Dorsomedial medullary 5-HT2 receptors mediate immediate onset of initial hyperventilation, airway dilation, and ventilatory decline during hypoxia in mice

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Kanamaru M, Homma I. Dorsomedial medullary 5-HT2 receptors mediate immediate onset of initial hyperventilation, airway dilation, and ventilatory decline during hypoxia in mice. Am J Physiol Regul Integr Comp Physiol 297: R34–R41, 2009. First published April 22, 2009; doi:10.1152/ajpregu.90802.2008.—The dorsomedial medulla oblangata (DMM) includes the solitary tract nucleus and the hypoglossal nucleus, to which 5-HT neurons project. Effects of 5-HT in the DMM on ventilatory augmentation and airway dilation are mediated via 5-HT2 receptors, which interact with the CO2 drive. The interaction may elicit cycles between hyperventilation with airway dilation and hypoventilation with airway narrowing. In the present study, effects of 5-HT2 receptors in the DMM on hypoxic ventilatory and airway responses were investigated, while 5-HT release in the DMM was monitored. Adult male mice were anesthetized, and then a microdialysis probe was inserted into the DMM. The mice were placed in a double-chamber plethysmograph. After recovery from anesthesia, the mice were exposed to hypoxic gas (7% O2 in N2) for 5 min with or without a 5-HT2 receptor antagonist (LY-53857) perfused in the DMM. 5-HT release in the DMM was increased by hypoxia regardless of the presence of LY-53857. Immediate onset and the peak of initial hypoxic hyperventilatory responses were delayed. Subsequent ventilatory decline and airway dilation during initial hypoxic hyperventilation were suppressed with LY-53857. These results suggest that 5-HT release increased by hypoxia acts on 5-HT2 receptors in the DMM, which contributes to the immediate onset of initial hypoxic hyperventilation, airway dilation, and subsequent ventilatory decline. Hypoxic ventilatory and airway responses mediated via 5-HT2 receptors in the DMM may play roles in immediate rescue and defensive adaptation for hypoxia and may be included in periodic breathing and the pathogenesis of obstructive sleep apnea.

One of predominant excitatory 5-HT receptors in the nXII is the 5-HT2A receptor (46). The 5-HT2 receptor activity enhances hypoglossal nerve activity (7, 18). The nTS is located in the vicinity of the nXII. Some serotonergic neurons in the nXII and nTS originate from the caudal raphé nuclei, such as the nuclei of the raphé obscurus, the raphé pallidus, and the raphé magnus (21, 39). The role of 5-HT2 receptors in the nTS in respiration is not well understood, although their role in cardiovascular control is known as a part of the baroreceptor reflex arc (35). These facts make it necessary to investigate the role of 5-HT2 receptor activity in the DMM in respiratory and airway controls.

Some references indicate the importance of the nTS in respiratory regulation, especially in hypoxic ventilatory responses. For example, L-glutamate mediates afferent inputs from peripheral chemoreceptors and increases tidal volume (VT) and minute ventilation (VE) (40). Glutamate release during hypoxia, comes from the primary afferents of peripheral chemoreceptors (26). Substance P increases VT, and its receptor activity is desensitized by hypoxia (23). Dopamine, which mediates the hypoxic depressive phase (10), and adenosine (45) are increased by hypoxia. GABA mediates hypoxic ventilatory decline (38). The nTS plays a pivotal role in hypoxic ventilatory responses and has neuronal plasticity (2). However, roles of the 5-HT2 receptors in the nTS in hypoxic ventilatory response are not well characterized.

In patients with obstructive sleep apnea (OSA), airway obstruction during sleep causes an increase in the partial pressure of arterial CO2 (PACO2), respiratory acidosis, and a decrease in the partial pressure of arterial O2 (PACO2). We have demonstrated that interplay between 5-HT2 receptor activity in the DMM and respiratory CO2 drive elicits hyperventilation with airway dilation or hypoventilation with airway narrowing (14). The tongue protruder (genioglossus) and retractor (hyoglossus) muscles are stimulated by hypoxia (8). Therefore, the effect of the 5-HT2 receptors in the DMM on hypoxic airway responses, especially hypoxic airway resistance, was investigated.

In the present study, hypoxic response of 5-HT release in the DMM, and hypoxic ventilatory and airway responses mediated via local 5-HT2 receptor activity were investigated by using a microdialysis technique and double-chamber plethysmography in mice. The effects of 5-HT2 receptors in the DMM on chemical ventilatory and airway controls are discussed from both a physiological and pathophysiological viewpoint.

