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Pharmacology, Biochemistry and Behavior 74 (2003) 877–882
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Selective augmentation of genioglossus electromyographic activity by L-5-hydroxytryptophan in the rat

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Received 13 September 2002; received in revised form 12 December 2002; accepted 17 December 2002

Abstract

The present study was undertaken to determine the effects of intravenous L-5 hydroxytryptophan (5HTP), the immediate precursor of serotonin, on the electromyographic (EMG) activity of the genioglossus (gEMG) and diaphragm (dEMG) in the spontaneously breathing, vagotomized anesthetized male Sprague–Dawley rats (urethane 1.2–1.4 g/kg). Sequential administration of saline and 0.05-, 0.1-, 0.2-, 1-, and 5-mg/kg doses of 5HTP were given intravenously every 15 min. There was a significant increase (percent change from predrug) in both gEMG and dEMG amplitude at 1.0 and 5.0 mg/kg of 5HTP compared to saline. The percent increase in gEMG induced by 1.0 and 5.0 mg/kg 5HTP however was significantly greater than the increase in dEMG. There was no significant change in heart rate (HR), mean arterial blood pressure (MAP), or respiratory rate at any of the doses of 5HTP tested. These results suggest that intravenous 5HTP at doses of 1 and 5 mg/kg preferentially increased the gEMG in the anesthetized rat compared to the dEMG. We hypothesize that at appropriate doses serotonin precursors could increase genioglossus activity in humans during sleep and help maintain upper-airway patency.

Keywords: Serotonin; Genioglossus; 5-Hydroxytryptophan; Pharyngeal muscles

1. Introduction

The hypoglossal nerve innervates the genioglossus, a tongue protruder, along with other upper-airway muscles. Genioglossus activity is important for maintaining upper-airway patency during sleep (Remmers et al., 1978). Studies in decerebrate animal preparations (Kubin et al., 1992; Douse and White, 1996) and freely moving animals during natural sleep (Jelev et al., 2001) have shown that direct application of serotonin to the hypoglossal motor nucleus can augment hypoglossal nerve activity and genioglossus electromyographic (gEMG) activity. Serotonin receptors of the 5HT2a,2c type on the hypoglossal motor nuclei are thought to mediate this effect (Kubin et al., 1992; Veasey, 2001). The effects of systemic increases in serotonin on hypoglossal/genioglossus activity appear to be relatively more complex. Stimulation of different types of serotonin receptors in the central nervous system or periphery (Veasey, 2001) could have multiple effects on global genioglossus activity. Furthermore, serotonin does not cross the blood brain barrier. However, serotonin precursors (tryptophan, 5-hydroxytryptophan [5HTP]), serotonin-reuptake inhibitors, and serotonin receptor agonists do cross into the central nervous system and can potentially increase genioglossus activity by increasing serotonin or stimulating serotonin receptors.

The serotonin precursors could potentially be used as treatment for obstructive sleep apnea. In fact, one study found that tryptophan decreased the apnea + hypopnea index in obstructive sleep apnea (Schmidt, 1982). Another study found that the combination of tryptophan and trazodone (a weak serotonin-reuptake inhibitor and 5HT2 receptor blocker) decreased sleep-disordered breathing in the English bulldog model of obstructive sleep apnea (Veasey et al., 1999). The very large doses of tryptophan used in these studies potentially limited the clinical usefulness of this medication. Alternatively, smaller doses of 5HTP, the immediate precursor of serotonin, can be used to increase central nervous system serotonin (Byerley et al., 1987; Hudgel et al., 1995). This medication bypasses the rate-limiting step of serotonin synthesis. In addition, unlike tryptophan, the absorption of oral 5HTP is not dependent on dietary factors.

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0091-3057/03/$ – see front matter © 2003 Elsevier Science Inc. All rights reserved.
doi:10.1016/S0091-3057(03)00016-9

While 5HTP has been used in the treatment of depression (Byerley et al., 1987), relatively little is known about its effects on genioglossus activity.

