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Review article

Neurotransmission in the carotid body and anesthesia

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Introduction

Systemic hypoxia, which anesthesiologists wish to avoid, is a potentially lethal situation for the patient. During systemic hypoxia the carotid body, a primary sensory organ for arterial hypoxia, sends a message to the central nervous system and induces various responses in the cardiovascular, respiratory, renal, and endocrine systems. This is a unique feature of the carotid body. Many organs and cells detect hypoxia, but their responses are usually directed to protect themselves. However, in the case of the carotid body, the consequences of oxygen sensing are not confined to the organ, but are used to protect other organs from irreversible damage. The ventilatory responses induced by the excitation of the carotid body during acute hypoxia are not foreign to the anesthesiologist. However, a role of the carotid body in various health conditions and the effects of medical agents on carotid body function do not seem to be appreciated [1]. In this review, I will present the basic biology of the carotid body and its relationship with diseases. Subsequently, I will discuss three of our studies showing the effects of medical agents on chemotransmission in the carotid body. Not all issues will be explained in detail. However, excellent reviews and recent publications are cited in each section for interested readers.

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Biology of the carotid body

The carotid body is located where the common carotid artery bifurcates into the internal and external carotid arteries. The location is very close to the carotid sinus baroreceptor region. The carotid body has a distinct and global structure, with some variations [2]. It senses the changes in oxygen, carbon dioxide, and pH in the arterial blood. These changes are converted into an increase in the neural activity of the carotid sinus nerve. Figure 1 shows the gross anatomy of the carotid body (A) and carotid chemoreceptor neural activity (B) recorded from a whole carotid sinus nerve of a cat. Although baroreceptor activity is also transmitted in the carotid sinus nerve, in these recordings baroreceptor activity was mechanically eliminated and only chemoreceptor neural activity was recorded. Immediately after the carotid body is exposed to hypoxia or hypercapnia, the chemoreceptor nerve discharge increases. The signal is sent to the nucleus tractus solitarius via the petrosal ganglion, where the cell bodies of the chemosensory afferent neurons are located. Increased chemoreceptor neural activity during stimulation is a key function of the carotid body. This is found across species, such as the cat, dog, rat, rabbit, goat, pony (for a review, see Gonzalez et al. [3]), and mouse [4,5]. However, there appear to be species differences in the mechanisms of chemoreception and chemotransduction in the carotid body. The following are some examples. The expression of voltage-gated ion channels differs among the rat, rabbit, and cat. Hypoxia affects different types of voltage-gated K^+ channels in these species [6]. Muscarinic receptors outnumber nicotinic receptors in the rabbit, but the opposite is true in the cat [7,8]. Dopamine is a major catecholamine in the rabbit carotid body, but more norepinephrine than dopamine is present in the cat carotid body [3]. Because of these and other differences, physiological stimulation may cause variable cellular and molecular changes in the carotid body of

