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Intranodose ganglion injections of dronabinol attenuate serotonin-induced apnea in Sprague-Dawley rat

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Abstract

Obstructive sleep apnea represents a significant public health concern. Afferent vagal activation is implicated in increased apnea susceptibility by reducing upper airway muscle tone via activation of serotonin receptors in the nodose ganglia. Previous investigations demonstrated that systemically administered cannabinoids can be used therapeutically to decrease the apnea/hypopnea index in rats and in humans. However, cannabinoids have effects on both the central and peripheral nervous systems, and the exact mechanism of decreased apnea/hypopnea index with cannabinoids is unknown. Here, we hypothesized that intranodose ganglion injections of a cannabinoid will attenuate 5-HT-induced reflex apnea and increase upper airway muscle tone. We show that dronabinol injected locally into the nodose ganglia suppresses 5-HT-induced reflex apnea, and increases phasic, but not tonic, activation of the genioglossus. These data support the view that dronabinol stabilizes respiratory pattern and augments upper airway muscles by acting at the nodose ganglia. These findings underscore a therapeutic potential of dronabinol for the treatment of obstructive sleep apnea.

Keywords

OSA; serotonin; cannabinoids; dronabinol; nodose ganglia; genioglossus

1. Introduction

Obstructive sleep apnea (OSA) represents a significant public health concern that increases the risks of diseases such as type 2 diabetes, hypertension, stroke, and coronary artery disease (Marshall et al., 2008; Young et al., 2002). The “gold standard” of OSA treatment is continuous positive airway pressure, which is poorly tolerated and requires long-term

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adherence (Weaver and Grunstein, 2008). Current pharmacologic treatments of OSA are limited (Smith et al., 2006). Safe and effective pharmacotherapies are needed for the treatment of OSA.

Afferent vagal activation is implicated in increased apnea susceptibility by reducing upper airway muscle tone (Carley and Radulovacki, 2008; Garrigue et al., 2004). In rats, augmented vagal tone occurs via activation of serotonin (5-HT) receptors at the nodose ganglia (Carley and Radulovacki, 1999; Szereda-Przestaszewska and Kopczynska, 1997; Yoshioka et al., 1992). The role 5-HT in vagal activation in humans is unknown. However, in human patients with refractory epilepsy implanted with vagus nerve stimulators, increased vagal tone is implicated in the increase of AHI that follows implantation (Parhizgar et al., 2011). Cannabinoids (CBs) acting via cannabinoid receptor subtype 1 (CB_1) were shown to have an inhibitory action on serotonin type 3 ($5\text{-}HT_3$) receptors of the nodose ganglia (Fan, 1995). Previous investigations demonstrated that systemically administered CBs can be used therapeutically to decrease the apnea index during sleep in unanesthetized rats (Carley et al., 2002) and to decrease the apnea/hypopnea index (AHI) in humans (Prasad et al., 2013). However, CBs have effects on both the central and peripheral nervous systems (Croxford, 2003), and the exact mechanism of decreased AHI with CBs is unknown.

Here, we hypothesized that intranodose ganglion injections of a CB will attenuate 5-HT-induced apnea and increase upper airway muscle tone. By using a well-established rat model of reflex apnea (Yoshioka et al., 1992), we tested the impact of dronabinol, an exogenous FDA-approved non-selective CB receptor agonist, on attenuating reflex apnea and increasing upper airway muscle tone.

2. Materials and Methods

2.1. Animals

Twenty-four adult male Sprague-Dawley rats (326 ± 6 g; Harlan Laboratories, Indianapolis, IN, USA) were housed in duplicate, maintained on a 12:12 hour light:dark cycle at controlled temperature (22 ± 0.5 °C), and given *ad libitum* access to food and water. All procedures and protocols were approved by the Institutional Animal Care and Use Committee of the University of Illinois at Chicago.

