Effect of Vagus Nerve Stimulation on Serotonergic and Noradrenergic Transmission

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Received March 14, 2006; accepted May 9, 2006

ABSTRACT

Vagus nerve stimulation (VNS) is an antiepileptic treatment, which has recently shown promise as an antidepressant. Yet, its antidepressant mechanisms of action are unknown. Serotonergic [5-hydroxytryptamine (5-HT, serotonin)] and noradrenergic [norepinephrine (NE)] systems are involved in the pathophysiology of depression and in the mechanisms of action of antidepressants. The present study analyzes 5-HT and NE neuronal firing rates in their brainstem nuclei: the dorsal raphe nucleus (DRN) and locus coeruleus (LC), respectively. The basal firing rates in the DRN and LC were significantly increased after long-term treatments with VNS. After short-term VNS treatments, firing rates were significantly higher for LC (at 1 h and 3 days). As changes in their firing rate may have been due to altered autoreceptor sensitivities, the responses of autoreceptors to the acute administration of their respective agonists were assessed. However, no significant difference was seen in the DRN. No significant differences in dose response curves for 5-HT_1A somatodendritic and α_2-adrenergic autoreceptors were noticed between long-term VNS and controls. VNS appears to have a novel mechanism of antidepressant action, enabling its effectiveness in treatment-resistant depression. LC firing rates significantly increased earlier than the DRN basal firing. As the LC has an excitatory influence on DRN, it is possible that the increased DRN firing rate is secondary to an initial increased LC firing rate from VNS.

The vagus nerve (cranial nerve 10) is generally thought of as a group of efferent parasympathetic fibers regulating autonomic functions. However, this nerve consists of 80% afferent fibers (Foley and DuBois, 1937) from the head, neck, and body, leading up toward the cerebrum. These afferent fibers (Foley and DuBois, 1937) from the head, neck, and body, leading up toward the cerebrum. These afferent fibers were targeted for therapeutic use by stimulation in medically

This work was supported by the Canadian Institute in Health Research and Cyberonics Inc.

The data presented in this manuscript were part of a thesis accepted at McGill University in April 2005, entitled The Effect of Vagus Nerve Stimulation on the Efficacy of Serotonergic and Noradrenergic Transmission: an Electrophysiological Study in the Rat.

Portions of the data included in this manuscript were presented at various conferences: Debonnel G and Dorr AE (2003) Effects of vagus nerve stimulation (VNS) on dorsal raphe serotonergic neurons: an electrophysiological study in the rat; 2003 December 12–16; Puerto Rico, PR. The American College of Neuropsychopharmacology, San Juan, PR; Dorr AE and Debonnel G (2004) Electrophysiological investigation into the antidepressant effects of vagus nerve stimulation (VNS); 2004 Jun; Paris France. The Collegium Internationale Neuro-Psychopharmacologicum, Paris, France; and Dorr AE, Lucas GC, and Debonnel G (2004) In-vivo effects of chronic vagus nerve stimulation (VNS) on serotonin and noradrenergic systems; 2004 Oct; San Diego, CA. The Society for Neuroscience, Washington, DC.

Article, publication date, and citation information can be found at http://jpet.aspetjournals.org.
doi:10.1124/jpet.106.104166.

ABBREVIATIONS: VNS, vagus nerve stimulation; ECT, electroconvulsive therapy; 5-HT, 5-hydroxytryptamine, serotonin; DRN, dorsal raphe nucleus; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; NE, norepinephrine; LC, locus coeruleus; YM992, (S)-2-[[fluoro-4-indanyl]oxy][methyl]morpholine monohydrochloride; LSD, lysergic acid diethylamide; 8-OH-DPAT, 8-hydroxy-2-dipropylaminotetralin; WAY-106635, [2-[[4-(2-methoxyphenyl)-1-piperazinyl][ethyl]-N-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride; ANOVA, analysis of variance.
Serotonin and norepinephrine are involved in the pathophysiology of depression and mechanisms of action of antidepressant treatments (reviewed in Millan, 2004). The major brainstem cell body nucleus for 5-HT is the dorsal raphe nucleus (DRN). Acute MAOI and SSRI treatments, both of which increase extracellular 5-HT levels, show an initial decrease in DRN 5-HT firing rate in rats, whereas long-term firing in immature rats was due to negative feedback from inhibitory 5-HT1A somatodendritic autoreceptors, and these receptors become desensitized during long-term exposure to endogenous or exogenous agonists (reviewed in Blier, 2003).