Richmonds and Hudgel (1996) found that intravenous 5HTP over a large dose range increased both hypoglossal and phrenic activity in the urethane-anesthetized rat. Other investigations have found that serotonergic agents preferentially change hypoglossal activity. Bonora et al. (1985) found that intravenous administration of protriptyline (a serotonin- and norepinephrine-uptake inhibitor) in the decerebrate cat preferentially increased hypoglossal compared to phrenic nerve activity. Veasey et al. (1996) found that the 5HT2 serotonin antagonist ritanserin preferentially decreased upper-airway muscle activity compared to the diaphragm in the English bulldog. The lack of a preferential effect of 5HTP on the hypoglossal activity in the study of Richmonds and Hudgel could have been secondary to their method of rapid sequential dose administration and a relatively high dose range.

To further investigate the potential role of 5HTP in selective activation of genioglossus activity, the present study was undertaken. We hypothesized that 5HTP could be demonstrated to preferentially increase genioglossus activity if a relatively low dose was used and if the doses were given at relatively long intervals.

2. Methods

All experiments were performed on adult male Sprague–Dawley rats (320–420 g; Harlan). The animals were housed in the university animal care facility and exposed to a normal 12-h light (6 a.m. to 6 p.m.)/12-h dark cycle (6 p.m. to 6 a.m.). The University Animal Care and Use Committee approved all experimental procedures.

2.1. General preparation

Animals were anesthetized with an intraperitoneal injection of urethane (1.2–1.4 g/kg) and instrumented with femoral arterial and venous catheters (PE 50 tubing) for recording of arterial pressure and administration of intravenous fluids, respectively. While in the supine position, a midline incision was made on the ventral surface of the neck, a tracheostomy was performed, and the animal was intubated. Cervical vagus nerves were isolated bilaterally and sectioned just caudal to the insertion of the superior laryngeal nerve into the vagus nerve (the nodose ganglion was left intact). Vagotomy was performed to eliminate tonic inhibition of genioglossus activity by lung stretch receptors (Brouillette and Thach, 1980; Mateika and Fregosi, 1997). All animals were spontaneously breathing and were breathing room air mixed with 100% oxygen. For measurement of diaphragmatic activity, two small (0.003 mm diameter) Teflon-coated, stainless steel wires with bared tips were inserted subcostally into the right side of the diaphragm through the abdominal musculature. For measurement of genioglossus activity, two thin wire hook electrodes were inserted into the ventral surface of the tongue, parallel to the frenulum. Body temperature was continuously monitored with a rectal temperature probe (Harvard Apparatus) and kept within normal range 38 ± 1 °C with a heating blanket. Supplemental anesthesia was given when necessary (0.1 g/kg), as evidenced by fluctuations in blood pressure (BP), heart rate (HR), or respiration during surgery or in response to a pinch of the hindpaw.

The arterial catheter was attached to a pressure transducer (Statham) connected to an amplifier (Stoelting). The genioglossus and diaphragm electromyographic (EMG) wires were connected to high-impedance Grass preamplifier probes and P511 amplifiers. The EMG signals were then amplified (20,0000–50,0000 times), band pass-filtered (0.3–3.0 kHz), rectified, and integrated (Paynter Filter, BAK Electronics). Pulsatile BP, rectified and integrated gEMG (20 ms time constant), and diaphragmatic (dEMG; 50 ms time constant) EMG signals were fed into the Cambridge Electronics Design 1401 computer interface data sampling system and recorded simultaneously. Baseline gEMG and dEMG amplitudes were arbitrarily adjusted to a value of 1.0–2.0 (arbitrary units) at the beginning of the experiment.

2.2. Protocol

Intravenous administration of 5HTP began approximately 15–20 min following vagotomy, when gEMG, dEMG, and the respiratory pattern had stabilized. All animals received six intravenous bolus injections administered at 15-min intervals. The injections were saline (0.2 ml as control) and then five separate doses (0.05, 0.1, 0.2, 1, and 5 mg/kg) in order of increasing concentration. The 5HTP (Sigma) was prepared as 2–4 mg/ml, dissolved in saline. Each dose of 5HTP was flushed into the venous catheter with 0.2 ml of saline (0.9% NaCl). During each trial, arterial pressure, dEMG, and gEMG were continuously monitored for 700 s. Baseline activity was collected for 100 s prior to each intravenous injection and 600 s following each intravenous injection. Just prior to the beginning of experimentation and immediately following the completion of the experiment, arterial blood samples (0.1 ml) were drawn. Blood samples were then analyzed for pH, PCO_2, and PO_2 (iSTAT, Heska). At the end of the experiment, the animal was euthanized.