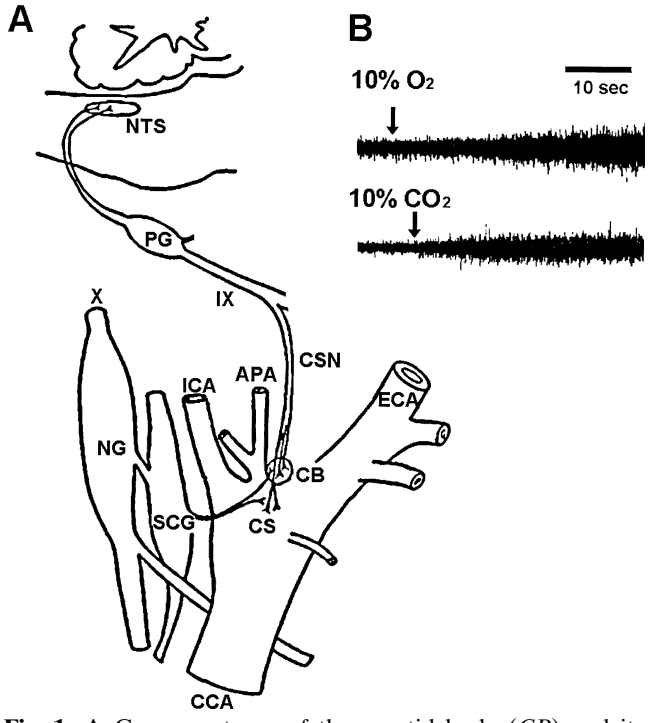


Fig. 1. A Gross anatomy of the carotid body (*CB*) and its innervation. Chemoreceptor afferent information is carried in the carotid sinus nerve (*CSN*), a branch of the IXth cranial nerve, and reaches to the nucleus tractus solitarius (*NTS*) via the petrosal ganglion (*PG*). The petrosal ganglion contains the cell bodies of chemoreceptor afferent neurons and baroreceptor neurons. Sympathetic nerves from the superior cervical ganglion (*SCG*) innervate vessels within the carotid body. *APA*, Ascending pharyngeal artery; *CCA*, common carotid artery; *CS*, carotid sinus; *ECA*, external carotid artery; *ICA*, internal carotid artery; *NG*, nodose ganglion. **B** Chemoreceptor neural activity recorded from whole carotid sinus nerves of anesthetized cats. At the *arrows*, the animals were exposed to either 10% O_2 or 10% CO_2. Both hypoxia and hypercapnia increase chemoreceptor neural activity. It is known that chemoreceptor activity also increases with low pH, high temperature, and high osmolarity; chemoreceptor activity decreases with high glucose [13,18,39]

different species. Nonetheless, evoked changes in the carotid body must be transformed into an increased chemoreceptor neural output to the brain in order to accomplish the main function of the carotid body—sensing chemical changes in the arterial blood and informing the brain of them. Increased chemoreceptor neural activity is integrated in the brain and induces an impressive array of reflex responses. This aspect of carotid body function has been reviewed elsewhere [9–12].

Although the systemic responses induced by stimulation of the carotid body are well known, the mechanisms of chemoreception and chemotransmission in the carotid body are still not clear, despite vigorous investigation. Currently, many investigators believe that neurotransmitters are involved in the excitation of chemoreceptor afferent nerve endings. Glomus cells (type I cells or chief cells) are putative chemoreceptor cells, and they contain many kinds of neurotransmitters (dopamine, norepinephrine, epinephrine, serotonin, acetylcholine [ACh], substance P, gamma-aminobutyric acid, enkephalins, ATP, etc.) [2,3,8,13]. The role of each neurotransmitter in chemotransmission of the carotid body has not yet been established. ACh, dopamine, and substance P have been vigorously investigated and proposed as possible excitatory neurotransmitters. The release of these neurotransmitters in response to hypoxia or hypercapnia has been experimentally confirmed [3,14,15]. On the basis of many pharmacological and electrophysiological studies, it seems fair to say that ACh, ATP, and substance P act as excitatory neurotransmitters, and dopamine acts as an inhibitory neurotransmitter. Several investigators have recently summarized their views [8,16–18]. The release of neurotransmitters from the glomus cell is assumed to be regulated by intracellular calcium ($[Ca^{2+}]i$), and many experimental data support the concept. A close correlation between $[Ca^{2+}]i$ level and catecholamine release has been shown in cultured adult rabbit glomus cells [19,20]. Further, the influx of Ca^{2+} from the extracellular milieu appears essential for the release of neurotransmitters during hypoxia, because the removal of extracellular Ca^{2+} inhibits the release of catecholamines [21–25] and substance P [15]. Several reports indicate that the influx of Ca^{2+} via L-type voltage-gated Ca^{2+} channels is responsible for catecholamine release [22,24,26]. However, glomus cells express several types of Ca^{2+} channels [27,28], and N-type calcium channels, in addition to L-type Ca^{2+} channels, appear to be responsible for the release of substance P [15]. Contrariwise, agents that mobilize Ca^{2+} from intracellular stores do not affect catecholamine release [29].

Because voltage-gated Ca^{2+} channels are activated by depolarization of the plasma membrane, mechanisms involved in depolarizing the glomus cell have been a major focus of investigation. López-Barneo et al. first reported that voltage-gated K (Kv) channels of adult rabbit glomus cells were inhibited by hypoxia [30]. Their studies and those of others have revealed the basic characteristics and the O_2-sensitivity of both the Kv channels and the large-conductance Ca^{2+}-activated K (maxi-K) channels in rabbit, rat, and cat glomus cells (for a review, see Shirahata and Sham [6]). These results coalesced into the hypothesis that hypoxic inhibition of Kv channels induces the depolarization of glomus cells. Significant variability, however, was seen among species [6]. Further, some investigators have questioned the role of Kv or maxi-K channels in the hypoxic excitation of glomus cells. The activation thresholds of these channels are approximately −30 mV. Therefore, most chan-

nels would be closed at the normal resting membrane potential of glomus cells (about −50 mV) [6]. Hypoxic inhibition of these channels, which are mostly closed, may not significantly influence the membrane potential. In addition, the experimental results using Kv channel and maxi-K channel blockers are controversial [31–34]. Recently, it was reported that hypoxia inhibited TASK-like background K^+ channels [34,35] or voltage-gated HERG-like channels [36]. These channels are active at resting membrane potential, and their inhibition has been proposed to initiate the depolarization of glomus cells. These controversial data suggest that we do not have a unified view of the mechanisms involved in glomus cell depolarization in response to hypoxia (see also Prabhakar [37]).