2.2. Acute Experimental Preparation

Rats were anesthetized (initial injection ketamine:xylazine 100:10 mg/kg) and the femoral vein was cannulated for 5-HT injection. Insulated stranded stainless steel wire electrodes were inserted bilaterally into the genioglossi muscles (1 mm lateral to the midline) to monitor genioglossus electromyogram (EMGgg). A piezoelectric strain gauge (Ambu, Glen Burnie, MD, USA) placed around the abdomen was used to monitor respiratory pattern (RESP). During recordings, surgical plane of anesthesia was monitored by toe pinch, and if necessary, rats were re-injected with anesthetic (ketamine:xylazine 100:5 mg/kg).

2.3. Protocol

Figure 1 depicts the experimental protocol used. Baseline (before neck surgery) EMGgg and RESP of 2–3 reflex apneas were recorded after 2–3 infusions 5-HT hydrochloride (12.5 μg/kg; MP Biomedicals, Solon, OH, USA) in PBS (pH 7.4; 0.35 ml/kg) via the femoral vein using an infusion pump (63 ml/hr; KD Scientific, Holliston, MA, USA). After baseline recordings, nodose ganglia were exposed and 2–3 5-HT-induced apneas were recorded to confirm that the nerves/ganglia were functionally intact (Surgery Baseline recording). In a balanced design, rats (n = 6) received either high (100 μg/5 μl sesame oil)or low (10 μg/5 μl

sesame oil) dose dronabinol (Mylan Pharmaceuticals, Morgantown, WV, USA), or vehicle (5 μl sesame oil) injected directly into the nodose gangla, and then 2–3 5-HT infusions and recordings were repeated (Nodose Injection recording). Sham surgeries ($n = 6$) with 2–3 5-HT infusions and recording were also performed. 5-HT infusions were performed at intervals greater than 5 minutes to prevent tachyphylaxis (Ginzel and Kottegoda, 1954; Nishi, 1975; Yoshioka et al., 1992).

2.4. Data Analysis

EMGgg and RESP signals were amplified (CyberAmp, Sunnyvale, CA, USA), band-pass filtered (10–240 Hz and 1–10 Hz, respectively), digitized at 500 Hz using a DT9804 DAQ Module (Data Translation, Marlboro, MA, USA), and recorded using Sciworks Experimenter software (DataWave Technologies, Loveland, CO, USA). After acquisition, EMGgg was rectified and smoothed with a time constant of 100 ms using Spike2 software (Cambridge Electronic Design, Cambridge, England). Tonic EMGgg was defined as the nadir of smoothed genioglossus activity during expiration. Phasic EMGgg was defined as the peak of smoothed genioglossus activity during inspiration minus tonic EMGgg. Breath durations and phasic and tonic EMGgg amplitudes were averaged from the five previous breaths before each 5-HT infusion. Apnea durations were defined as the longest breath duration following 5-HT infusion. Since each rat received 2–3 infusions of 5-HT per recording (3 recordings: Baseline, Surgery Baseline, and Nodose Injection), the EMGgg and RESP from the 2–3 infusions were averaged together.

2.5. Statistical Analysis

For statistical analysis, SigmaStat version 3.11 (Systat Software, Inc., Chicago, IL, USA) was used. Data (mean ± SEM) were analyzed using two-way repeated measures ANOVA (time [within subjects]: Baseline, Surgery Baseline, and Nodose Injection; treatment [between groups]: sham, vehicle, dronabinol 10 μg, and dronabinol 100 μg) with Tukey's *post hoc* multiple comparison test. Statistical significance was set at $p < 0.05$. To evaluate the presences or absence of tachypnea after 5-HT infusion, Chi-square analysis was used.

3. Results

Figure 2 depicts representative tracings before surgery (Baseline, upper panels), after surgery (Surgery Baseline, middle panels), and after nodose ganglia injections (Nodose Injection, lower panels) of 100 μg of dronabinol (left panels) and of vehicle (right panels). Within each panel, the lower tracing depicts EMGgg and the upper tracing depicts respirations before, during, and after intravenous infusion of 5-HT (vertical line signifies infusion). Before nodose injections (top and middle panels), 5-HT infusion induced apneas indicated by the absence of respiration and genioglossus activity. In the experiment where the nodose ganglia were injected with 100 μg of dronabinol, 5-HT-induced apnea induction was attenuated or eliminated (left lower panel). In contrast, the experiments where the nodose ganglia were injected with vehicle (right lower panel), 5-HT-induced apnea was unaltered compared to before surgery (upper right panel) and after surgery (middle right panel).