2.3. Data analysis

All data were analyzed off-line using SPIKE2 software (Cambridge Electronics Design). First, the effects of 1 mg/kg 5HTP on peak gEMG burst amplitude were quantified every 40 s (3 breath average) beginning 80 s prior to and for 700 s following intravenous administration (see Fig. 2). Analysis of the effects over time demonstrated a sharp increase in gEMG amplitude that peaked around 75 s

following 5HTP administration and was sustained for approximately 4 min. Based on this preliminary analysis, two time windows were selected for further data analysis so measurements before and following drug or vehicle administration would be analyzed consistently. The two time windows included measurements taken 30 s just prior to drug (or saline) administration and 30 s between 75 and 105 s following onset of intravenous drug administration.

Within these two 30-s time windows, for each dose trial, mean arterial pressure (MAP), HR, respiratory frequency, and peak inspiratory gEMG and dEMG amplitudes were measured and averaged. MAP was calculated from the average systolic (P_{sys}) and diastolic (P_{dia}) pressures measured from individual pressure peaks using the standard equation $MAP=(P_{sys}-P_{dia})/3+P_{dia}$. HR was derived from the average interpulse interval between individual peak systolic pressure pulses. Respiratory frequency was calculated from the interval between the onsets of adjacent dEMG bursts and averaged. Peak inspiratory (burst) amplitude of gEMG and dEMG was measured from individual bursts and then averaged. The gEMG and dEMG averages taken between 75 and 105 s postinjection were then expressed as a percentage change from the preinjection period [(postinjection EMG − preinjection EMG) × 100/(preinjection EMG)]. To assess the relative changes in gEMG and dEMG for each dose administered, the difference in the percent change in dEMG was subtracted from the percent change in gEMG calculated (difference in percent change).

Significant changes in the gEMG or dEMG activity (percent change from preinjection baseline) or the difference in percent change in dEMG vs. gEMG amplitude as a function of 5HTP dose were identified using an analysis of variance for repeated measures followed by post hoc comparison to saline using the Dunnett's test (Sigma Stat, Jandel Scientific). The MAP, HR, and respiratory rate were analyzed using a two-way analysis of variance for repeated measures with the dose of 5HTP and pre- vs. postinjection as the two factors. Changes were considered significant when $P<.05$. All data are reported as mean ± S.E.M.

3. Results

Eight male rats of mean weight 339 ± 8 g were studied. In Fig. 1, a sample tracing of gEMG and dEMG (moving time average) and arterial pressure for one animal is shown. Thirty seconds after intravenous administration of 5HTP (5 mg/kg), there was a selective increase in inspiratory gEMG burst amplitude that peaked between 60 and 180 s following injection. Only modest changes in dEMG burst amplitude were observed following 5HTP administration and there were no changes in tonic gEMG activity (i.e., during the expiratory phase of respiration). The gEMG returned to baseline within 10 min. BP changed only modestly following 5HTP injection.

Fig. 2 shows the average change in gEMG burst amplitude and MAP plotted as a function of time following administration of 1.0 mg/kg 5HTP vs. saline. Within the first 40 s of 5HTP administration, there was a rise in gEMG burst amplitude. This increase in amplitude reached a peak between 80 and 180 s following injection and gEMG burst amplitude returned to baseline levels by 15 min. Intravenous administration of saline produced no significant change in gEMG burst amplitude at anytime following injection. Neither saline nor 5HTP induced any significant changes in MAP.