METHODS

The protocol for the present study was reviewed and approved by the Institutional Animal Care and Use Committee of Showa University.
EFFECT OF 5-HT2 RECEPTOR ON HYPOXIC RESPIRATORY RESPONSE

General procedures. Adult male C57BL/6N mice (CLEA Japan, Tokyo, Japan) [12 ± 0.6 wk of age, 25.1 ± 0.6 g (mean ± SE)] were housed on a 12:12-h light-dark cycle with lights on at 8:00 AM and had free access to food and water. The procedure for surgical implantation of the microdialysis probe in the DMM has been described in detail previously (14). Briefly, each mouse was anesthetized with pentobarbital sodium (0.5 mg·0.1 ml saline·1 g body wt·1 ip). The head region was cleaned with an antiseptic (isodine) and locally anesthetized by a 2% xylocaine injection to induce preemptive analgesia. A skin incision was then performed. The bone was drilled and a microdialysis probe (CS5–01; 1 mm membrane length; 0.22 mm outer diameter; 50,000 Da cutoff; EiCOM) inserted into the DMM (coordinates: 0.45 mm lateral to the midline, 0.8 mm rostral to the obex; and a depth of 1 mm from the dorsal brain surface), and was fixed to the cranial bone with dental cement. The skin incision was closed with sterilized 5-0 silk sutures.

The mice were placed into a double-chamber plethysmograph with two continuous airflows of 150 ml/min with a vacuum pump. The rectal temperature was controlled at 37°C with a heating blanket and lamp (model ART-1100; Nihon Kohden, Tokyo, Japan) during operations and experiments, respectively. Mice seem to be almost awake as suggested by our preliminary EEG experiments in the chamber (unpublished data).

Experimental protocols. The inserted microdialysis probe was perfused with artificial cerebrospinal fluid (aCSF; 121.1 mM NaCl, 5 mM KCl, 24 mM NaHCO3, and 1.5 mM CaCl2 adjusted to pH 7.4 with 95% O2 and 5% CO2) at a flow rate of 1.2 μl/min. After a 4-h period to recover from anesthesia and habituation, each mouse in the double-chamber plethysmograph was exposed to air from a gas cylinder over a 25-min period at a flow rate of 2 l/min with overflow.

Subsequently, the inserted microdialysis probe in the DMM was perfused for 25 min with aCSF or a 5-HT2 receptor antagonist, LY-53857 (10−3 M), dissolved in aCSF. Following that, the inspired gas was switched from air to a hypoxic gas mixture (7% O2 with a balance of N2) for 5 min and was then replaced with air. Dialysate (6 μl/5 min) was collected into a sampling loop of an auto injector (model EAS-20; EiCOM) every 5 min. After the experiments, microdialysis probe sites were verified in 50-μm-thick coronal sections fixed in 10% buffered formalin under a light microscope.

5-HT analysis with an HPLC system. 5-HT was analyzed every 5 min using an HPLC system (model HETC-500; EiCOM) equipped with an electrochemical detector (ECD), a column (model PP-ODS; 4.6 mm ID × 30 mm; EiCOM), and an auto injector. The mobile phase was composed of 0.1 M sodium phosphate-buffer containing 1% methanol, 50 mg/l EDTA, and 500 mg/l sodium 1-decanesulfonate. The flow rate was 0.5 ml/min. The column temperature was maintained at 25°C. 5-HT was oxidized at 400 mV on a graphite electrode relative to an Ag–AgCl reference electrode. Chromatograms were recorded with a PowerChrom (model EPC-300; EiCOM). The detection limit of the HPLC system for 5-HT was 0.7 fmol/6 μl (signal-to-noise ratio = 3).

Measurements of ventilation and specific airway resistance. Two respiratory flow curves from the head and body chambers were obtained with pneumotachographs (model TV-241; Nihon Kohden) and pressure transducers (model TR-602T; Nihon Kohden) recorded at a 10-kHz sampling rate with a PowerLab (AD Instruments, NSW, Australia). Changes in VT, respiratory rate (RR), VE, and specific airway resistance (sRaw) during a hypoxic period were calculated every 0.5 or 1 min. Ventilatory volume was calculated with the head chamber flow calibrated with injections of 0.5 ml of air. sRaw was calculated with a time delay between head chamber and body chamber flows (32).

