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ORIGINAL INVESTIGATION

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Modification of norepinephrine and serotonin, but not dopamine, neuron firing by sustained bupropion treatment

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Abstract *Rationale*: Bupropion is widely used in the treatment of depression and as an anti-craving medication for the cessation of tobacco smoking. Because it is a very weak inhibitor of norepinephrine (NE) and dopamine (DA) reuptake, its mechanisms of action remain to be elucidated. *Methods*: Bupropion was administered subcutaneously via osmotic minipumps over 2 days to determine its effects on the spontaneous firing activity of NE, serotonin (5-HT), and DA neurons in the brain of anaesthetised male Sprague-Dawley rats. This treatment was used in order to obtain levels of the parent compound and its putatively active metabolites that would more adequately reflect the clinical condition than utilizing acute injections. *Results*: When given by minipump for 2 days, bupropion produced a dose-dependent attenuation of the mean spontaneous firing NE neurons (7.5 mg/kg per day: 15%; 15 mg/kg per day: 61%; 30 mg/kg per day: 80%) which was reversed by the α_2-adrenoceptor antagonist idazoxan. At the highest regimen, the mean firing rate of 5-HT neurons was 100% higher than in control rats, but unaffected in NE-lesioned rats. In contrast, DA neurons in the ventral tegmental area displayed a normal firing rate during the latter bupropion treatment. *Conclusions*: Sustained bupropion administration decreased the firing rate of NE neurons due to an increased activation of their inhibitory somatodendritic α_2-adrenoceptors. This effect of the bupropion treatment would be attributable mainly to an enhancement of NE release and not to reuptake inhibition. This contention is based essentially on the observation that NE reuptake blockers leave unaltered the firing rate of 5-HT neurons, whereas bupropion enhanced it via a NE-dependent mechanism. The present study did not put into evidence any DA activity of bupropion at the level of the cell body of mesolimbic/cortical DA neurons at a regimen exerting profound alterations of the firing activity of NE and 5-HT neurons.

Keywords Antidepressant · Locus coeruleus · Dorsal raphe · Ventral tegmental area · α_2-Adrenoceptors and autoreceptors

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Introduction

Bupropion is an effective antidepressant drug that was synthesized by modifying the structure of the anorexic agent diethylpropion. It has also been marketed recently as an anti-craving medication for tobacco smoking cessation (Hurt et al. 1997). Its purported mechanism of action is generally believed to be the blockade of the reuptake process of dopamine (DA) and norepinephrine (NE). The affinity of bupropion for these two reuptake transporters is, however, in the micromolar range (Ferris et al. 1981). It is thus doubtful that such concentrations of bupropion are achieved in humans using standard and equally effective doses of 150–300 mg per day (Posner et al. 1985; Reimherr et al. 1997). Indeed, in electrophysiological and microdialysis experiments in laboratory animals, high acute doses of bupropion are necessary to observe either a decrease in firing rate of NE and DA neurons or an increase of extracellular concentrations of DA in projection areas (Nomikos et al. 1989; Cooper et al. 1994). These two alterations are known to take place following either reuptake blockade or monoamine release. Nevertheless, bupropion is metabolized mainly into hydroxy-, threo- and erythro-derivatives, the former achieving plasma levels about 10–100 times higher than that of the parent compound in humans (Posner et al. 1985). As this hydroxy metabolite is active on NE reuptake, it appears that experiments examining the effects of acute administration of bupropion are not best suited to draw conclusions on the putative mechanism(s) of action of bupropion on monoaminergic systems.

The present study was thus undertaken to examine the effects of sustained administration of bupropion on rat

firing activity of catecholamine (NE and DA) neurons, as well as of serotonin (5-HT) neurons, upon presumed achievement of steady state levels of the parent compound and its metabolites (Perumal et al. 1986; Cooper et al. 1994). The latter pharmacological condition is thought to mimic better the levels of bupropion and its metabolites attained in patients than that achieved by acute injections, because bupropion has a shorter elimination half-life in rats than in humans (Perumal et al. 1986), as for most antidepressant drugs. The assessment of the firing rate of 5-HT neurons was justified on the basis of the important excitatory NE influence on the firing of dorsal raphe 5-HT neurons.