Health issues related to the carotid body

Basal ventilation

The contribution of the carotid body to basal ventilation has been controversial. Some investigators claimed that a minimal contribution came from the carotid body, because transient hyperoxia caused only 10%–15% reduction in ventilation in healthy human subjects (for reviews, see Heath and Smith [2], Fitzgerald and Lahiri [9], and Comroe [38]). However, in these studies hyperoxia was assumed to eliminate carotid body chemoreceptor neural activity. This, however, disagrees with experimental data. Hyperoxia reduces chemoreceptor neural activity, but never eliminates it (for reviews, see Eyzaguirre et al. [13] and Fidone and Gonzalez [39]). Recently, the contribution of the carotid body to the basal level of ventilation has been reevaluated. When the carotid bodies of awake dogs were bilaterally perfused with hypocapnic blood, the ventilation decreased by 30% [40]. Further, bilateral denervation of the carotid body caused hypoventilation in the dog without recovery for up to 3 weeks [41]. Hypoventilation due to carotid body denervation was observed in the rabbit [42], pony [43], goat [44], and piglet [45]. These data indicate that the neural input from the carotid body plays an important role not only in increasing ventilation under hypoxic, hypercapnic, and acidic conditions, but also in normal ventilation (see also Forster et al. [46]).

Congenital disorders

Because carotid body function greatly influences many other systems, malfunction of the carotid body or even normal function of the carotid body can be associated with health problems. Ventilatory abnormalities found in some congenital disorders may be, at least in part, due to a malfunction of the carotid body. A clear association between carotid body anatomy and congenital hypoventilation syndrome was indicated recently. A detailed examination was performed in two patients with congenital hypoventilation syndrome [47]. Their carotid bodies were small (<50% of control), and the number of glomus cells was markedly decreased, together with a decrease in dense core vesicles (a storage site of amine and peptide neurotransmitters). The number of sheath cells (type II cells or sustentacular cells), which are glia-like cells in the carotid body, increased twofold. On the other hand, no structural abnormalities were observed in the area associated with respiratory control in the central nervous system.

Prader-Willi syndrome is a genetic disorder with abnormalities in chromosome 15 (1:10000 newborns). Sleep-disordered breathing is often noted in these patients, and dysfunction of the carotid body and/or central ventilatory integration has been suspected. Gozal et al. tested 17 patients with Prader-Willi syndrome and control subjects matched for age, sex, and body mass [48]. Hypoxic, hyperoxic, and hypercapnic challenges were compared. They found that patients with Prader-Willi syndrome did not respond to these stimuli. These observations indicate that abnormal ventilatory responses in these patients are, at least in part, due to dysfunction of the carotid body.

Sudden infant death syndrome

In a more common pediatric disorder, sudden infant death syndrome, some investigators have found either an increased or a decreased volume of the carotid body [49]. Overgrowth of sheath cells [50], reduction of dense core vesicles and glomus cell numbers [51], and increased content of dopamine and norepinephrine [52] have also been reported. However, the results of later studies with a larger number of subjects did not agree with these studies [53,54]. The exact cause of sudden infant death syndrome is not yet known, but it is likely that subtle abnormalities exist in the cardiorespiratory control systems [55–58]. Compromised carotid body function may influence the stability of the respiratory system in these patients. For example, parental smoking is a major risk factor for this syndrome [57,59–61], and animal experiments suggest that nicotine impairs carotid body function. Injection of nicotine into newborn rats and developing lambs reduced the hypoxic or hyperoxic ventilatory response [62,63]. Further, administration of nicotine to rats during gestation caused high mortality in newborns exposed to hypoxia [64].

Hypertension

Functional abnormality of the carotid body has been shown in patients with essential hypertension [65–67]. A

series of studies was conducted comparing carotid body function in young, mildly hypertensive subjects with that in age-matched normotensive subjects. Ventilatory and cardiovascular responses to hypoxia or hyperoxia were examined. The results indicated that reflex responses evoked by carotid body stimulation were significantly augmented in subjects with hypertension. Although increased size of the carotid body and hyperplasia of sheath cells were noted in established hypertensive subjects, it is not known whether the structural changes occur in the carotid body in an early phase [2]. Interestingly, the carotid body of the spontaneously hypertensive rat started to increase in size before the onset of hypertension [68].