NE reuptake inhibitors show beneficial effects with depression treatment (Massana et al., 1999; Montgomery et al., 2003), as do dual 5-HT-NE reuptake inhibitors (Stahl et al., 2002) and α2-receptor antagonists (Nutt and Pinder, 1996). The locus coeruleus (LC) is the major NE brainstem nucleus that sends projections to many brain areas, including limbic structures. It receives innervation from the nucleus of the solitary tract (Van Bockstaele et al., 1999), a brainstem nucleus for vagus nerve afferents (Barraco, 1994). In addition, the DRN innervates the LC (Cedarbaum and Aghajanian, 1978; Leger and Descarries, 1978), and, conversely, the LC gives NE inputs to the DRN (Baraban and Aghajanian, 1980), creating ample opportunity for cross-modulation. Antidepressant treatments affecting one system, either NE or 5-HT, can indirectly affect the other on the basis of this cross-modulation. For instance, NE acts on 5-HT DRN neurons to induce tonic activation mediated by excitatory α2-adenoreceptors (Baraban and Aghajanian, 1980), whereas SSRI treatments produce a net inhibition of LC firing rate after 2 weeks (Szabo et al., 2000; Grant and Weiss, 2001). NE neurons have inhibitory α2-adrenergic autoreceptors on the soma and terminals that decrease the NE firing rate or NE terminal release, respectively, in the presence of excess endogenous NE or α2-agonists such as clonidine. After long-term treatment with the dual SSRIs and 5-HT2A antagonist YM992, NE neurons showed an increase in firing rate induced by a decrease in sensitivity of the α2-adrenergic autoreceptor (Szabo and Blier, 2002). Interestingly, lesioning the LC in animal studies blocks the antiepileptic action of VNS, suggesting that the LC is involved in its effective circuitry (Krahl et al., 1998). Recent electrophysiological evidence showing an increased discharge rate of LC NE neurons in response to acute VNS within a very short time frame of seconds to minutes poststimulation has come to light (Groves et al., 2005). It is interesting to note, however, that no significant change in cerebrospinal fluid metabolites of NE and 5-HT was seen in VNS patients treated for 3 months compared with pretreatment levels (Carpenter et al., 2004).

The present study examines the effect of VNS on 5-HT and NE systems. In vivo extracellular unitary recordings were obtained in anesthetized rats to assess the basal firing rates of 5-HT and NE in the DRN and LC, respectively. The sensitivity of the 5-HT1A somatodendritic autoreceptor in the DRN and the α2 somatodendritic autoreceptor in the LC was assessed by administration of their agonists, LSD and clonidine, respectively.
10-s histogram (as obtained by the Spike2 program during recording) and dividing by length of time recorded in seconds. All neuronal firing rates for all rats in one group were added together and divided by the number of neurons recorded per group. Lysergic acid diethylamide (LSD), an agonist for 5-HT1A receptors, was administered i.v. with the last 5-HT neuron, after at least 60 s of recording for baseline firing rate determination, to test the sensitivity of the 5-HT1A somatodendritic autoreceptor. LSD was used instead of 8-OH-DPAT, as the latter 5-HT1A receptor agonist can also inhibit 5-HT firing through a long feedback loop from the frontal cortex (Romero et al., 1994). The 5-HT1A receptor antagonist WAY-100635 was administered i.v., after at least 60 s of LSD inhibition, to bring the firing rate back to basal levels, confirming that the inhibition was indeed due to the agonistic action at the somatodendritic 5-HT1A receptor. Percentage inhibition for each neuron was calculated by first determining the basal firing rate and then the firing rate after agonist administration, expressing the firing rate due to the agonist as a percentage of the basal firing rate. The percentage inhibition was 100 minus this percentage.