Figure 3 illustrates apnea duration and breath duration of RESP recordings from sham, vehicle, and dronabinol injected rats. There was a significant interaction between the effects of treatment and time on apnea duration (Fig. 3; $F_{6, 40} = 3.04$, $p = 0.02$). Post hoc analysis revealed a decrease in apnea duration with 100 μg dronabinol nodose injections compared with apnea duration values obtained at baseline ($p < 0.01$) and surgery baseline ($p = 0.04$). Post hoc analysis also revealed a decrease in apnea durations in 10 μg dronabinol nodose injections compared to respective baseline ($p = 0.03$), but no decrease in apnea duration

compared to surgery baseline ($p = 0.07$). In sham or vehicle nodose injected groups, there was no decrease in apnea durations compared to baseline or surgery baseline.

Interestingly, there was only a main effect of time on breath duration (data not shown; $F_{2, 40} = 33.7$, $p < 0.001$). Post hoc analysis revealed increases in breath duration from baseline to surgery baseline ($p = 0.02$), and from surgery baseline to nodose injections ($p < 0.01$). Whether the increased breath duration was the result of surgery or from the effects of anesthesia remains unknown.

Tachypnea between the serotonin injection and apnea was seen in most rats at baseline, following neck surgery and following nodose ganglion injection, irrespective of what was injected into the ganglia. However, for a small subset of rats, divided across all injection groups, exhibited longer pre-serotonin-infusion breath durations. These rats lacked the tachypnea response following 5-HT infusion. Figure 1 illustrates a case where breath intervals were longer before serotonin infusion, and tachypnea was absent. Chi-square analysis indicates that the presence or absence of tachypnea following serotonin injection was not related to time-point (baseline, post-surgery baseline, post nodose injection) or agent (sham, vehicle, 10 μg dronabinol, 100 μg dronabinol) ($p = 0.996$).

Figure 4 shows data of phasic (A) and tonic (B) genioglossus activity from EMGgg recordings of sham, vehicle, and 100 μg and 10 μg dronabinol injected rats. There was a significant interaction between the effects of treatment and time on phasic genioglossus activity (Fig. 4A; $F_{6, 40} = 2.83$, $p = 0.02$). Post hoc analysis uncovered an increase in phasic EMGgg in 100 μg dronabinol injections compared to respective baseline ($p < 0.01$) and surgery baseline ($p < 0.001$), and compared to sham ($p < 0.01$), vehicle ($p = 0.02$), and 10 μg dronabinol ($p = 0.01$) nodose injections. There were no main effects on tonic genioglossus activity (Fig. 4B).

4. Discussion

The prevalence of OSA, its comorbidity with other diseases, and poor patient adherence to current treatment options highlight the need for other viable treatments, including pharmacotherapies (Marshall et al., 2008; Smith et al., 2006; Young et al., 2002). Preliminary evidence in rats (Carley et al., 2002) and patients with OSA (Prasad et al., 2013) suggests a potential therapeutic role for CBs in the amelioration of disordered breathing events during sleep. The hypothesized mechanism for this effect has been the activation of CB receptors in the nodose ganglia of the vagus nerves (Carley and Radulovacki, 2008; Zhuo et al., 1997).

The present study demonstrates for the first time that a non-selective CB receptor agonist, dronabinol, acting only locally at the nodose ganglia, increases respiratory phasic activation of the genioglossus muscle, providing a possible mechanism for the previously reported attenuation of apneas and hypopneas in OSA patients treated with dronabinol (Prasad et al., 2013). Further, intranodose dronabinol administration attenuated 5-HT-induced reflex apnea, supporting the view that activation of CB receptors within the nodose ganglia also diminishes the destabilizing effects of vagal afferents on the central respiratory pattern generator (Fan, 1995; Hilaire et al., 2010; Zhuo et al., 1997).

