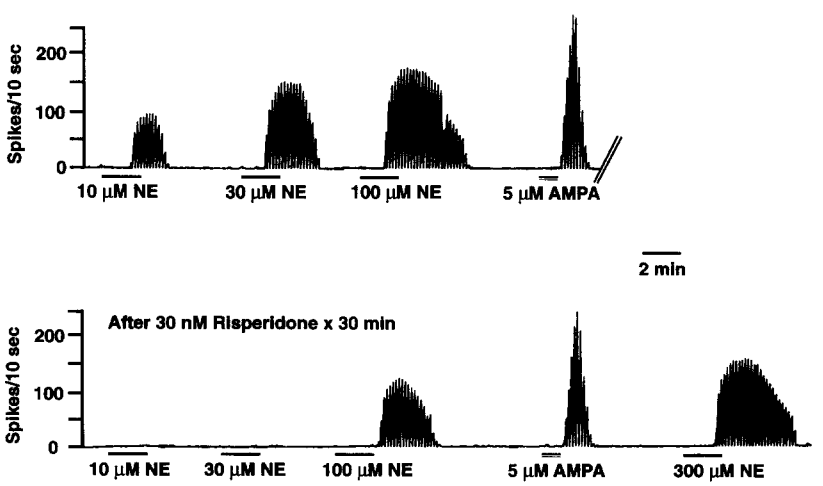

Fig. 2. Firing rate histogram of a piriform cortical interneuron before (top panel) and after a 30 min perfusion with 30 nM risperidone (bottom). Norepinephrine (NE; 10, 30, 100 and 300 μM, indicated with solid lines) and AMPA (5 μM, indicated with a double line) were applied in ACSF for the times indicated. The pA_2 for blockade of excitation by norepinephrine in this interneuron was 8.61.

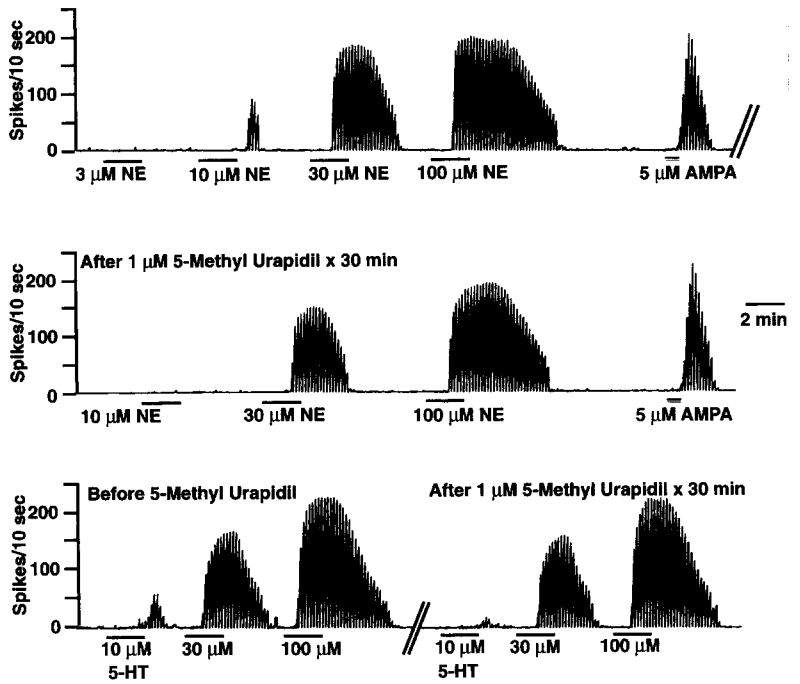

Fig. 3. Firing rate histogram of a piriform cortical interneuron before (top panel) and after a 30 min perfusion with 1 μM 5-methyl urapidil (bottom panel). Norepinephrine (NE; 3, 10, 30 and 100 μM, indicated with solid lines) and AMPA (5 μM, indicated with a double line) were applied in ACSF for the times indicated. The pA_2 for blockade of excitation by norepinephrine in this interneuron was 5.82. A 5-HT dose-response determination (10, 30 and 100 μM) in this same interneuron (C) is also shown both before and after the 5-methyl urapidil application.

in a separate cell with a higher risperidone concentration (100 nM) was 8.37. In contrast, relatively high concentrations of the α_{1A}-adrenoceptor antagonist 5-methyl urapidil (1 μM) were required to produce only a small inhibition of the norepinephrine-mediated excitation of cortical interneurons (Fig. 3). The pA_2 value for the blockade of norepinephrine-mediated excitation by 5-methyl urapidil was 6.15 ($n = 3$, Table 1). The pA_2 value obtained with 5-methyl urapidil similarly appeared to be independent of the antagonist conentration as the pA_2 values were 6.71 and 6.47 in the same cell for 100 nM and 1 μM 5-methyl urapidil, respectively.