Electrophysiological Experiments: Locus Coeruleus. Similarly to the DRN experiments, LC experiments were done with the inactivated stimulator in place. Rats were anesthetized with chloral hydrate i.p at 400 mg/kg. Extracellular unitary in vivo recordings were conducted with a pulled single-barrel glass micropipette. The electrode was filled with 2% pontamine sky blue solution, 0.5 M, with an impedance range of 2 to 4 MΩ. A burr hole was drilled 1.1 mm posterior to lambda and 1.1 mm lateral to the midline. The electrode was lowered at 0.7 mm interaural and 1.1 to 1.4 mm lateral (Paxinos and Watson 1986). Spontaneously active NE cells were identified by their regular 1-to 5-Hz firing rate, a positive action potential of long duration (0.8–1.2 ms), and their burst discharge due to noxious pinch of the contralateral hind paw (Aghajanian, 1978). For averaging the firing rate for each group, at least five descents were made per rat with the electrode at 100 μm from previous descents. Each neuron was recorded for at least 60 s. Neuronal firing rates were calculated by adding each discharge per 10-s histogram (as obtained by the Spike2 program during recording) and dividing by length of time recorded in seconds. All neuronal firing rates for all rats in one group were added together and divided by number of neurons recorded per group. Clonidine, an agonist for α2-adrenergic receptors, was administered i.v. with the last NE neuron, after at least 60 s of recording for baseline firing rate determination, to test the sensitivity of LC α2 autoreceptors. The α2-adrenergic receptor antagonist idazoxan was administered i.v., after clonidine inhibition of at least 60 s, to bring LC firing rates back to basal levels, confirming that the inhibition was indeed due to the agonistic action at the α2-adrenergic autoreceptor. Percentage inhibition for each neuron was calculated by first determining the basal firing rate and then the firing rate after agonist administration, expressing the firing rate due to the agonist as a percentage of the basal firing rate. The percentage inhibition was 100 minus this percentage.

Drugs and Materials. The following drugs were used: LSD (Sandoz, Boucherville, QC, Canada), WAY-100635 (Sigma Chemical, Oakville, ON, Canada), clonidine (Sigma), and idazoxan (Sigma). All drugs were dissolved in distilled water. Concentration ranges were chosen on the basis of previous successful experiments in our laboratories. Cyberonics (Houston, TX) provided the leads, 102 pulse stimulators, and dummy stimulators.

Statistical Comparisons. Basal firing rates are expressed as mean ± S.E.M. Nonparametric tests were used as firing rates were not normally distributed. Average firing rates for control and sham groups were compared using Mann-Whitney rank sum tests. Average firing rates for control and treated groups were compared using the Kruskal-Wallis one-way analysis of variance on ranks test. Post hoc tests were performed using Dunn’s multiple comparisons test to assess the difference between control and treated groups. The numbers of neurons encountered per track were analyzed using the Kruskal-Wallis one-way analysis of variance on ranks test. Regression analysis was used to assess any difference between dose-response curves for control and treated groups and to find the effective dose for inhibiting neuronal activity by 50% (ED50).

Results

Effect of Sham VNS Surgery on Basal DRN 5-HT and LC NE Firing Rates. The sham data from all time lengths of VNS treatments were pooled as no significant difference in firing rates were noticed between different sham VNS groups (data not shown). Comparing control and sham basal 5-HT firing rates in anesthetized rats revealed no significant difference [Mann-Whitney rank sum test, T(174) = 6670.51, p = 0.340] (Fig. 1A). Comparing control and sham basal NE firing rates in anesthetized rats also showed no significant difference [Mann-Whitney rank sum test, T(139) = 4158.50, p = 0.111] (Fig. 1B). Therefore, the surgery itself, following a sufficient recuperation time of 2 days, had no effect on DRN 5-HT or LC NE neuronal basal firing rates.

Effect of Short-Term and Long-Term VNS Treatment on Basal 5-HT Firing Rates. To determine the basal 5-HT firing rate changes due to short- and long-term VNS, in vivo extracellular neuronal activity was sampled from five to six rats per treatment group, with at least 10 neurons per rat. No significant difference for short-term VNS (1-h, 1-day, and 3-day treatments) was found when compared with control treatment.
Effect of VNS on 5-HT and NE Transmission

5-HT firing rates [Kruskal-Wallis one-way ANOVA on ranks, H(3) = 6.86; p = 0.076] (Fig. 2A). However, there was a clear significant group effect for long-term VNS (14-, 21-, and 90-day treatments) compared with control 5-HT firing rates [Kruskal-Wallis one-way ANOVA on ranks, H(3) = 41.87, p < 0.001]. Post hoc analysis of long-term VNS groups revealed a statistically significant increase in firing rate for 14-, 21-, and 90-day treatments versus control [Dunn's method, p < 0.05] (Fig. 2B). Ninety-day treated rats had a mean 5-HT firing rate that was 2-fold higher compared with control (2.22 ± 0.42 Hz for 90-day VNS versus 1.11 ± 0.18 Hz for control), indicating a substantial increase in 5-HT firing due to long-term VNS. In addition, mean firing rates showed a trend to increase as length of stimulation increases (slope = 0.18) (Fig. 2C).