The average percent change in gEMG and dEMG peak inspiratory amplitude calculated following saline injection

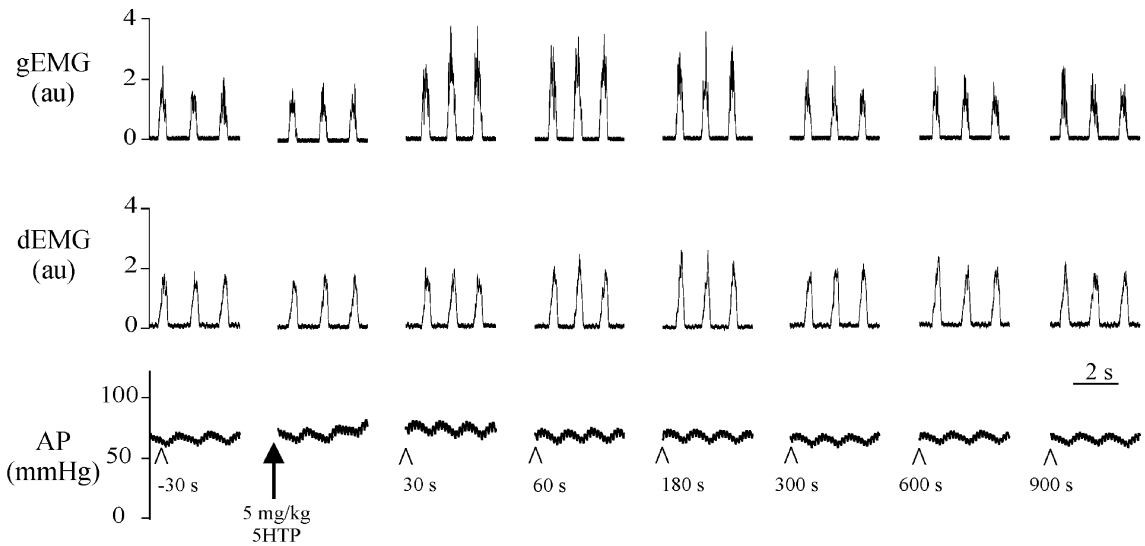

Fig. 1. Tracings of the moving time average of the gEMG and dEMG activity and arterial pressure (AP) from one animal are shown at 30 s prior to (− 30 s) and 30, 60,180, 300, 600, and 900 s following intravenous administration of 5 mg/kg 5HTP. Arrow indicates time of 5HTP injection. The arterial pressure tracing shows a very brief alteration in baseline that returned to preinjection levels within 60 s of 5HTP injection.

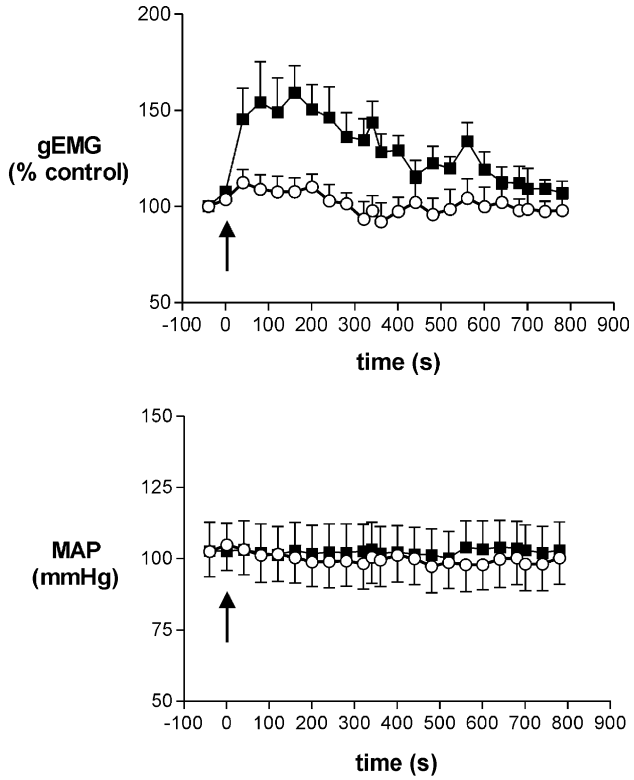

Fig. 2. Average change in gEMG burst amplitude and MAP before and following intravenous injection of saline (open circles) vs. 1 mg/kg 5HTP (filled squares) as a function of time (mean ± S.E.M., $n = 8$). gEMG data points reflect a three-breath average taken every 40 s. MAP data points reflect average pressure during corresponding three breath periods. Arrow indicates time of drug administration (time zero).

and each dose of 5HTP is illustrated in Fig. 3. Between trials, the average preinjection burst amplitude of both gEMG and dEMG was similar to the immediately preceding