Materials and methods

Animals

Electrophysiological experiments were performed in male Sprague-Dawley rats (250–300 g) anaesthetised with chloral hydrate (400 mg/kg, IP) and supplemental doses being given throughout the experiment to maintain constant anaesthesia. Animals were kept in standard laboratory conditions (12:12 light: dark cycle with free access to food and water, at a room temperature of 21°C). They were placed in a stereotaxic apparatus and their body temperature was maintained at 37°C throughout the experiments.

Treatments

The rats were anaesthetised with fluothane in a vehicle containing a 2:1 O_2:N_2O mixture, and osmotic Alzet 2ML1 minipumps (Alza, Palo Alto, Calif., USA) delivering bupropion at a rate of 7.5, 15 or 30 mg/kg per day, were implanted subcutaneously (SC). Control rats were implanted with osmotic minipumps containing physiological saline. The lesion of locus coeruleus NE neurons was carried out with the selective neurotoxin-(2-chloroethyl)-*N*-ethy-1-2 bromobenzylamine (DSP-4) injected intraperitoneally (IP; 40 mg/kg; Cheetham et al. 1996; Hughes and Stanford 1998). All electrophysiological experiments were carried out with the minipump in place in order to mimic as much as possible the clinical condition. The lesioned rats were allowed to recover for 5 days before implanting a bupropion minipump delivering 30 mg/kg per day for 2 days.

Preparation of electrophysiological experiment

The extracellular recordings were carried out using single glass micropipettes (R & D Scientific Glass, Spencerville, Md., USA). The single micropipettes were used for recording dorsal raphe 5-HT neurons, locus coeruleus NE neurons and VTA (A10) DA neurons. Their tips were of 1–3 µm in diameter. The impedance of such electrodes typically ranged between 5–7 MΩ. All glass micropipettes were preloaded with fiberglass strands in order to promote capillary filling with a 2 M NaCl solution.

Recording of dorsal raphe 5-HT neurons

The single-barred glass micropipette was positioned 1 mm anterior to lambda on the midline and lowered into the dorsal raphe, usually attained at a depth of between 5.5 and 6.5 mm from the brain surface. The dorsal raphe 5-HT neurons were identified according to the following criteria, i.e. a slow (0.5–2.5 Hz) and regular firing rate and a long-duration (0.8–1.2 ms) positive action potential. In order to appraise possible changes of firing activity of 5-HT neurons during the course of sustained administration of bupropion, five descents were carried out through the dorsal raphe in each control and treated rat using single micropipette (Blier and de Montigny 1983).

Recording from locus coeruleus neurons

The single-barred glass micropipette was lowered at 1.1–1.4 mm lateral and –0.7 mm posterior to lambda into the neurons locus coeruleus. The NE neurons were identified by their regular firing rate (1–5 Hz), long-duration (0.8–1.2 ms) positive action potentials and their characteristic burst discharge in response to nociceptive pinch of the contralateral hind paw. In order to observe possible changes of firing activity of NE neurons during the course of sustained administration of bupropion, five descents were performed through the locus coeruleus (Blier and de Montigny 1985).

Recording from dopamine neurons

Unitary extracellular recording were performed with single-barrelled glass micropipette, which was positioned 2–3 mm anterior to lambda and 0.2–0.6 mm lateral to the midline in the VTA. DA neurons were identified according the basis of their location, waveform (notched initial positive deflection and long action potentials, duration 2–4 ms), firing rate (0.5–10 spikes/s) and firing pattern (Bunney et al. 1973; Grace and Bunney 1983).

Drugs

Bupropion HCI, clonidine hydrochloride, apomorphine and DSP-4 HCI were purchased from RBI (Research Biochemicals, Natick, Mass., USA) and LSD from the Ministry of Health and Welfare (Ottawa, Canada).

Statistical analysis

All results are expressed as mean±SEM. The numbers given refer to the number of neurons studied, unless otherwise stated. Data were obtained from a minimum of eight neurons per rat and two to six rats were used per experimental group. Statistical comparisons between control and treatment groups were carried out using the Dunnett test, after ensuring that all animals within each group had comparable mean firing rates (with SDs overlapping means). The effects of idazoxan were analysed using a two-way ANOVA followed by Tukey tests for subsequent pairwise multiple comparison procedures. Statistical significance was taken as $P<0.05$.