Increased vagal tone has been implicated in OSA in humans (Carley and Radulovacki, 2008; Garrigue et al., 2004). For example, patients with vagus nerve stimulators to control refractory epilepsy have an increase in AHI after implantation (Parhizgar et al., 2011). Pharmacotherapeutic modulation of vagal afferents to attenuate or eliminate apneas has been previously studied in humans (Carley et al., 2007; Prasad et al., 2010) and animal models (Carley and Radulovacki, 1999; Fenik et al., 2001; Veasey et al., 2001). Afferent vagal

neurons relay important visceral information that regulates respiratory drive and upper muscle tone via synaptic input to the nucleus of the solitary tract (NTS), and are modulated by numerous excitatory and inhibitory receptors. NTS neurons relay this information to the ponto-medullary pattern generator, which in turn projects to the phrenic and hypoglossal motor nuclei. Modulation of this circuitry can activate or inhibit respiratory drive, and increase or decrease upper airway muscle tone, thus providing a potential targets for pharmacotherapy of sleep-related breathing disorders (Haji et al., 2000).

The neuropharmacology of the nodose ganglia is very rich, and two abundantly expressed receptors were explored with respect to apnea: excitatory 5-HT_3 ligand-gated ion channel receptors and inhibitory CB_1 $G_{i/o}$ protein coupled receptors (Zhuo et al., 1997). Intravascular administration of 5-HT evokes dose-dependent reflex apnea by activating 5-HT_3 receptors in the nodose ganglia – an effect that is blocked by supranodose vagotomy or pre-administration of 5-HT_3 receptor antagonists such as ondansetron or MDL 72222 (Kopczynska and Szereda-Przestaszewska, 2004; Veasey et al., 2001; Yoshioka et al., 1992). Here, we demonstrate that intranodose ganglionic administration of 100 μg of CB receptor agonist, dronabinol, also attenuates or eliminates 5-HT-evoked reflex apnea, and increases phasic EMGgg. This may reflect an allosteric modulation of 5-HT_3 receptor that inhibits the 5-HT-induced excitation and/or a direct interaction between the inhibitory CB_1 receptor and the excitatory 5-HT_3 ion channel. In primary nodose ganglion cell culture, activation of CB_1 receptors interferes with 5-HT-induced cell depolarization (Fan, 1995). However, in the same study, allosteric modulation of the 5-HT_3 ion channel could not be excluded. Moreover, in HEK293 cell cultures containing 5-HT_{3A} receptors and lacking CB receptors, CBs inhibited currents through 5-HT_{3A} receptors independently of CB receptors (Barann et al., 2002). Conversely, however, 5-HT-induced emesis was attenuated by CBs, and that attenuation could be reversed by CB antagonists, providing evidence of a role of CB receptors in inhibiting activation of vagal afferents (Darmani and Johnson, 2004). In the present study, inhibition of apnea through CB receptors or allosteric modulation of 5-HT_3 cannot be determined. However, the previous three studies mentioned did observe a dose-dependent inhibition of 5-HT_3 activation (Barann et al., 2002; Darmani and Johnson, 2004; Fan, 1995), similar to the present study where injection of 10 μg of dronabinol did not attenuate apnea, but 100 μg of dronabinol attenuated or eliminated apnea.