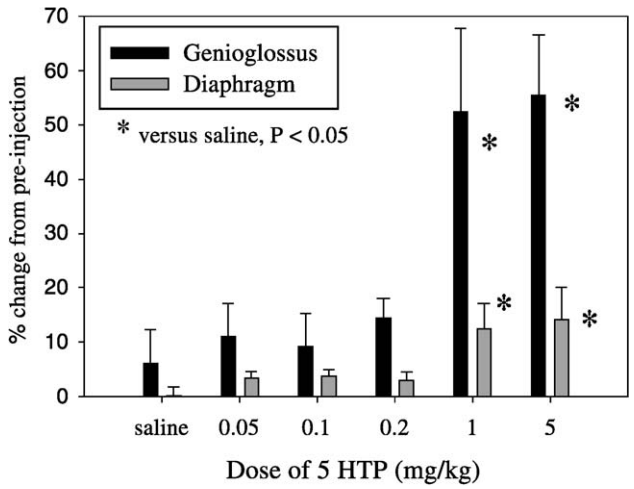

Fig. 3. Average gEMG and dEMG activity (mean ± S.E.M., $n = 8$) following saline and each dose of 5HTP is shown (expressed as percent of preinjection value). Asterisks indicated significant increase after 5HTP injection compared to the effects of saline injection. Note that at both 1 and 5 mg/kg, there was a larger increase in the response of the gEMG relative to the dEMG.

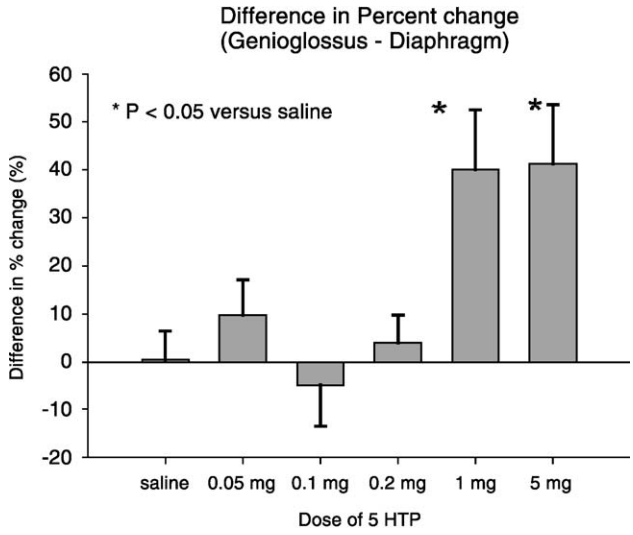

Fig. 4. The difference in the percent change (gEMG − dEMG) (mean ± S.E.M., $n = 8$) for saline and various doses of 5HTP. Asterisks indicate there was a significant increase in the difference in percent change following 1 and 5 mg/kg of 5HTP compared to that observed following saline injection. At these doses, there was a preferential increase in gEMG.

preinjection value (101 ± 7% and 101 ± 1% of preceding control, gEMG and dEMG, respectively; range 85–102%). At 1 and 5 mg/kg, there was a significant increase in both the gEMG and dEMG peak inspiratory amplitudes compared to saline control that was not observed at the lower doses. The relative effect of 5HTP on the gEMG and dEMG was analyzed by calculating the difference in the percent change of gEMG and dEMG induced by 5HTP. Fig. 4 shows that at 1 and 5 mg/kg, there was a preferential increase in gEMG over dEMG that was not observed at the lower doses.

Analysis of other cardiorespiratory factors following 5HTP administration demonstrated no significant change in the respiratory rate, HR, or MAP (Table 1) at any of the doses studied. The average arterial pH, PCO_2, and PO_2 measured at the beginning and end of the study were not significantly different (pH: pre 7.34 ± 0.03 vs. post 7.32 ± 0.03; PCO_2: pre 45 ± 3 vs. post 47 ± 5 mmHg; and PO_2: pre 211.3 ± 13.5 vs. post 215.5 ± 20.4 mmHg).