Statistical analysis. All data are presented as means ± SE. Significant differences between the aCSF- and the LY-53857-perfused groups were evaluated by two-way ANOVA. Significant time of hypoxic respiratory response was analyzed by one-way ANOVA with Dunnett’s test. Significant differences in sRaw in the two groups were estimated with two-way ANOVA and with Student's t-test at each equivalent time until 2 min. The statistical analyses were carried out with SPSS software (SPSS Japan, Tokyo, Japan). Repeated-measures ANOVA with Greenhouse-Geisser correction was used to analyze 5-HT release changes (15). P < 0.05 was considered statistically significant.

RESULTS

The baseline value of 5-HT release in the DMM averaged from three sequential 5-HT releases during air inhalation just before hypoxic gas inhalation was 4.1 ± 2.4 fmol/6 μl in the aCSF-perfused group (n = 5) and 1.3 ± 0.4 fmol/6 μl in the LY-53857-perfused group (n = 5). The difference in the baseline values of 5-HT release between aCSF and LY-53857 perfusions was not significant. The basal 5-HT release in the DMM was significantly increased 5.7-fold in the aCSF-perfused group and six-fold in the LY-53857-perfused group by hypoxic gas inhalation. The increased rates of 5-HT release in the DMM were not significantly different (Fig. 1A).

The probe sites of microdialysis in the aCSF- and the LY-53857-perfused groups were located in the DMM, including the nTS, the dorsal motor nucleus of the vagus, and the nXII. The distributions were similar in the two groups (Figs. 1, B and C).

The respiratory curves changed due to hypoxic gas inhalation in the aCSF- and the LY-53857-perfused groups (Fig. 2). Hypoxic ventilatory facilitation in the LY-53857-perfused group was likely less than that in the aCSF-perfused group during the first 30 s of the hypoxic gas inhalation. In the respiratory curves of the aCSF-perfused and the LY-53857-perfused groups, one or more of apnea, augmented breath, and rapid breathing were periodically observed during hypoxia in all 10 mice. Periodic breathing, such as cheyne-stokes breathing, was observed in one of five mice in the aCSF-perfused group for the last 3 min of hypoxia; however, it was observed in two of five mice in the LY-53857-perfused group for the initial 2 min of hypoxia.

Body temperature decreased from 36.8 ± 0.14°C to 36.4 ± 0.14°C in the aCSF-perfused group and decreased from 36.9 ± 0.07°C to 36.3 ± 0.13°C in the LY-53857-perfused group (n = 5 each). During hypoxia over the period from 3 to 5 min, a significant fall in body temperature was observed despite the mouse being heated with a lamp at ~37°C. In the LY-53857 group, this was observed over the period of 2 to 5 min. The difference in the decreases in body temperatures between the two groups was not statistically significant.

The baseline value of VT, 0.065 ± 0.006 ml/10 g body wt, was significantly increased to 0.109 ± 0.015 ml/10 g body wt via hypoxic gas inhalation in the aCSF-perfused group (n = 5). In the LY-53857-perfused group, 0.069 ± 0.008 ml/10 g body wt was significantly increased to 0.104 ± 0.007 ml/10 g body wt (n = 5). The VT increase was not significantly different between the aCSF- and the LY-53857-perfused groups. However, the VT in the aCSF-perfused group was significantly increased from 1 to 5 min during hypoxic gas inhalation. In the LY-53857-perfused group, the VT significantly increased from 2 to 5 min. LY-53857 perfusion in the DMM showed a delay in the onset of a significant increase in the VT during hypoxic gas inhalation (Fig. 3A).

The baseline value of RR, 205 ± 12/min was significantly increased up to 270 ± 16/min in the aCSF-perfused group (n = 5). In the LY-53857-perfused group, the baseline value of RR,
201 ± 23/min, increased to 237 ± 26/min \((n = 5)\). The difference in RR during hypoxic gas inhalation between the aCSF- and LY-53857-perfused groups was not statistically significant. However, the RR increase during the first 0.5 min of hypoxic gas inhalation was significantly different from the baseline value in the aCSF-perfused group. This was not significant in the LY-53857-perfused group (Fig. 3B).