Dronabinol's stimulating effects on upper airway muscles can implicate its use in therapeutic intervention for increasing upper airway patency in OSA patients. This increase in upper airway patency has been reported before with other pharmacotherapies (Berry et al., 2005; Besnard et al., 2007; Fenik et al., 2001) or by direct stimulation of the hypoglossal nerve (Eisele et al., 2003). Our data show that dronabinol administration also increases phasic, but not tonic, EMGgg, which has been reported in previous animal studies (Berry et al., 2005; Fenik et al., 2001). This difference remains to be clarified, but the differential activation of phasic and tonic upper airway muscles could be attributed to rat airway patency that is stabilized by a firmly attached hyoid bone and is not collapsible, and therefore does not need increased tonic activation (Lu and Kubin, 2009). Also, the model used in this study is an animal model of reflex apnea, which involves vagal afferents that modulates respiratory drive and upper airway muscle activation common to mammals and implicated in OSA (Carley et al., 2007; Haji et al., 2000; Kubin et al., 2006; Yoshioka et al., 1992). The induction of apnea by activation of sensory vagal fibers is suspected in the pathogenesis of OSA in humans and can be attenuated by antagonizing peripheral 5-HT_3 receptors (Carley et al., 2007). The effects of dronabinol's attenuation of vagal afferents on phasic EMGgg in the present study can be of relevance to the treatment of OSA in humans (Prasad et al., 2013).

Intraperitoneal administration of 5-HT to unanesthetized rats produced a 3-fold increase in the AHI during sleep due to activation of peripheral 5-HT receptors. This effect can be

blocked by pretreatment with dronabinol (Carley et al., 2002). In view of the above, the results of the present study support the likelihood that systemically delivered dronabinol acts to reduce sleep-related apnea by acting at receptors in the nodose ganglia. It is possible that amelioration of central apneas, as in the unanesthetized rat model (Carley et al., 2002), results from stabilization of the central respiratory pattern generator, and that reduction of obstructive apnea in patients with OSA reflects both stabilization of respiratory pattern and increased activation of upper airway muscles (Prasad et al., 2013). However, more studies to elucidate dronabinol's central effects on stabilization of respiratory pattern are needed.

In summary, we conclude that dronabinol injected locally into the nodose ganglia suppresses 5-HT-induced apnea, and increases phasic activation of the genioglossus. These data support the view that systemic dronabinol stabilizes respiratory pattern and augments upper airway muscles by acting at the nodose ganglia. These findings underscore a therapeutic potential of dronabinol for the treatment of OSA.

Acknowledgments

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Highlights

- Dronabinol injected locally into the nodose ganglia suppresses 5-HT-induced reflex apnea.
- Dronabinol injected locally into the nodose ganglia increases phasic but not tonic, activation of the genioglossus.
- These data support the view that dronabinol stabilizes respiratory pattern and augments upper airway muscles by acting at the nodose ganglia.

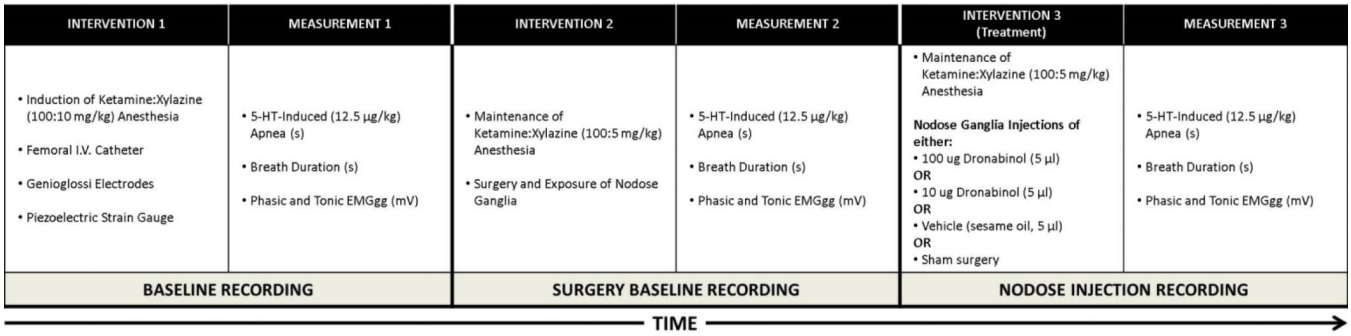

Figure 1.