Table 1
Baseline cardiorespiratory parameters before vs. following systemic 5HTP or saline injection

5HTP dose	MAP (mmHg)	HR (bpm)	Respiratory rate (breaths/minute)
Saline	107 ± 11 vs. 108 ± 10	457 ± 11 vs. 455 ± 8	48 ± 3 vs. 47 ± 3
0.05 mg/kg	112 ± 14 vs. 112 ± 12	455 ± 9 vs. 452 ± 9	46 ± 2 vs. 47 ± 3
0.1 mg/kg	108 ± 10 vs. 107 ± 10	457 ± 6 vs. 454 ± 10	45 ± 2 vs. 48 ± 2
0.2 mg/kg	105 ± 8 vs. 108 ± 10	449 ± 7 vs. 440 ± 10	44 ± 2 vs. 46 ± 3
1 mg/kg	108 ± 10 vs. 108 ± 10	440 ± 11 vs. 434 ± 12	48 ± 3 vs. 47 ± 3
5 mg/kg	116 ± 9 vs. 118 ± 9	445 ± 8 vs. 434 ± 9	48 ± 3 vs. 47 ± 3

4. Discussion

The interest in the effects of serotonin on upper-airway muscle activity has been generated by the desire to find a pharmacological treatment for obstructive sleep apnea. Augmentation of upper-airway muscle activity by a medication could theoretically prevent upper-airway closure during sleep. Yet, there have been relatively few studies on the effects of serotonin precursors on upper-airway muscle activity or sleep-disordered breathing. To date, the effects of certain serotonergic agents in humans have been somewhat disappointing (Hanzel et al., 1991; Berry et al., 1999; Kraiczi et al., 1999). Studies using serotonin-reuptake inhibitors have shown modest decreases in the apnea + hypopnea index only during NREM sleep. While two studies suggest that serotonin-reuptake inhibitors may enhance genioglossus activity (Berry et al., 1999; Sunderram et al., 2000), these agents tend to disturb sleep. They did not reduce the frequency of arousals in OSA patients (Hanzel et al., 1991; Kraiczi et al., 1999). Alternatively, the serotonin-precursor tryptophan (the precursor of 5HTP), given systemically, has been reported to improve the amount of REM sleep in OSA patients (Schmidt, 1982). The combination of tryptophan and trazodone (weak serotonin-reuptake inhibitor) also improved sleep quality in the English bulldog model of OSA (Veasey et al., 1999). Therefore, it is possible that serotonin precursors might improve sleep quality in patients with OSA. The conversion of tryptophan to 5HTP is the rate-limiting step in the formation of serotonin (5HT). For this reason, relatively high doses of tryptophan are required to increase central serotonin. Administration of 5HTP to increase central serotonin has been used as a treatment for depression (Byerley et al., 1987) and to evaluate neuroendocrine sensitivity to serotonin challenge (Hudgel et al., 1995).

The results of our study demonstrate that at appropriate doses, 5HTP significantly increases both gEMG and dEMG activity, but the increase in genioglossus activity is significantly larger. Thus, at least at the low doses investigated here, the effects of 5HTP are relatively selective for augmenting genioglossus activity. This is in agreement with the findings of previous studies that have reported a preferential change in gEMG or hypoglossal nerve activity relative to dEMG or phrenic nerve activity following peripheral administration of serotonergic agonists or antagonists (Bonora et al., 1985; Veasey et al., 1996). At the dose range we studied, 5HTP did not significantly alter respiratory rate, HR, or MAP. Arterial blood gas values were also stable over the study period. Thus, changes in BP, HR, PCO_2, or PO_2 should not have influenced our findings.

We observed that intravenous administration of 1 and 5 mg/kg 5HTP typically induced a rise in gEMG within 30 s following injection. The 5HTP-induced change in amplitude peaked within 1–2 min, remained elevated level for 3–5 min, and then gradually returned to control levels by 10–15 min postinjection. The onset of the 5HTP-induced change in respiratory activity is similar to that reported by Mitchell et al. (1992) in spinalized rats when tonic phrenic nerve activity was monitored. In their study, 5 mg/kg 5HTP was reported to increase tonic activity in the spinalized preparation within 30–60 s after administration, suggesting that peripherally administered 5HTP can influence central activity with 30 s.