Results

Effects of sustained bupropion administration on NE, 5-HT and DA neuronal firing activity

Following the highest regimen of bupropion (30 mg/kg per day, SC), the spontaneous firing rate of NE neurons was 80% lower in four rats than the mean value obtained in the three controls (Fig. 1,3; t=12.48, df=150). In order to determine whether this marked alteration in spontaneous firing was due solely to enhanced activation of the somatodendritic α_2-adrenoceptors of NE neurons, in three controls and three bupropion treated rats, systematic electrode descents were carried out before and immediately after the intravenous (IV) injection of the α_2-adrenoceptor antagonist idazoxan. In such idazoxan treated

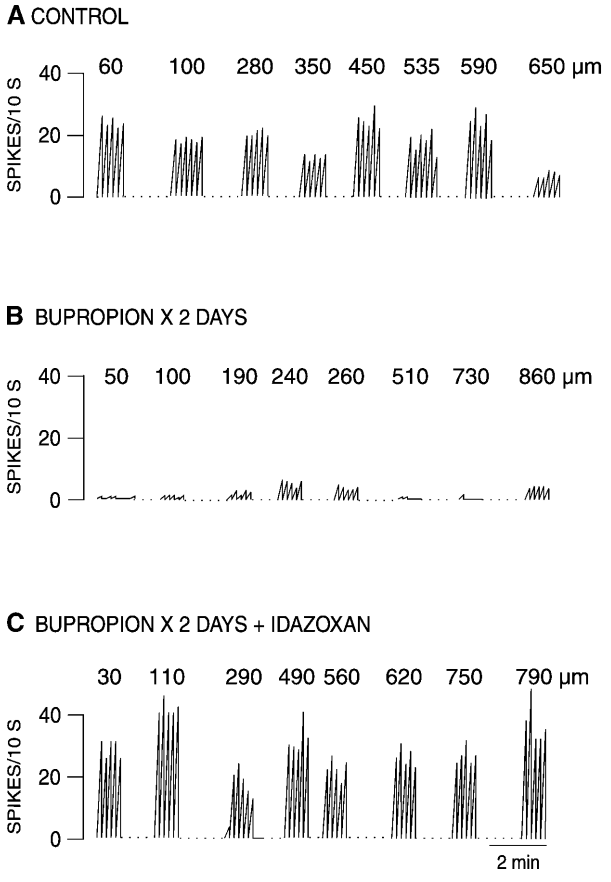

Fig. 1. Examples of single electrode descents carried out through the locus coeruleus of a control rat (**A**), a rat treated for 2 days with 30 mg/kg per day of bupropion administered using an osmotic minipump implanted SC (**B**), and following the IV injection of the α_2-adrenoceptor antagonist idazoxan (**C**). The *dots* represent interruptions of the recordings and each number above the tracings indicates the distance of each neuron from the floor of the fourth ventricle. The time base applies to all three panels

rats, the mean firing rates of NE neurons were nearly identical in the control (prior to: 2.03±0.12 Hz, *n*=49, following: 3.74±0.28 Hz, *n*=28) and the bupropion groups (prior to: 0.40±0.06 Hz, *n*=98, following: 3.71±0.32 Hz, *n*=26; Fig. 1, Fig. 2). These results revealed a significant interaction between the bupropion and the idazoxan factors (F=24.3, P<0.001). Subsequent pairwise comparisons for these four means were significant with the exception of the post-idazoxan values in controls and bupropion treated animals. The suppressant action of sustained bupropion administration was dose-dependent, as the mean spontaneous firing rate of NE neurons was 0.77±0.08 Hz with the 15 mg/kg per day regimen (*n*=73 in three rats; *t*=7.92, *df*=125) and in the 7.5 mg /kg/day group, there was only a non-significant attenuation of 15% (1.70±0.16 Hz, *n*=28 in two rats; *t*=1.40, *df*=80) when compared to controls.

Unexpectedly, the mean firing activity of 5-HT neurons was twice as high in the 30 mg/kg per day bupropion group (*n*=6 rats) when compared to controls (*n*=4 rats; *t*=6.56, *df*=225; Fig. 2, Fig. 3). In order to assess whether this resulted from an action of NE on 5-HT neurons, the same regimen was given to rats that had their NE neurons lesioned with the selective neurotoxin DSP-4. In such three such pretreated rats, the firing rate of 5-HT neurons was not different from that of controls (*t*=0.63, *df*=165; Fig. 2, Fig. 3).