Protocol of acute 5-HT-induced apneas. For baseline recording, rats under ketamine/xylazine anesthesia were instrumented with femoral I.V. catheters, genioglossus electrodes, and a piezoelectric strain gauges, and then infused with 5-HT to induce apneas and record genioglossus activity. After baseline recordings, surgical exposure of nodose ganglia was performed, and 5-HT infusion and surgery baseline recordings were performed to confirm that the nerves were functionally intact. After confirmation that nerves were intact, nodose injections of 100 µg or 10 µg of dronabinol or vehicle, or sham surgery were performed, and 5-HT infusion and nodose injection recordings were performed. EMGgg = genioglossus electromyogram.

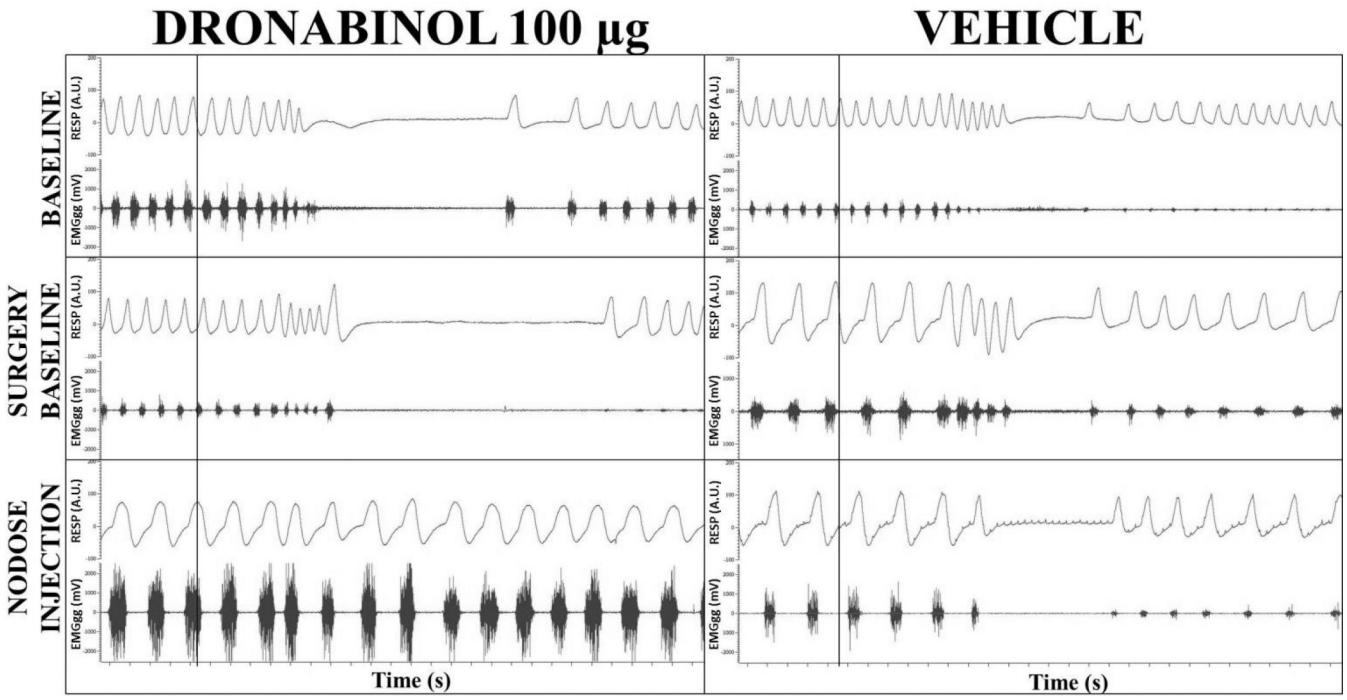

Figure 2.