Assessment of 5HT1A Somatodendritic Autoreceptor Activity. LSD dose-response curves for control and long-term VNS were constructed to compare the sensitivity of the 5-HT1A somatodendritic autoreceptor. The sensitivity of the 5-HT1A receptor was not assessed after short-term VNS treatment, as there was no significant difference in 5-HT firing rate for short-term VNS versus control. After recording a 5-HT neuron for 60 s (Fig. 3A), various doses of LSD (ranging from 1 mg/kg to 60 μg/kg) were administered i.v. The ED50 value for control was 11.22 μg/kg whereas the ED50 for long-term VNS was 10.47 μg/kg (Fig. 3B). There is no significant difference between the dose-response curves for control and long-term VNS (r²control = 0.94; r²VNS = 0.95; F(12, 2) = 3.85, p = 0.688) (Fig. 3C). In all cases, the suppression of the firing activity induced by LSD was reversed by the subsequent administration of WAY 100635 (Fig. 3A).

Effect of Short-Term and Long-Term VNS Treatment on Basal NE Firing Rates. To determine the basal NE firing rate changes due to short- and long-term VNS, in vivo extracellular neuronal activity was sampled in the LC from five to six rats per treatment group, with at least 10 neurons per rat. After a short-term treatment with VNS, a significant main group effect was observed between VNS and controls [Kruskal-Wallis one-way ANOVA on ranks, H(3) = 9.60, P = 0.022] (Fig. 4A). Dunn’s method for post hoc analysis revealed a significant difference in the direction of a higher NE firing rate comparing acute (p < 0.05) and 3-day (p < 0.05) treatments with control; however, 1-day (24 h) treatment showed no significant difference.

Long-term VNS treatment showed a highly significant difference in firing rates compared with controls [H(3) = 57.20, p < 0.001]. Dunn’s method for post hoc analysis revealed significant differences for 14-, 21-, and 90-day versus control (p < 0.05) (Fig. 4B). NE firing rate proved to be 2-fold higher for 90-day treatment compared with control (4.75 ± 0.13 Hz for 90-day VNS versus 2.23 ± 0.36 Hz for control), indicating a large facilitatory effect on NE firing due to VNS. These data show a trend for a time-dependent increase in firing rate (slope = 0.34) (Fig. 4C).

Fig. 2. Histograms representing mean ± S.E.M. spontaneous firing activity of DRN 5-HT neurons. The numbers at the bottoms of the columns represent numbers of neurons tested. A, average firing rates for control and short-term VNS groups. Five to six rats were used per group. Kruskal-Wallis one-way ANOVA revealed no significant difference between groups. B, average firing rates for control and long-term VNS groups. Five to six rats were used per group. Kruskal-Wallis one-way ANOVA revealed significant differences for all long-term VNS groups versus control (p < 0.05). C, average firing rates showing a trend for a time-dependent increase in firing rate.
Assessment of α2-Adrenergic Autoreceptor Activity on NE Soma. Clonidine dose-response curves were compared between control and long-term VNS treatments to assess the sensitivity of the α2-adrenergic autoreceptors on the LC NE cell bodies. After recording a LC neuron for 60 s (Fig. 5A), various doses of clonidine (ranging from 1 to 60 μg/kg) were administered i.v. The ED₅₀ values were 7.50 and 8.13 μg/kg for control and long-term VNS, respectively (Fig. 5B). Regression analysis revealed no significant difference between control and VNS dose-response curves ($r^2_{control} =$).
suggesting that there is no desensitization of the \( \alpha_2 \)-adrenergic autoreceptors.