Sustained bupropion administration for 2 days (30 mg/kg per day) in three rats did not alter the spontaneous firing activity of VTA DA neurons when compared to seven controls (*t*=0.03, *df*=73), thus suggesting an unmodified synaptic availability of DA in the vicinity of D_2 autoreceptors controlling the firing rate of these DA neurons.

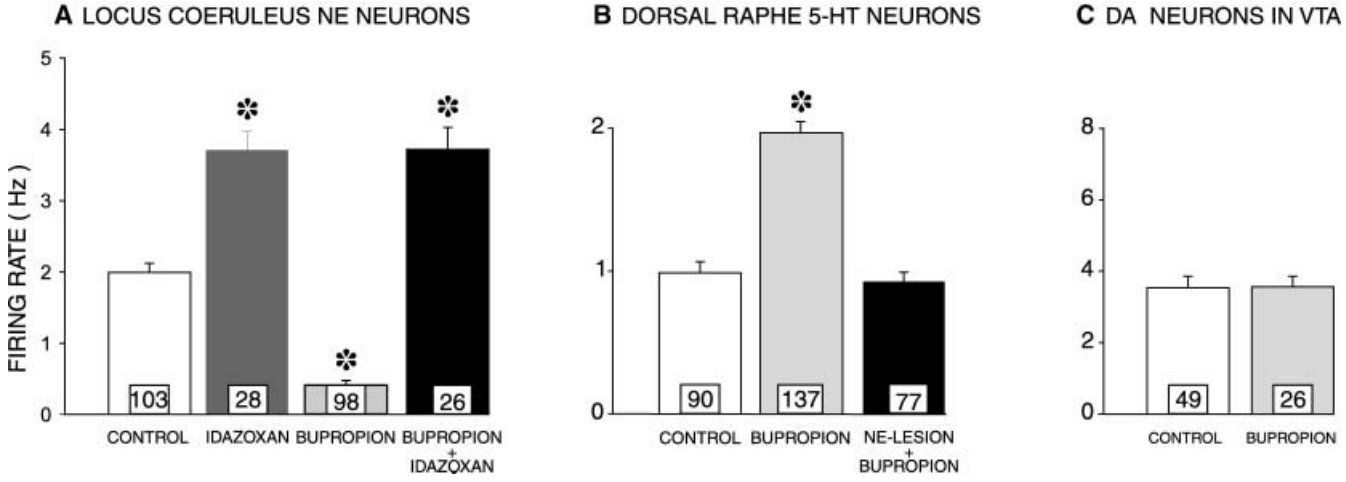

Fig. 2 **A**-**C** Histograms representing the mean (±SEM) firing rate of norepinephrine (*NE*), serotonin (*5-HT*), and dopamine (*DA*) neurons in control and treated rats. The control value in **A** represents data obtained in two separate series of experiments that were merged because their means±SEM were nearly identical (1.99±0.12 Hz, *n*=54 and 2.03±0.12 Hz, *n*=49). The α_2-adrenoceptor antagonist idazoxan (1 mg/kg, IV) was given immediately prior to the recordings to reverse the inhibition of NE neuron firing obtained with the sustained bupropion treatment. The DSP-4 pretreatment (40 mg/kg, IP, 5 days prior to initiating the 30 mg/kg per day regimen of bupropion) was used to show the noradrenergic mediation of the increase in firing of 5-HT neurons exemplified in **B**. The numbers at the bottom of each histogram indicate the number of neurons recorded