The pA_2 values for the blockade of norepinephrine-mediated piriform cortical interneuron excitation by a series of antagonists (benoxathian, 5-methyl urapidil, phentolamine, prazosin, spiperone, and WB 4101) given in Table 1 were compared to literature pK_i's for the antagonist binding to native and cloned α_1-adrenoceptor subtypes (Ford et al., 1994). The pA_2 values for antagonist blockade of norepinephrine-mediated interneuron excitation was significantly correlated to the pK_i's for antagonist binding to the rat liver α_{1B}-adrenoceptor ($r = 0.919$, $P < 0.01$, $n = 6$; Fig. 4) and the cloned α_{1b}-adrenoceptor ($r = 0.849$, $P < 0.05$, $n = 6$). In contrast, the pA_2 values for antagonist blockade of norepinephrine-mediated interneuron excitation was not correlated to the pK_i's of antagonist binding to the rat submaxillary gland α_{1A}-adrenoceptor ($r = 0.256$, $n = 6$; Fig. 4) and the cloned α_{1a}-adrenoceptor (formerly the cloned α_{1c}-adrenoceptor, Michel et al., 1995; $r =$

Table 1
Antagonist pA_2 values against norepinephrine-mediated interneuron excitation ($n = 3$, except $n = 6$ for prazosin)

Antagonist	pA_2
Prazosin (10 nM)	8.92 ± 0.07
Risperidone (30 nM)	8.23 ± 0.20
Spiperone (30 nM)	7.63 + 0.22
WB 4101(1 μM)	7.45 ± 0.18
Phentolamine (1 μM)	6.25 ± 0.08
5-Methyl urapidil (1 μM)	6.15 ± 0.15
Benoxathian (1 μM)	5.95 ± 0.08

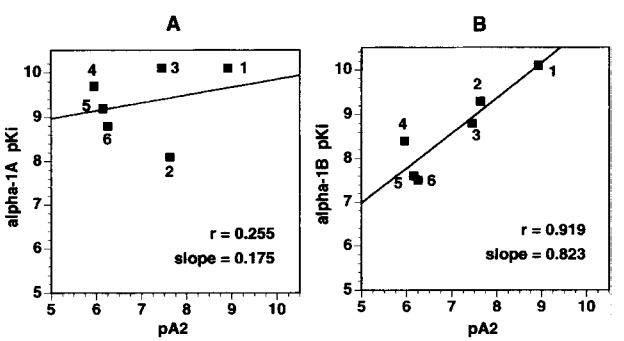

Fig. 4. Correlations of antagonist pA_2 values at α_1-adrenoceptors in rat piriform cortex slices and antagonist affinity estimates (pK_i values from Ford et al., 1994) in (A) rat submaxillary gland α_{1A}-adrenoceptors and (B) rat liver α_{1B}-adrenoceptors: (1) prazosin; (2) spiperone; (3) WB 4101; (4) benoxathian; (5) 5-methyl urapidil; (6) phentolamine.

0.116, $n = 6$). In addition, the pA_2 values for antagonist blockade of norepinephrine-mediated interneuron excitation was not significantly correlated to the pK_i's of antagonist binding to the cloned α_{1d}-adrenoceptor ($r = 0.452$, $n = 6$, data not shown).

Several, but not all, of the α_1-adrenoceptor antagonists tested also blocked the excitatory effects of 5-HT on the same interneurons at the same concentrations in which they blocked the excitatory effects of norepinephrine. The excitatory effects of 5-HT in this subpopulation of interneurons is known to be mediated via stimulation of 5-HT_{2A} receptors (Sheldon and Aghajanian, 1990, 1991; Marek and Aghajanian, 1994). The pA_2 values found were 8.88 ± 0.09 for risperidone ($n = 2$); 8.12 ± 0.05 for spiperone ($n = 3$); and 5.86 for benoxathian ($n = 1$). Prazosin (10 nM), phentolamine (1 μM), 5-methyl urapidil (1 μM), and WB 4101 (1 μM) did not block the effects of 5-HT. None of the antagonists blocked the excitatory effects of the excitatory amino acid agonist AMPA (Figs. 2 and 3).