**Effect of VNS on Number of Neurons Per Track.** The number of neurons encountered per descent into the brain was analyzed for both short-term and long-term VNS in the DRN and LC. Indeed if more neurons are encountered per track, it is possible that a previously silent population of neurons have been activated during VNS, thus affecting the average firing rates and our comparisons with control groups. For the DRN, a Kruskal-Wallis one-way ANOVA on ranks revealed no significant difference versus control for all VNS groups \( [H(6) = 5.03; p = 0.541] \) (Fig. 6A). Similarly for the LC, the Kruskal-Wallis one-way ANOVA on ranks revealed no significant difference versus control for all VNS groups \( [H(6) = 3.03; p = 0.805] \) (Fig. 6B). It therefore appears that VNS does not activate a previously silent population of neurons in either brainstem nuclei of interest in this study.

**Discussion**

The main results of our studies are that VNS treatments induce large time-dependent increases in basal neuronal firing in the brainstem nuclei for serotonin and norepinephrine: the dorsal raphe nucleus and locus coeruleus, respectively. All classes of antidepressant treatments, including norepinephrine reuptake inhibitors, ECT, and neurokinin-1/substance P antagonists, act at least in part, by increasing 5-HT neurotransmission (reviewed in Haddjeri et al., 1995; Hadjjeri and Blier, 2000; Santarelli et al., 2001); however, NE probably also plays an important role in antidepressant effects, and NE is thought to be involved in the pathophysiology of depression (Delgado and Moreno, 2000). Long term, SSRIs increase 5-HT neurotransmission, while decreasing spontaneous NE activity (Szabo et al., 2000; Grant and Weiss, 2001). Conversely, norepinephrine reuptake inhibitors are efficient antidepressant treatments and seem to affect 5-HT neurotransmission (Massana et al., 1999; Montgomery et al., 2003) as do dual 5-HT and NE reuptake inhibitors (Stahl et al., 2002). However, to our knowledge VNS represents the first reported antidepressant treatment able to induce increased firing activity of both serotonergic and noradrenergic neurons.

Indeed, endogenous or local applications of exogenous 5-HT in the DRN decrease the 5-HT firing rate through activation of 5-HT\(_{1A}\) somatodendritic autoreceptors, as do the 5-HT\(_{1A}\) agonists LSD and 8-OH-DPAT (Aghajanian et al., 1968). Prolonged exposure to increased 5-HT levels or 5-HT agonists progressively desensitizes these receptors, leading to recovery of the 5-HT firing rate. Antidepressant treatments that increase 5-HT concentrations in the vicinity of 5-HT cell bodies, such as SSRIs and MAOIs, initially decrease the firing activities of DRN 5-HT neurons, whereas long-term treatments return the firing rate back to the baseline level due to 5-HT\(_{1A}\) autoreceptor desensitization while keeping the high synaptic availability of 5-HT (reviewed in Blier, 2003). These treatments increase the efficacy of 5-HT neurotransmission via a change in the amount of 5-HT released and altered sensitivity of several subtypes of 5-HT

\[ 0.47, r^2_{\text{VNS}} = 0.60; F(10,2) = 0.27 \quad p = 0.769 \] (Fig. 5C),
receptors, but they never increase the firing activity of 5-HT neurons above their baseline activity.

Our results indicate a large increase in 5-HT firing rate, which is normally associated with increased endogenous 5-HT release, which should activate the somatodendritic autoreceptor. Activation of 5-HT$_{1A}$ somatodendritic autoreceptors would hyperpolarize the cell through $G_{i/o}$ proteins and decrease the 5-HT firing rate (Innis and Aghajanian, 1987). We therefore tested the sensitivity of 5HT$_{1A}$ somatodendritic autoreceptors after long-term VNS treatments. We chose LSD, as the 5HT$_{1A}$ agonist 8-OH-DPAT seems to have a stronger effect on postsynaptic 5HT$_{1A}$ receptors (Romero et al., 1994). The postsynaptic 5-HT$_{1A}$ receptors are involved in a long-loop inhibitory feedback mechanism (Artigas et al., 1996; Hajos et al., 1998); therefore, using 8-OH-DPAT may cause DRN 5-HT inhibition that is unrelated to 5HT$_{1A}$ somatodendritic autoreceptor inhibition. LSD cannot be considered as highly selective for the 5-HT$_{1A}$ receptor. However, the fact that its suppression of the firing activity of 5-HT neurons was reversed by the selective WAY-100635 (Fig. 3A) suggests that this effect was indeed mediated by the 5HT$_{1A}$ receptor. Despite the significantly increased DRN 5-HT firing rate with long-term VNS (Fig. 2B), no change in 5-HT$_{1A}$ receptor sensitivity was observed (Fig. 3, B and C). In contrast with results for SSRIs published so far, despite an increase in the firing activity of DRN 5-HT neurons, the 5HT$_{1A}$ somatodendritic autoreceptors were fully functional after long-term VNS. The increase in firing rate was therefore not due to a desensitization of these autoreceptors but rather to a distinct mechanism. One possible explanation for the absence of 5-HT$_{1A}$ receptor desensitization could be that VNS increases the release of 5-HT in the terminal regions such as the hippocampus or the medial prefrontal cortex but not in the vicinity of DRN 5-HT cell bodies.