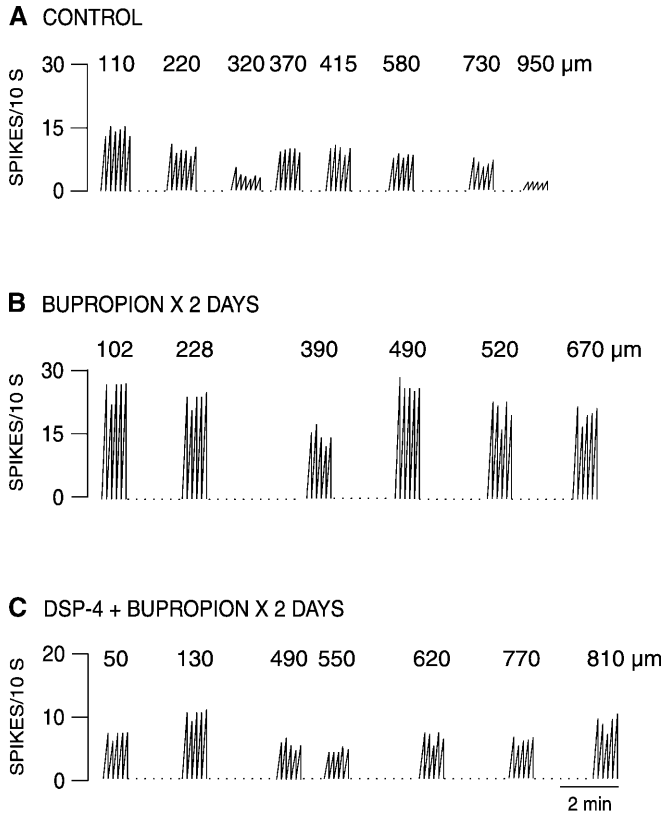

Fig. 3 Examples of single electrode descents carried out through the dorsal raphe of a control rat (**A**), a rat which received 30 mg/kg per day bupropion (30 mg/kg per day) administered through an osmotic minipump implanted subcutaneously (**B**), and in a rat with a lesion of NE neurons using the selective neurotoxin DSP-4 (40 mg/kg, IP) (**C**) given 5 days prior to the beginning of the same bupropion treatment used in **B**. The *dots* represent interruptions of the recording and each number above the tracings indicates the distance of each neuron from the floor of the third ventricle. The time base applies to all three panels

Discussion

The results of the present study clearly showed that sustained administration of bupropion, via osmotic minipumps implanted SC, produced an attenuation of the mean spontaneous firing rate of NE neurons that was dose-dependent. At the highest regimen, that of 5-HT neurons was 100% higher than in controls and, unexpectedly, bupropion did not alter the firing rate of DA neurons.

It is noteworthy that a previous report had documented a clear suppressant action of acute bupropion injections on NE and DA neurons (Cooper et al. 1994). However, this was achieved with acute IP doses of 12 and 40 mg/kg, respectively, to obtain a 50% inhibitory action. The inhibitory action of bupropion metabolites was also assessed in the latter experiments. Only the hydroxy derivative exerted a significant inhibitory effect on the firing of NE neurons. These authors concluded that the marginal suppression of firing of DA neurons using large doses of bupropion was probably not relevant to the clinical actions of this antidepressant. Nevertheless, the lack of any effect of bupropion on VTA neuronal firing using the 30 mg/kg per day regimen was somewhat unexpected (Figure 2), given the 40% decrease observed by Cooper et al. (1994) after a cumulative dose of 10 mg/kg. Certainly, such acute IP injections of a drug may lead to very different levels of the parent compound and its metabolites than those resulting from a sustained treatment given SC, which bypasses first-pass liver elimination. Whether bupropion acts on DA terminals by blocking reuptake or via an amphetamine-like releasing action, it should have attenuated VTA DA neuron firing in the present study because the activation of either mechanism also releases dopamine at cell body level to overactivate somatodendritic DA autoreceptors (Einhorn et al. 1988). Consequently, if the clinical actions of bupropion are in part mediated by these DA terminals in projection fields, the present data indicate that they are not exerted through an impulse flow dependent mechanism early in treatment.

The much lower firing rate of NE neurons after the 2-day bupropion treatment was thus not unexpected, given the prior results of Cooper et al. (1994). However, it remains to be determined whether this effect was exerted by the parent compound alone or also by metabolites. It is important to mention that the hydroxy metabolite of bupropion is equipotent to the antidepressant itself in suppressing NE neuron firing, but that it does not achieve plasma levels as high as those of bupropion in rats when compared to humans (Posner et al. 1985; Perumal et al. 1986). Sustained bupropion administration therefore resulted from an overactivation of somatodendritic α_2-autoreceptors because an optimal dose of the α_2-adrenoceptor antagonist idazoxan brought the firing frequency of NE neurons in the bupropion treated rats to the same level as that attained in controls (Freedman and Aghajanian 1984; Fig. 1, Fig. 2). The inhibitory effect of the bupropion treatment on the mean spontaneous firing rate of NE neurons could theoretically be attributed to the blockade of NE reuptake, as the potent NE reuptake blockers and reboxetine desipramine exert the same effect under identical conditions (Szabo and Blier 2000; Szabo et al. 2000). This possible interpretation of the data, however, is probably incorrect for the following two reasons. First, desipramine and reboxetine leave unaffected the firing activity of 5-HT neurons in this paradigm, whereas a marked increase of the discharge rate of 5-HT neurons was observed in the present experiments (Mongeau et al. 1997; Szabo and Blier 2000; Fig. 2, Fig. 3). Second, it was recently observed that 1-week treatments with 150 or 300 mg per day of bupropion did not attenuate the increase in systolic blood pressure produced by IV injection of tyramine in humans (Gobbi et al. 2000). Usually, any drug which blocks the NE reuptake carrier prevents entry of tyramine into NE terminals via this transporter, thereby preventing the calcium-independent release of NE that leads to the increase of systolic blood pressure. It is thus likely that the mechanism by which bupropion affected the firing rate of 5-HT neu-