Obstructive sleep apnea

Obstructive sleep apnea syndrome is a major health problem in the United States. A population study showed that approximately 2% of women and 4% of men suffer from this syndrome [69]. In Japan, lower rates in women (0.5%) and men (3.28%) were reported [70]. The disease is not rare in children, and a estimated 2%–4% of children are affected [71,72]. Patients with obstructive sleep apnea syndrome have a loss of upper airway muscle tone during sleep, resulting in collapse of the airway. This obstruction causes progressive hypoxemia and eventually evokes reflex arousal from sleep, restoring muscle tone to the upper airway. The cycle of sleep, airway obstruction, hypoxemia, and arousal is repeated. In severe cases, the cycle is repeated hundreds of times in a single night [73]. The carotid body plays an essential role in arousal. This has been experimentally shown in the dog [74] and the lamb [75]. In animals with a denervated carotid body, arousal did not occur even when oxygen saturation fell below 60%. The role of the carotid body in arousal has also been shown in humans. As mentioned above, patients with Prader-Willi syndrome lack the ventilatory response to acute hypoxia, hyperoxia, and hypercapnia, and hypoxia is not effective in arousing these patients from sleep [76]. A possible vulnerability to hypoxic death during sleep has been suggested for asthma patients with bilateral carotid body resection, although systematic studies are not available [77].

Carotid body excitation by hypoxemia during apnea also has cardiovascular effects. Increases in blood pressure and sympathetic discharge during airway obstruction in sleep are caused mainly by stimulation of the carotid body [78,79]. Obstructive sleep apnea syndrome is strongly associated with systemic hypertension. Although some controversy still exists, recent studies indicate that repeated excitation of the carotid body induces a prolonged increase in basal sympathetic discharge and daytime hypertension [80–83].

Because obstructive sleep apnea is a chronic disease, an important question is whether the function of the carotid body changes with time. In other words, does repeated intermittent hypoxia, as seen in obstructive sleep apnea syndrome, affect the function of the carotid body? Although some studies suggest that modification of carotid body function occurs [84], this is a new area of investigation, and we do not have enough reliable information at present. However, extensive investigation has been performed in various laboratories, including ours, and we can expect more information in the near future.

Anesthetic agents

Chemicals used as medicine could modify the function of the carotid body. For example, many anesthetics, such as halothane, enflurane, fentanyl, morphine, barbital, and propofol, inhibit carotid body excitation [85]. These anesthetic agents are known to influence various ion channels [85–88]. It is most likely that anesthetics also affect ion channels in the glomus cell and in the chemoreceptor afferent nerve endings. Few studies have been reported, but Buckler et al. have recently shown that halothane enhanced TASK-like K^+ channels in the rat glomus cell [35]. These channels are inhibited by hypoxia, hypercapnia, and acidosis and are considered the critical channels for hypoxic excitation of the rat glomus cell [89]. Halothane is known to inhibit the hypoxia-induced increase in neural output from the carotid body [90,91]. This phenomenon may be due to the augmentation of TASK-like channels. Anesthetic agents also influence the activity of ligand-gated ion channels. Excitation of $GABA_A$ receptors and inhibition of neuronal nicotinic ACh receptors (nAChRs) are associated with the mechanisms of general anesthesia [92–94]. These receptors are also present in the carotid body (see below).

Neuronal nAChRs in the carotid body and the effect of nondepolarizing muscle relaxants.

Neuronal nAChRs in the carotid body

ACh is synthesized in glomus cells [95], stored in the vesicles [96], and released on stimulation [14]. Exogenously applied ACh increases chemoreceptor afferent activity in many species (for reviews, see Eyzaguirre et al. [13] and Zapata [18]). Many studies have shown the presence of nAChRs on glomus cells and afferent nerve endings [7,97–101]. Blockers of nAChRs attenuate the chemoreceptor neural response to hypoxia [102–105]. These data indicate that ACh is a major excitatory neurotransmitter in the carotid body [16]. Hence, modification of ACh metabolism in the carotid body would

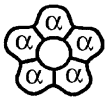
Type	Muscle	Neuronal	
Structure			
Subunits	α1, β1, δ, γ: fetal α1, β1, δ, ε: adult	α (2-6), β (2-4)	α (7-9)
Ca^{2+} permeability (Ca^{2+}/Na^{+})	0.2	1-1.5	20
EC50 for ACh	7 - 17 μM	0.3 - 100 μM (α4β2) 39 - 2919 μM (α3β4) 7 - 733 (α3β2)	112 - 320 μM (α7)
Antagonists	α-bungarotoxin α-conotoxin MI muscle relaxants	DHβE for α4β2>α3β2>α3β4 α-conotoxin AuIB for α3β4 α-conotoxin MII for α3β2 d-tubocurarine pancuronium (α4β2) vecuronium (?)	α-bungarotoxin methyllcaconitine α-conotoxin Iml d-tubocurarine vecuronium (?)