Our results are also in partial agreement with the findings of Richmonds and Hudgel (1996). Using a similar preparation (vagotomized urethane-anesthetized male rats), Richmonds and Hudgel reported that intravenous 5HTP increased both hypoglossal and phrenic activities. At doses of 1 and 5 mg/kg, we also observed significant changes in both dEMG and gEMG. However, in their study, *parallel* increases in *both* phrenic and hypoglossal nerve burst amplitudes were reported following the systemic administration of low doses of 5HTP (2–5 mg/kg) and a preferential increase in phrenic burst amplitudes at doses >20 mg/kg. Furthermore, following the separate administration of several general serotonin antagonists, the investigators concluded that the resultant depressant effects of those drugs on respiratory activity levels were equivalent between the hypoglossal and phrenic motoneuron pools. Our results differ in the fact that we found 5HTP preferentially increased genioglossus activity in the dose range studied.

There are several possible explanations for the differences in the results of our study and those of Richmonds and Hudgel (1996). For example, in their study, only a small number of animals were used ($n = 4$) and each animal received multiple doses of 5HTP given at 3-min intervals. The results of our study suggest that when 5HTP is administered at intervals less than 15 min, even at the lowest dose, the effects of the previous dose may not have worn off. Consequently, the dose–response relationship presented by Richmonds and Hudgel may not have been accurate and may have been better represented by the cumulative dose given. This is supported by their observation that 5HTP tended to decrease MAP. In both our study and the study by Mitchell et al. (1992), 5 mg/kg 5HTP did not significantly alter MAP. Yet at higher doses (10–20 mg/kg), Mitchell et al. reported that 5HTP consistently decreased MAP. A second possibility for differences between our results and those of Richmonds and Hudgel may be related to the preparation. Our rats were spontaneously breathing and EMG activity was measured. In the study of Richmonds and Hudgel, their rats were paralyzed, artificially ventilated with a hyperoxic mixture, and nerve activity was measured, but the state of the animals was not monitored. Marked changes in baseline pH or PCO_2 could have altered their results. Alternatively, in their study, the hypoglossal and phrenic nerve activity was expressed as a percent of the maximum response observed during brief hypoxia. Yet if response characteristics between the two-motoneuron pools to hypoxia are inherently different (Hutt et al., 1989), representing the data as a percent of maximum could bias the effect of 5HTP in one motoneuron pool compared to another. Thus, although we also used vagotom-

ized animals, we concentrated on identifying the change induced by 5HTP from the preceding baseline rather than the absolute magnitude of nerve activity. Finally, we studied only a lower dose range of 5HTP. The choice of testing only the lower doses was based on knowledge that this dose range might have fewer side effects and therefore might better reflect a dose range that has greater potential for clinical use. The side effects from high doses of 5HTP include nausea (Hudgel et al., 1995), low BP (Richmonds and Hudgel, 1996), and the potential for depression of phrenic nerve activity (McCrimmon and Lalley, 1982; Richmonds and Hudgel, 1996). These findings suggest that only low to moderate doses of 5HTP may be useful in raising baseline genioglossus activity.

One potential limitation of our methodology was that we used anesthesia instead of a decerebrate animal model. A preferential suppression of hypoglossal activity by use of some anesthesia (Hwang et al., 1983) has been demonstrated. Bonora et al. (1985), using a decerebrate preparation, showed a very large preferential increase in hypoglossal compared to phrenic activity following injection of protriptyline (a 5HT- and norepinephrine-reuptake inhibitor). Despite the use of anesthesia, we were able to show a preferential response in the genioglossus. Thus, it is possible that the use of a decerebrate preparation or systemic administration of 5HTP in a conscious animals would have allowed demonstration of an even greater selective augmentation of the genioglossus with 5HTP at the low dose range used in the current study.

In summary, this study found that 5HTP at appropriate doses did increase both genioglossus and diaphragmatic activities in the anesthetized rat. There was a larger increase in the genioglossus activity at 1 and 5 mg/kg suggesting that at least at some doses enhancement of serotonin activity preferentially increases genioglossus activity. The relevance of these findings for human sleep and patients with obstructive sleep apnea remains to be determined.

Acknowledgements

This work was supported by the Department of Veterans Affairs (RBB) and HL-52607 (LFH).

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