rons was in part mediated through a NE-releasing effect as discussed below.

The clear effect of bupropion treatment on 5-HT neuron firing is the first report, to our knowledge, of a significant action of this antidepressant on the 5-HT system. The only agents capable of producing an increase in 5-HT neuron firing upon acute injection are the following: α_2-adrenoceptor antagonists (idazoxan and mirtazapine), α_1-adrenoceptor agonists (phenylephrine and cirazoline), and amphetamine (Baraban and Aghajanian 1980; Marwaha and Aghajanian 1982; Lejeune et al. 1994; Haddjeri et al 1996). All these agents are believed to act by increasing the degree of activation of α_1-adrenoceptors in the dorsal raphe which exert an excitatory action on 5-HT neuron firing. Since bupropion and its metabolites do not have significant α_1- or α_2-adrenoceptor affinities (Cusak et al. 1994), it is thus likely that the present bupropion treatment exerted a NE-releasing effect in the locus coeruleus as well as at the level of NE terminals in the dorsal raphe. This was supported by the observation that bupropion no longer modified the firing rate of 5-HT neurons in NE-lesioned rats (Fig. 2, Fig. 3). Given that the locus coeruleus is an important source of NE projections to the dorsal raphe (Sakai et al. 1977; Herbert and Saper 1992) and that DSP-4 is a neurotoxin that is quite selective for locus coeruleus neurons (Fritschy and Grzanna 1991), it can be postulated that the primary site of action of bupropion in exerting its enhancing effect on 5-HT neurons is the NE neurons originating from the locus coeruleus. It was noteworthy that 5-HT neurons regain their normal firing activity within 4 days after the lesion of NE neurons (Svensson et al. 1975; Baraban et al. 1978). It is somewhat unexpected that bupropion administration could lead to an enhancement of the mean firing rate of 5-HT neurons without being counteracted by the inhibitory action of the cell body 5-HT_{1A} autoreceptor after a 2-day treatment. Indeed, an increase in the firing rate of 5-HT neurons leads to an enhanced availability of synaptic 5-HT in the raphe which, in turn, overactivates the 5-HT_{1A} autoreceptor, thus normally bringing down the firing rate. For instance, a 2-day treatment with mirtazapine, in contrast to a single injection, leaves unchanged the mean firing rate of 5-HT neurons (Haddjeri et al 1996; Besson et al. 2000). The reason for this apparent inoperative mechanism during subacute bupropion administration is under study in our laboratory. Nevertheless, the doubling of the mean firing activity of 5-HT neurons by bupropion does not imply that 5-HT neurotransmission was necessarily increased throughout the brain. It is possible that 5-HT neuronal elements, such as the 5-HT reuptake transporter and the terminal 5-HT autoreceptor, could counteract the effect of this increment in firing rate. It will thus be crucial to study the effects of sustained bupropion administration over the course of a 2- to 3-week treatment on 5-HT and NE neurotransmission in order to determine which system, if not both, contribute to its antidepressant properties.

In conclusion, the present report confirms and extends previous findings indicating that bupropion has the capacity to increase synaptic availability of NE. More importantly, this study provides for the first time evidence that bupropion acts on the 5-HT system. This effect of bupropion action might be relevant to its antidepressant action. In contrast, the present experiments did not put into evidence any action on mesolimbic/cortical DA neurons using a treatment regimen that exerted a profound noradrenergic action, not only on locus coeruleus NE neurons, but also on dorsal raphe 5-HT neurons.

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