The baseline value of \(\dot{V}_E\), 13.4 ± 1.5 ml·min\(^{-1}\)·10 g body wt\(^{-1}\), was significantly increased to 25.6 ± 3.9 ml·min\(^{-1}\)·10 g body wt\(^{-1}\) in the aCSF-perfused group \((n = 5)\). In the LY-53857-perfused group a value of 13.7 ± 2.1 ml·min\(^{-1}\)·10 g body wt\(^{-1}\) significantly increased to 24.6 ± 1.3 ml·min\(^{-1}\)·10 g body wt\(^{-1}\) \((n = 5)\). The change in rates of \(\dot{V}_E\) was similar in the two groups. However, the \(\dot{V}_E\) responses through a 5-min hypoxic period were significantly different between the two groups. The \(\dot{V}_E\) of the aCSF-perfused group was increased soon after hypoxic gas inhalation and significantly increased from 1 to 2 min, compared with the baseline value in the group. The \(\dot{V}_E\) of the LY-53857-perfused group was increased with a delayed onset and was significantly increased from 2 to 4 min of hypoxic gas inhalation. Namely, LY-53857 perfusion in the DMM showed a delay in the onset of a significant increase in \(\dot{V}_E\) during hypoxic gas inhalation (Fig. 3C). Subsequent ventilatory decline was not different from the peak \(\dot{V}_E\) in the LY-53857 perfusion in the DMM, which was different from the remarkable ventilatory decline in the aCSF perfusion in the DMM.

The baseline value of \(s_{R_{aw}}\) was 8.8 ± 3.7 cm H$_2$O·s in the aCSF group and 5.3 ± 1.6 cm H$_2$O·s in the LY-53857 group. The baseline values were not significant in the two groups. A change in \(s_{R_{aw}}\) was expressed as the difference from each mean value for the last 0.5 min just before hypoxic gas inhalation. The hypoxic \(s_{R_{aw}}\) changes were not significantly different between the aCSF- and the LY-53857-perfused groups \((n = 5\) each). However, the \(s_{R_{aw}}\) changes until the initial 2 min of hypoxic gas inhalation were significantly different in both groups (Fig. 3D). The \(s_{R_{aw}}\) values at 0.5 and 1.5 min were significantly higher in the LY-53857-perfused group than in the aCSF-perfused group.

**DISCUSSION**

In the present study, the effects of 5-HT release on 5-HT2 receptors in the DMM on hypoxic ventilatory and airway responses were investigated by using a microdialysis technique with an HPLC with an ECD, and double-chamber plethysmography in adult mice. The results suggest that release of 5-HT in the DMM is increased by hypoxia and that 5-HT release acting...
on 5-HT2 receptors in the DMM contributes to immediate onset of an increase in $V_T$ and $RR$, to airway dilation, and to hypoxic ventilatory decline.

The basal value of 5-HT release in the DMM was not significantly different between the LY-53857- and aCSF-perfused groups and was similarly increased by hypoxic gas inhalation. The results suggest that 5-HT release in the DMM is increased by hypoxia, which is not affected by local 5-HT2 receptors in the DMM.

Initial ventilatory response to hypoxia. An increase in respiratory frequency during hypoxia and posthypoxia frequency decline are mediated via systemic 5-HT2 receptors (16). Ventilatory long-term facilitation induced by intermittent-hypoxia is mediated via systemic 5-HT2 receptors (24). 5-HT2 receptors are distributed in the nTS (6, 33), which are partially present on catecholaminergic fibers (28). Hypoxia evokes Fos expression in the nTS of adult rats (1). In our experiments, initial hypoxic $V_T$ and $V_E$ responses were significantly delayed and initial hypoxic $RR$ increase was blunted by a 5-HT2 receptor antagonist in the DMM. The ventilatory phenomena mediated via 5-HT2 receptors in the DMM are quite similar to the short-term potentiation in the hypoxic ventilatory response, defined by Powell et al. (34).

In unanesthetized and unrestrained rats, glutamate release in the nTS is increased by hypoxia, which is due to peripheral chemoreceptor stimulation, and contributes to ventilatory facilitation (26). The 5-HT2 receptors and NMDA receptors are distributed in single cells, mainly dendrites, in the nTS (12). We have already reported that 5-HT2 receptor antagonism in the DMM elicits a downward shift of $V_T$ and $V_E$ in hypercapnic ventilatory responses with or without airway narrowing (14). These results suggest that a suppressive effect on the respiratory network induced by 5-HT2 antagonism in the DMM elicits a delayed onset of hypoxic ventilatory response with 5-HT2 antagonism in the DMM. On the other hand, negative pressure applied to the isolated upper airway de-

Fig. 2. Hypoxic effects on respiratory flow curves during aCSF or LY-53857 perfusion in the DMM. $FI_{O_2}$ (% $O_2$) is the inspired $O_2$ fraction expressed as a percentage, which was changed from 21% to 7% $O_2$. 