Fig. 2. Characteristics of nicotinic acetylcholine receptors (*nAChRs*). The subunit composition of nAChRs substantially differs in muscle-type and neuronal-type nAChRs. Nicotinic AChRs are cation channels. Ca^{2+} permeability varies depending on the receptor type, and neuronal nAChRs are highly permeable to Ca^{2+} [107,140]. Acetylcholine (*ACh*) binding sites are located at the interface between α and non-α subunits. The EC_{50} for ACh varies significantly among different types of nAChRs, experimental conditions, and fitting models [141–147]. The affinity of antagonists also varies among different nAChRs [107,148]. *DH*β*E*, Dihydro-β-erythroidine

affect the role of endogenous ACh in chemoreceptor neural activity. In this context it is important to understand that many anesthetics as well as neuromuscular blocking agents affect the function of nAChRs.

Nicotinic AChRs are ligand-gated cation channels made from five receptor subunits (Fig. 2). Muscle-type nAChRs are present on the muscle at neuromuscular junctions. These receptors are among the best-studied ligand-gated ion channels [106]. Nicotinic AChRs in neurons are distinct from muscle-type nAChRs and are divided into two types. One type is a heteromeric receptor composed of two α and three β subunits. The second type is a homomeric receptor made up of five α subunits (α7, 8, or 9). Knowing the subunit composition of nAChRs in a particular tissue is important, because the permeability of the receptor to Ca^{2+} and the effects of agonists and antagonists depend on the subunit composition [107].

Although autoradiographic studies have suggested the presence of nAChRs in the carotid body glomus cell of the cat, rabbit, and rat [7,97–99], their subunit composition was not known. Recently, we have applied molecular biological and immunocytological techniques and have found that the α3, α4, β2, and β4 subunits are localized in cat glomus cells (Hirasawa et al. [101] and unpublished observations). These subunits of nAChRs are widely distributed within the nervous system. It is believed that α4β2 type nAChRs are the major type in the central nervous system and that α3β4 type nAChRs are mainly localized in the sympathetic nervous system [107]. Although the exact structure of nAChRs in the cat carotid body cannot be evaluated from our molecular biological and immunohistological studies, patch-clamp studies (measuring ACh-induced current) and microfluorometric studies (measuring intracellular Ca^{2+}) suggest that α3β2 and possibly α4β2 nAChRs are the functionally major types in the glomus cell of the cat carotid body (Shirahata et al. [108] and unpublished observations). On the other hand, nAChRs on the afferent nerves appear to have a different subunit composition. Immunohistology showed that nerve fibers within and between the glomeruli (a group of glomus cells surrounded by sheath cells) expressed α7 subunits of nAChRs, but glomus cells did not [100]. Further, immunoreactivity for α3, α4, α7, and β2 subunits of nAChRs is found in the cell bodies of the majority of petrosal ganglion neurons, suggesting that these subunits are present in the chemosensory afferent neurons [100,101].

What are the roles of these nAChRs in chemotransmission of the carotid body? It appears that nAChRs in glomus cells modulate the release of neurotransmitters. It has been shown that the activation of nAChRs increases intracellular Ca^{2+} in glomus cells [108,109]. This increase can trigger the release of neurotransmitters. In fact, several reports indicate that nicotine increases the release of catecholamines [99,110,111]. Further, the activation of nAChRs in glomus cells may be involved in hypoxia-triggered neurotransmitter release. Dinger et al. showed that α-bungarotoxin inhibited hypoxia-induced dopamine release by 50% [99]. Our preliminary studies suggest that α4β2 nAChRs contribute to regulating catecholamine release during hypoxia [112]. Regarding a role of nAChRs in chemoafferent neurons, Nurse and his colleagues showed persuasive data indi-

cating that the activation of nAChRs in the chemoreceptor afferent neurons evokes action potentials in the rat [96,113,114]. Our data also showed that ACh triggered action potentials in some cat petrosal ganglion neurons [115].