Sample recordings from acute 5-HT-indudced apnea experiments. The **left panels** are from an acute experiment of dronabinol (100 µg) injections into the nodose ganglia. The **right panels** are from an acute experiment of vehicle (sesame oil) injections into the nodose ganglia. Genioglossus electromyogram and respiratory recordings were taken before surgery (**Baseline, top panels**), after surgery (**Surgery Baseline, middle panels**), and after nodose ganglia injections (**Nodose Injection, bottom panels**). Apnea was attenuated, and EMGgg was increased, in the dronabinol injections. Vertical line signifies femoral intravenous 5-HT (12.5 µg/kg) infusion to induce reflex apnea. A.U. = arbitrary units; EMGgg = genioglossus electromyogram; RESP = respiratory pattern.

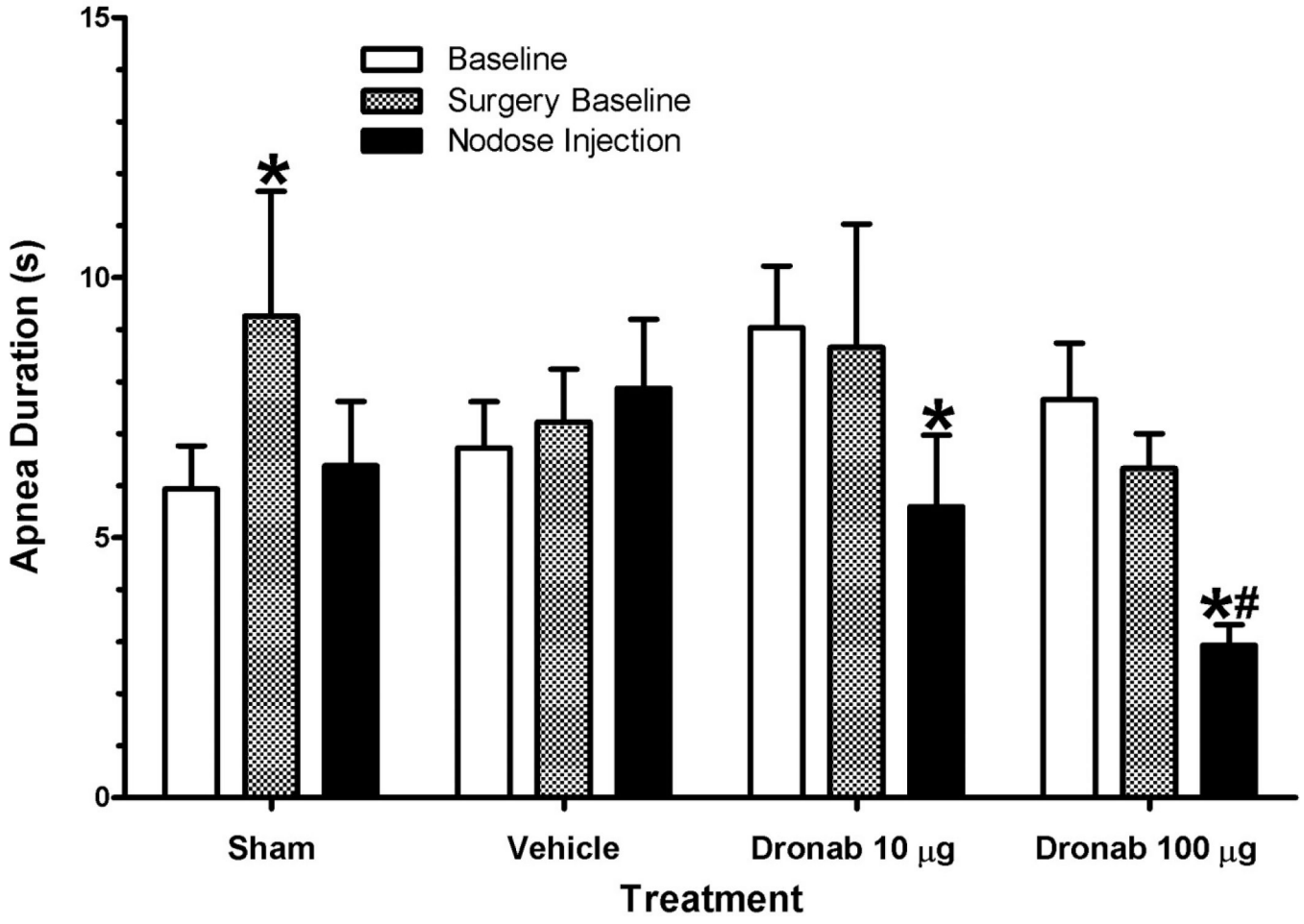

Figure 3.