The next step was to examine the basal firing rate of LC NE neurons. We found a progressive and statistically significant increase in NE firing over long-term VNS treatments. This is in keeping with previous data showing that an intact NE system is necessary for effective VNS treatments, at least for epilepsy (Krah et al., 1998) and that increased NE levels were present in LC terminal areas in VNS-treated animals (Hassert et al., 2004). LC firing activity is normally controlled by the tonic activation of somatodendritic $\alpha_2$-autoreceptors (Mongeau et al., 1997). Similarly to the 5-HT$_{1A}$ receptors, a desensitization of $\alpha_2$-autoreceptors has been shown to appear progressively, after prolonged exposure to increased NE concentrations. However, if most studies agree on a desensitization of terminal $\alpha_2$-autoreceptors, there is still some controversy regarding the existence of such desensitization of LC somatoautoreceptors (for a review, see Invernizzi and Garattini, 2004).

Thus, the sensitivity of NE $\alpha_2$-adrenergic receptors on LC NE neurons was also investigated. Our findings do not indicate any desensitization of the $\alpha_2$-adrenergic autoreceptors on the NE cell bodies and thus an increased firing rate must result through alternative methods. These results are in keeping with those obtained with antidepressants acting selectively on the noradrenergic system (Invernizzi and Garattini, 2004). However, they differ from those obtained with compounds acting on both serotoninergic and noradrenergic neurotransmissions (Szabo and Blier, 2002). Because VNS is acting by modifying both neurotransmissions, one might expect to find a desensitization of $\alpha_2$-autoreceptors. Again, similarly to what has been proposed for 5-HT$_{1A}$ autoreceptors, the lack of $\alpha_2$-desensitization observed after treatment with VNS (up to 90 days), even in the presence of important increases in the firing activity of 5-HT and NE neurons, could suggest that VNS increases NE release in the terminal region but not in the LC. For both neurotransmitters, this hypothesis remains to be verified in microdialysis studies. A modification of terminal autoreceptors sensitivity (5-HT$_{1B}$ for 5-HT neurons and $\alpha_2$ for NE neurons) is unlikely to be involved in the observed firing activity changes as these autoreceptors regulate the amount of neurotransmitter released; however, our present experiments cannot rule out the possibility of such a desensitization.

One possibility for explaining the increased firing rate of 5-HT and NE neurons after VNS treatments might have been the appearance of fast firing neurons, which would have been silent in control conditions and become activated only after the VNS treatments. However, the number of neurons...
found per track was identical in all treatment conditions, suggesting that we were always recording from the same neuronal population.

The DRN and LC have wide projections within the cortex, acting on areas involved in mood, such as limbic structures (Levitt et al., 1984). In addition, the DRN and LC are highly interconnected, affecting each other's overall activity (Cedarbaum and Aghajanian, 1978; Leger and Descarries, 1978; Baraban and Aghajanian, 1980; Szabo and Blier, 2001), thereby playing a role in each other's downstream target areas. The LC, but not the DRN, receives direct inputs from the NTS (Van Bockstaele et al., 1999) which itself receives afferences from the vagus nerve. As we observed a more rapid increase in the LC NE firing rate than in the DRN 5-HT firing rate (3 days instead of 14 days), it can be postulated that VNS may act initially and/or predominantly on the LC, and indirectly with the DRN via afferents from the LC. Indeed, the DRN is tonically activated by the LC by way of excitatory α2-receptors (Baraban and Aghajanian, 1980). The activity of the 5-HT neurons may therefore be increased by enhanced noradrenergic tone on α1 adrenergic receptors. Testing the sensitivity of these receptors on 5-HT DRN neurons during the studies.

Acknowledgments

References


References


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