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creases respiratory frequency and is not associated with an increase in diaphragmatic muscle activity (22, 44). 5-HT has been ruled out as a candidate for mediating the short-term potentiation in mammals (5). These facts do not exclude the possibility that airway narrowing induced by 5-HT2 antagonism in the DMM elicits a decrease in respiratory drive and results in a delayed onset of hypoxic ventilatory response. Hodges et al. (11) found that central 5-HT contributes to the hypercapnic ventilatory response depending on respiratory rate; however, hypoxic ventilatory response is not affected. In the DMM, one of the central sites where 5-HT is a synaptic transmitter, 5-HT release is increased by hypercapnia or hypoxia; hypercapnic ventilatory responses are enhanced by 5-HT2 receptors depending on VT with airway dilation (14). In addition, the immediate onset of hypoxic ventilatory responses and airway dilation were mediated by 5-HT2 receptors. Taken together, these facts suggest that hypercapnic ventilatory response is partially mediated by central 5-HT and 5-HT2 receptors in the DMM. The hypercapnic ventilatory response dependent on VT is, at least in part, mediated by 5-HT2 receptors in the DMM, and that which is dependent on RR is controlled by other brain areas. These data also suggest that the peak hypoxic ventilatory response is not

Fig. 3. Hypoxic effects on tidal volume, respiratory rate, minute ventilation, and specific airway resistance during aCSF or LY-53857 perfusion in the DMM. A: VT, tidal volume. B: respiratory rate. C: Vt, minute ventilation. D: ΔRaw, difference from specific airway resistance at time 0. Data are means ± SE. ◊, aCSF-perfused group (n = 5); ●, LY-53857-perfused group (n = 5). *Significantly different (P < 0.05) from values at time 0 in the aCSF and the LY-53857 perfused groups, respectively. †Significant difference between both groups. §Significantly different from equivalent time in the aCSF-perfused group.
affected by central 5-HT and 5-HT2 receptors in the DMM; however, onset timing of hypoxic ventilatory response is accelerated by 5-HT2 receptors in the DMM, although the mechanism has still not been clarified.

5-HT2 receptor activity in the nTS decreases blood pressure and heart rate, and enhances bradycardia and depressor responses mediated by NMDA receptors in the nTS (25). So, the time delay between hypoxic gas inhalation and chemoreceptor stimulation is unlikely retarded by a 5-HT2 receptor antagonist in the nTS. The delayed onset of initial hypoxic hyperventilation elicited by a 5-HT2 receptor antagonist in the nTS may be independent of the responses in cardiovascular circulation.

Hypoxic ventilatory decline. Hypoxic ventilatory response consists of a biphasic response (19, 42). Initial hypoxic hyperventilation is followed by ventilatory roll off, which is also called hypoxic respiratory depression or hypoxic ventilatory decline. While ventilation was enhanced by 5-HT2 receptor antagonism during hypoxic ventilatory decline, a change in V'T in the 5-HT2 receptor antagonist group was similar to that in the aCSF group. The decrease in RR in the aCSF group tended to be suppressed by 5-HT2 antagonism in the DMM, although the difference of RR between the two groups was not statistically significant. So, the RR may play a larger role in hypoxic ventilatory decline than V'T.

The mechanism of hypoxic ventilatory decline has a central origin (42). Hypoxic ventilatory decline is caused by: 1) transient brainstem alkalosis, 2) neuronal hyperpolarization, and 3) metabolic insufficiency and toxic neuronal effects (27). We cannot deny the possibility that delayed initial hyperventilation induced by 5-HT2 receptor antagonism in the DMM may elicit a difference in PaCO2, which then may result in a difference in hypoxic ventilatory decline, although the contribution of hypocapnia to hypoxic ventilatory decline is described as a minor factor (9). Therefore, our results suggest that hypoxic ventilatory decline is directly mediated via 5-HT2 receptors in the DMM, in addition to 5-HT1A receptors in the ventral respiratory areas (37), or is indirectly elicited by the other mechanisms, such as hypocapnia from immediate hypoxic hyperventilation mediated via 5-HT2 receptors in the DMM, or both.

Hypoxic airway response. Each increase in diaphragmatic or genioglossal electromyogram response is linearly related to the decrease in oxygen saturation and is linearly related to each other during hypoxia (29). Hypoglossal and recurrent laryngeal nerves are stimulated by hypoxia (43). Nasal and pharyngeal resistances decrease with an increase in inspiratory drive during hypoxia (20). Hypoglossal motoneurons and nerve activity are activated via 5-HT2 receptors in the nXII (7, 18). 5-HT2 receptor antagonism in the DMM significantly increased airway resistance during initial hypoxic hyperventilation, while airway resistance did not change during hypoxia with aCSF perfusion in the DMM. Taken together, these facts suggest that airway dilation during initial hypoxic hyperventilation is, at least, mediated via 5-HT2 receptor activity in the DMM, and includes the excitations of hypoglossal nerve and genioglossus muscles. The mechanism is valuable for rapid and deep breathing during initial hypoxic hyperventilation.