Vecuronium and the carotid body

During general anesthesia, muscle relaxants are often used. Currently used neuromuscular blockers are believed to be specific for muscle-type nAChRs. However, a series of studies in humans has shown that nondepolarizing neuromuscular blockers, such as vecuronium and pancuronium, inhibit hypoxic ventilatory responses at very low concentrations [116–118]. Igarashi et al. hypothesized that vecuronium inhibits neuronal nAChRs in the carotid body, leading to depression of hypoxic ventilatory response [119]. To test this hypothesis, chemoreceptor neural activity was recorded from perfused rat carotid bodies in vitro. When perfusion was changed from hyperoxia to hypoxia, chemoreceptor neural activity increased as expected. This increase was significantly reduced when the carotid body was pretreated with vecuronium. The effect was somewhat dose-dependent (Fig. 3A). Further experiments confirmed that the inhibitory effect of vecuronium on hypoxic chemotransmission acts via the inhibition of nAChRs in the carotid body (Fig. 3B). ACh and nicotine increased chemoreceptor nerve activity, and this increase was inhibited by vecuronium. Thus, vecuronium inhibits the hypoxic response of the carotid body by blocking the nAChRs on the glomus cell and/or on the chemoreceptor afferent nerve endings. In the former case, vecuronium may attenuate the release of excitatory neurotransmitter(s) by inhibiting a nAChR-mediated increase in intracellular Ca^{2+} and nAChR-mediated depolarization of the glomus cell. In the latter case, vecuronium may reduce action potentials by inhibiting nAChR-evoked depolarization.

Inhibition of chemoreceptor nerve activity by vecuronium occurred at a dose lower than the ED_{50} for the phrenic nerve–hemidiaphragm preparation in rats [120,121]. In humans, the ventilatory response to hypoxia was depressed during continual administration of vecuronium with which a train-of-four-ratio was maintained at 0.7 [116–118]. These studies indicate that postoperative residual neuromuscular blockade may be a significant risk factor for the development of hypoxia.

Dopamine D2 receptors in the carotid body and the effect of dopamine

Dopamine is one of the most abundant neurotransmitters in the carotid body. It is synthesized in glomus cells and released during hypoxic stimulation (for a review, see Gonzalez et al. [3]). These facts suggested the possibility that dopamine was an excitatory neurotransmitter. This possibility has been extensively explored [3,18], but the preponderance of pharmacological and electrophysiological data do not agree with the hypothesis that dopamine is an excitatory neurotransmitter. For example, exogenously applied dopamine usually

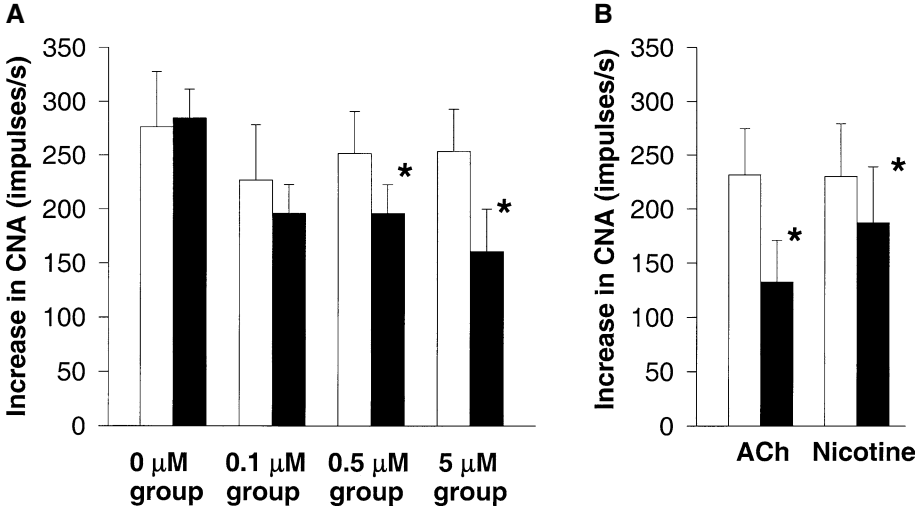


Fig. 3A,B. Effect of vecuronium on chemoreceptor neural activity (*CNA*) in rats. Experiments were performed in vitro. Data are reported as mean ± SEM. $N = 6$ in all groups. **A** Hypoxic response. *Open bars*, control; *filled bars*, vecuronium. Hypoxia increased chemoreceptor neural activity and vecuronium attenuated this response. **B** Cholinergic response. Both acetylcholine (*ACh*) and nicotine increased chemoreceptor neural activity. These increases were significantly attenuated by vecuronium. *Asterisk*, significantly different from control ($P < 0.05$). In the rat, 5.2 μM vecuronium inhibited the contraction of the diaphragm by 50% [120]. Modified from Igarashi et al. [119], with permission