Apnea duration quantified from acute 5-HT-induced apnea experiments. 100 μg of dronabinol injected into the nodose ganglia attenuated apnea duration compared to baseline and surgery baseline. 10 μg of dronabinol injected into the nodose ganglia attenuated apnea duration compared only to baseline. * $p<0.05$ compared to baseline recording; # $p<0.05$ compared to surgery baseline recording; two-way repeated measures ANOVA (treatment × time) with Tukey's post hoc multiple comparison test. Dronab = dronabinol.

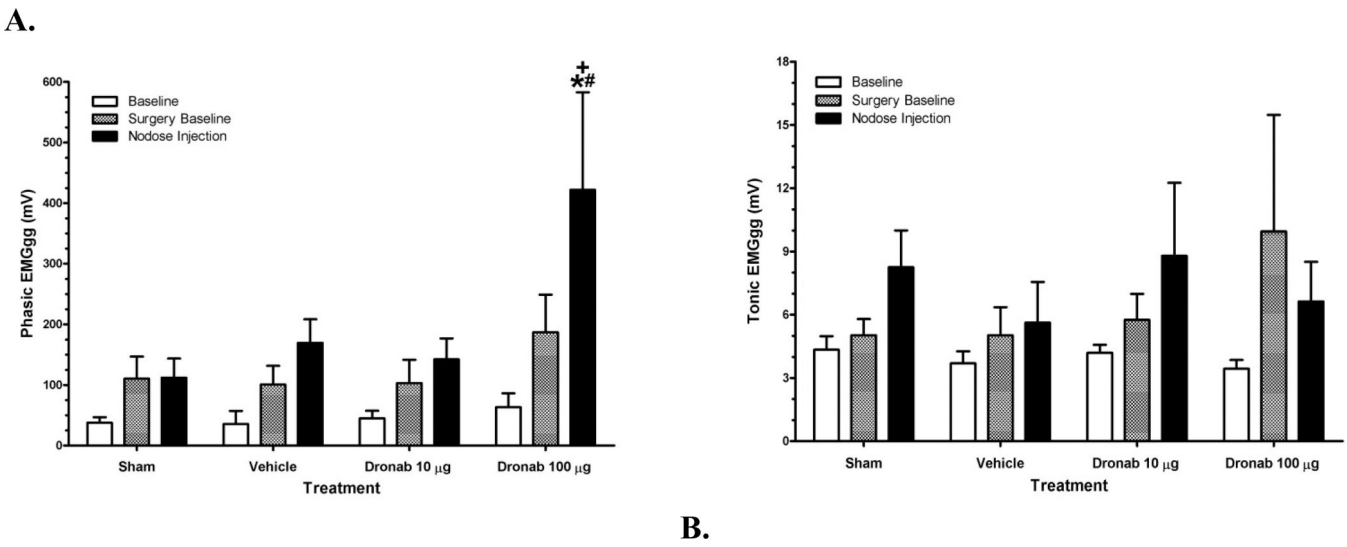

Figure 4.

Phasic and tonic genioglossus electromyogram amplitude quantified from acute 5-HT-induced apnea experiments. (*A*) 100 μg of dronabinol injected into the nodose ganglia increased phasic genioglossus muscle activity. (*B*) There were no differences in tonic genioglossus muscle activity among the treatment groups. * $p<0.05$ compared to baseline; # $p<0.05$ compared to surgery baseline recording; + $p<0.05$ compared to other nodose injection treatments; two-way repeated measures ANOVA (treatment × time) with Tukey's post hoc multiple comparison test. EMGgg = genioglossus electromyogram, Dronab = dronabinol.