Airway resistance through a 5-min hypoxic period, including airway response during subsequent hypoxic ventilatory decline, with 5-HT2 receptor antagonism in the DMM was not significantly different from that with the aCSF perfusion, while hypoxic ventilatory decline was different in both groups. The results suggest that initial hypoxic airway narrowing elicited by the 5-HT2 receptor antagonist in the DMM is reversed by other mechanisms during hypoxic ventilatory decline. We have reported that a low level of airway resistance is maintained via 5-HT2 receptors in the DMM, and that airway narrowing elicited by a 5-HT2 receptor antagonist in the DMM is compensated by hypercapnia (14). These results suggest that a large amount of hypoxic- and/or hypercapnic drives to the airway reverses airway narrowing induced by the low activity of 5-HT2 receptors in the DMM.

In the present study, whenever periodic breathing, such as cheyne-stokes breathing, appeared, it was observed during the hypoxic ventilatory decline phase with aCSF in the DMM and was observed during the initial hypoxic hyperventilation with a 5-HT2 receptor antagonist in the DMM. Periodic breathing is potentiated by an increase in respiratory controller gain, such as hypoxia and system damping of CO2/pH (3). PaCO2, afferent inputs in addition to PaO2 play an important role in regular ventilation, which might be modified by 5-HT2 receptors in the DMM.

In summary, hypoxia increases 5-HT release in the DMM. The increased 5-HT release acts on 5-HT2 receptors in the DMM and elicits 1) the immediate onset of initial hypoxic hyperventilation; 2) airway dilation, especially during initial hypoxic hyperventilation; and 3) subsequent hypoxic ventilatory decline.

Limitations

The present study aimed to clarify the effects of 5-HT2 receptor activity in the DMM on ventilatory and airway responses to hypoxia because anatomical pathways of 5-HT neurons in the medulla oblongata suggested coactivation of 5-HT2 receptors in the nTS and the nXII (21, 39). Further studies are needed to define the mechanisms of hypoxic ventilatory and airway responses mediated via 5-HT2 receptors in the DMM. For example, PaCO2 measurement, and each evaluation of 5-HT2 receptor activity in the nTS or the nXII, may help to clarify the contribution of hypocapnia to hypoxic ventilatory decline and the mechanism of delayed onset of hypoxic hyperventilation, respectively. However, it is a fact that low activity of 5-HT2 receptors in the DMM leads to the phenomena, such as the delayed onset of hypoxic hyperventilation, airway narrowing during initial hyperventilation, and suppression of hypoxic ventilatory decline.

Perspectives and Significance

During sleep onset, ventilation decreases and PaO2 decreases, which elicits hyperventilation. 5-HT neurons in the caudal raphé nuclei project to the nTS and nXII and their activities are increasingly suppressed from quiet waking to slow-wave sleep and rapid eye movement sleep (41). Therefore, we speculate that first, during deep sleep, 5-HT2 receptor activity in the DMM decreases, which leads to a delayed onset of hypoxic hyperventilation, increases in airway resistance, and continued hyperventilation until PaO2 recovers. In OSA patients, having anatomical airway narrowing, those processes easily lead to airway obstruction and apnea. Second, during light sleep or the awake state, 5-HT2 receptor activity in the DMM increases, by which hypoxia elicits immediate onset of
initial hyperventilation with airway dilation and immediate recovery of PaO2. During brief wakefulness in OSA patients, having an enhanced number or raised sensitivity or both of 5-HT receptors in the brain, those processes cause immediate recovery of PaO2 and PaCO2. Third, sleep is subsequently reestablished, and ventilatory drive and airway dilation decrease until PaO2 decreases and/or PaCO2 increases. These three cycles may cause physiological periodic breathing during sleep onset, and repetitive airway obstruction and apneahypopnea in OSA patients. Namely, hypoxic ventilatory and airway responses mediated via 5-HT2 receptors in the DMM may contribute to immediate rescue and defensive adaptation for hypoxia in the awake state, and physiological periodic breathing and pathophysiological repetitive OSA in the sleep state.

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