reduces chemoreceptor neural activity (for reviews, see Fidone et al. [8], Eyzaguirre et al. [13], Zapata [18]). Dissociation between catecholamine release and chemoreceptor neural response has also been reported [122–124]. Based on all the data, the generally accepted current understanding is that dopamine is an inhibitory neurotransmitter in the carotid body. In certain conditions (e.g., administration of a large dose), dopamine could work as an excitatory neurotransmitter. This excitatory effect may be mediated via one of the serotonin receptors (5-HT_3 receptors), but not via dopamine receptors [125]. Among five types of dopamine receptors, the expression of mRNA for D2 receptors in the carotid body has been shown in the rat, rabbit, and cat [126–128]. Our immunocytochemical studies showed that D2 receptor proteins are present in cat glomus cells and petrosal ganglion neurons (unpublished observations). Although extensive effort has shown the expression of D1 receptor mRNA in the rabbit, cat, and rat carotid body [129], level of the expression is very low. Hence, it is most likely that exogenously applied dopamine inhibits carotid chemoreceptor neural activity by activating D2 receptors. D2 receptor agonists inhibit chemoreceptor neural activity [130], and inhibiting D2 receptors increases spontaneous chemoreceptor neural activity at any level of PO_2 [131–133].

Dopamine is often used during surgery and in postoperative management. Ide et al. investigated whether a clinical dose of dopamine affected carotid body function [134]. In anesthetized cats, continuous infusion of dopamine ($5\,\mu g \cdot kg^{-1} \cdot min^{-1}$) significantly depressed the chemoreceptor neural response to hypoxia (Fig. 4A). This inhibition correlated well with the depression of the hypoxic ventilatory response during dopamine infusion (Fig. 4B). These results suggest that a clinical dose of dopamine inhibits hypoxic ventilatory response by activating D2 receptors in the carotid body. Consistent with our studies, van de Borne et al. showed that dopamine infusion ($5\,\mu g \cdot kg^{-1} \cdot min^{-1}$) depressed the ventilatory response to hypoxia in normal subjects, and that it depressed ventilation even during normoxia in patients with heart failure [135]. These data suggest that close ventilatory monitoring is necessary for patients receiving dopamine.

$GABA_A$ receptors in the carotid body and the effect of benzodiazepines

Although its role in the carotid body is not known, gamma-aminobutyric acid (GABA) is localized in glomus cells [136]. Immunocytochemical experiments revealed that $GABA_A$ receptors are localized in the nerve fibers within the carotid body and some neurons in the petrosal ganglion in the cat, suggesting that the chemoreceptor afferent nerve has $GABA_A$ receptors (unpublished observations). Because benzodiazepines bind $GABA_A$ receptors, Igarashi et al. examined whether benzodiazepines affected the hypoxic response of the carotid body [137]. Relatively low doses of midazolam and diazepam reduced the chemoreceptor neural response to hypoxia (Fig. 5A). This depression was reversed by bicuculline, a $GABA_A$ receptor antagonist (Fig. 5B). Therefore, it is reasonable to conclude that midazolam and diazepam inhibit the hypoxic response of the carotid body by activating $GABA_A$ receptors on the chemoreceptor afferent. The well-known ventilatory depression by benzodiazepines [138,139] appears partly due to inhibition of chemoreceptor afferent activity.