4. Discussion

The major finding of the present study is that the norepinephrine-mediated excitation of interneurons in the piriform cortex appears to be due to stimulation by the α_{1B}-adrenoceptors rather than the α_{1A}-adrenoceptors. This conclusion is supported by the highly significant correlation between the pA_2 values for a series of six α_1-adrenoceptor antagonists against the norepinephrine-mediated excitation of interneurons vs. the K_i's of the adrenoceptor antagonists at the α_{1B}-adrenoceptor both in native tissue and in cells expressing the cloned α_{1b}-adrenoceptor (Ford et al., 1994). In contrast, the pA_2 values of the adrenoceptor antagonists against norepineprhine-mediated excitation of interneurons is not correlated to the K_i's for the antagonists at the α_{1A}-adrenoceptor (Ford et al., 1994). In addition, the pA_2 values of the adrenoceptor antagonists against the norepinephrine-mediated excitation of interneurons is not correlated to the K_i's for the antagonists against either the cloned α_{1a}-adrenoceptor (formerly the α_{1c}-adrenoceptor, Ford et al., 1994; Faure et al., 1994; Rokosh et al., 1994; Pimoule et al., 1995; Michel et al., 1995) or the cloned α_{1d}-adrenoceptor. This, to our knowledge, represents the first electrophysiological discrimination of the α_1-adrenoceptor subtypes in the cortex.

The present results are consistent with the localization of α_{1B}-adrenoceptors in the piriform cortex by in vitro autoradiography (Blendy et al., 1990) and in situ hybridization (Pieribone et al., 1994). Interestingly, Pieribone et al. (1994) noted detection of α_{1b}-adrenoceptor mRNA only in the anterior piriform cortex. While in the present study we did not record in the posterior piriform, in a previous published report in which recordings were made near the middle (anterior vs. posterior) of the piriform cortex we observed that only about 40% of the interneurons that were excited by 5-HT were also excited by norepinephrine (Marek and Aghajanian, 1995). In the present study, recordings were made from the anterior piriform cortex and we have observed that about 80% of the interneurons that were excited by 5-HT were also excited by norepinephrine. The pharmacology and the localization of the norepinephrine-mediated excitation of interneurons in the rostral-caudal gradient of the piriform cortex are consistent with the conclusion that α_{1B}-adrenoceptors mediate the excitation by norepinephrine on the subpopulation of interneurons that are also excited by 5-HT via a 5-HT_{2A} receptor.

A second important finding is that the present pharmacological study is consistent with a recent report that risperidone, which is an atypical antipsychotic drug, is a potent α_{1B}-adrenoceptor antagonist (Sleight et al., 1993). This finding may have relevance to the design of new atypical antipsychotic drugs. The relative low affinity of clozapine for dopamine$_2$ (D_2) receptors has emphasized the need to examine the role of other pharmacological sites for the mediation of the therapeutic effects of the atypical antipsychotic drugs. Cohen and Lipinski (1986) have suggested that blockade of α_1-adrenoceptors in vivo is more consistent within both typical and atypical antipsychotics than is blockade of D_2 receptors. The potential contribution played by blockade of α_1-adrenoceptors in mediating the therapeutic effects appears to be underappreciated given the high potency of almost all antipychotic drugs for the α_1-adrenoceptor.

The present findings may also have relevance to understanding the mechanism underlying the therapeutic effects of somatic antidepressant treatments. Repeated electroconvulsive shock treatments increase α_{1B}-adrenoceptor binding, but not α_{1A}-adrenoceptor binding (Blendy et al., 1990, 1991). Chronic, but not acute, administration of tricyclic antidepressants and the atypical antidepressant iprindole enhance electrophysiological α_1-adrenoceptor responses in the facial motor nucleus (Menkes et al., 1980) and a behavioral α_1-adrenoceptor response, the acoustic startle reflex stimulated by phenylephrine (Menkes et al., 1983). However, the α_1-adrenoceptor subtype(s) mediating these electrophysiological and behavioral effects are not known. Thus, these cortical neurons that are excited by norepineprhine and 5-HT via α_{1B}-adrenoceptors and 5-HT_{2A} receptors, respectively, may provide a useful substrate for studying monoaminergic interactions that may have relevance to the clinical effects of both antipsychotic drugs and antidepressant treatments.

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