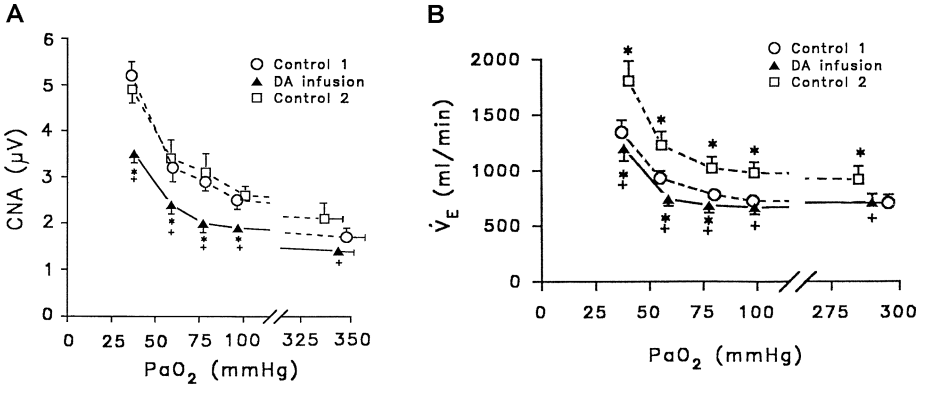


Fig. 4A,B. Effects of dopamine on chemoreceptor neural activity (*CNA*) and ventilation. Experiments were performed in anesthetized cats. **A** A continuous infusion of dopamine ($5\,\mu g \cdot kg^{-1} \cdot min^{-1}$) attenuated chemoreceptor neural activity at any level of PaO_2. **B** Dopamine (*DA*) infusion ($5\,\mu g \cdot kg^{-1} \cdot min^{-1}$) significantly attenuated the ventilatory response to hypoxia. *Open circles*, control 1 (before dopamine infusion); *closed triangles*, dopamine infusion; *open squares*, control 2 (after dopamine infusion); *asterisk*, significantly different from control 1 ($P < 0.05$); *plus sign*, significantly different from control 2 ($P < 0.05$). Modified from Ide et al. [134], with permission

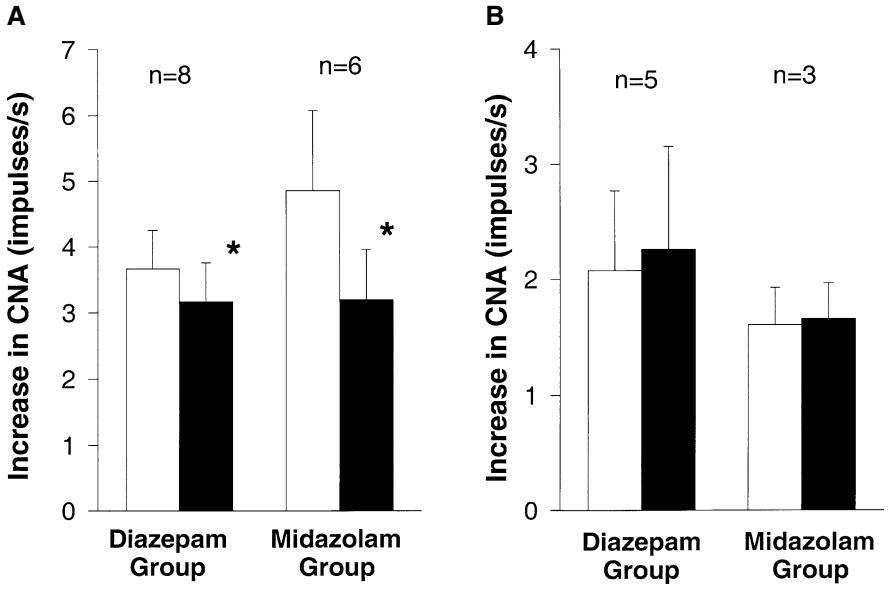


Fig. 5A,B. Effect of benzodiazepines (diazepam and midazolam) on chemoreceptor neural response to hypoxia. Experiments were performed in vitro using cat carotid bodies. Carotid bodies were perfused with modified normoxic or hypoxic Krebs solution. Chemoreceptor neural activity (*CNA*) was recorded from a whole carotid sinus nerve after barodenervation. **A** Before the administration of bicuculline both diazepam (10 μM) and midazolam (3.3 μM) attenuated the chemoreceptor neural response to hypoxia. *Open bars*, without benzodiazepine; *filled bars*, with benzodiazepine. **B** After administration of bicuculline (10 μM), a $GABA_A$ receptor antagonist, the inhibitory effect of diazepam and midazolam on the chemoreceptor neural response to hypoxia was eliminated. *Asterisk*, significantly different from the neural activity without benzodiazepine ($P < 0.05$)

Summary and clinical implications

Recent investigations have revealed that the carotid body plays a significant role in basal ventilation as well as in various health conditions by changing the neural output to the brain. Various neurotransmitters are critically involved in chemotransmission of the carotid body. Medical agents used for anesthetic management influence chemotransmission of the carotid body at many different levels. I have give the following examples: vecuronium inhibits carotid body excitation by blocking nAChRs in the carotid body; continuous infusion of dopamine inhibits carotid body excitation possibly by acting on D2 receptors in the carotid body; and benzodiazepines inhibit carotid body excitation by activating $GABA_A$ receptors in the carotid body. In clinical settings, these agents are usually used with other anesthetics that have various effects on ion channels and other neurotransmitter receptors [85–88,92,93]. It is known that halothane, enflurane, fentanyl, morphine, barbital, and propofol inhibit carotid body excitation [85]. Combined use of these anesthetics and some agents described above (e.g., vecuronium) could profoundly inhibit carotid chemoreceptor neural output. Neurotransmission in the carotid body is complicated, and many aspects are still under investigation. Understanding neurotransmission in the carotid body, as well as assessing background health problems that are related to carotid body function, is important for the perioperative management of respiratory function.

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