Oxygen-sensing neurons in the central nervous system

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Neubauer, Judith A., and Jagadeeshan Sunderram. Oxygen-sensing neurons in the central nervous system. J Appl Physiol 96: 367–374, 2004; 10.1152/japplphysiol.00831.2003.—This mini-review summarizes the present knowledge regarding central oxygen-chemosensitive sites with special emphasis on their function in regulating changes in cardiovascular and respiratory responses. These oxygen-chemosensitive sites are distributed throughout the brain stem from the thalamus to the medulla and may form an oxygen-chemosensitive network. The ultimate effect on respiratory or sympathetic activity presumably depends on the specific neural projections from each of these brain stem oxygen-sensitive regions as well as on the developmental age of the animal. Little is known regarding the cellular mechanisms involved in the chemotransduction process of the central oxygen sensors. The limited information available suggests some conservation of mechanisms used by other oxygen-sensing systems, e.g., carotid body glomus cells and pulmonary vascular smooth muscle cells. However, major gaps exist in our understanding of the specific ion channels and oxygen sensors required for transducing central hypoxia by these central oxygen-sensitive neurons. Adaptation of these central oxygen-sensitive neurons during chronic or intermittent hypoxia likely contributes to responses in both physiological conditions (ascent to high altitude, hypoxic conditioning) and clinical conditions (heart failure, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, hyperventilation syndromes). This review underscores the lack of knowledge about central oxygen chemosensors and highlights real opportunities for future research.

C3: sympathoexcitatory region; pre-Boëtzinger complex; caudal hypothalamus; chemosensitivity; brain; heme oxygenase; ion channels

CENTRAL SITES OF OXYGEN SENSITIVITY

Although many autonomic functions change their activity in response to hypoxia, overall survival is critically linked with appropriate changes in the cardiovascular and respiratory systems to maintain oxygen delivery to tissues. Central oxygen-sensitive sites that direct respiratory and sympathetic activity have been identified in the thalamus, hypothalamus, pons, and medulla (29, 59, 69, 81, 126, 132). Activation of these oxygen-sensitive sites produce increases in sympathetic and respiratory activity or, in the fetus, in which increasing respiratory efforts are further by “channel” arrest (10). However, not all neurons reduce their activity during hypoxia. In some hypoxia-tolerant species, e.g., painted turtles, the metabolic cost of ion pumping is reduced even further by “channel” arrest (10). However, not all neurons reduce their activity during hypoxia. There are populations of neurons in the brain that act in a way analogous to classical oxygen chemosensors. These central oxygen sensors presumably monitor brain oxygen levels and, when activated, coordinate critical functions necessary for the overall survival of the whole organism. By remaining “vigilant,” these chemosensors are likely important in both short-term and long-term adaptations to hypoxia (11).

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response to hypoxia in the neonate and the hypoxic ventilatory decline in the adult.

The majority of studies suggest that this inhibitory chemosensitive network resides within the pons and thalamus. Lesions of the rostral pons reverse hypoxic inhibition of respiration in fetal sheep (29) and respiratory depression in neonatal rabbits (81). With the use of unilateral focal cooling or c-fos expression, hypoxic inhibition of respiration has been found to require areas of the dorsal pons proximate to the locus ceruleus and ventral to the parabrachial nucleus near the Kölliker-Fuse nucleus (17, 89). What these studies do not address is whether these regions are directly oxygen chemosensitive or are relay sites for an oxygen sensor located at a distant site, e.g., the thalamus. For example, lesions in or near the red nucleus and parafascicular nucleus of the thalamus can reduce or abolish central hypoxic inhibition or depression of respiration in fetal, neonatal, and adult animals (69, 80, 142). In addition, there is evidence that neurons within the red nucleus (1) and the parafascicular nucleus may be directly excited by hypoxia (72). Taken together, these observations suggest that one function of the brain stem oxygen-chemosensitive network is to mediate a respiratory inhibition.

Sympathetic and respiratory excitation. The recent use of c-fos expression has enabled many investigators to map brain stem areas activated during exposure to hypoxic hypoxia both in vivo, with and without peripheral chemoreceptor denervation (9, 33, 34, 57, 58, 74, 87, 138), and in vitro with the use of a brain stem-spinal cord preparation (15) as well as during exposure to carbon monoxide in the rat (16). Although these approaches avoid the influence of peripheral chemoreceptor activation and provide a useful mapping of brain stem regions activated by hypoxia, they are limited in their ability to distinguish these sites as oxygen sensors. There are, however, several studies that have identified regions of the caudal hypothalamus and rostral ventrolateral medulla (RVLM) that are directly excited by hypoxia, which, when activated, increase sympathetic and respiratory activity. For example, both in vivo and in vitro studies have shown that the posterior hypothalamus contains neurons intrinsically sensitive to hypoxia, which increase sympathetic activity, blood pressure, and heart rate (31, 32, 59, 60). Activation of these caudal hypothalamic regions during hypoxia also increases respiration (59). In addition, there is evidence that these hypothalamic oxygen-sensitive regions project to the sympahtoexcitatory C1 region and ventral respiratory regions in the medulla (72). Again, these studies suggest that an oxygen-chemosensitive network exists within the brain stem.

Medullary regions that are hypoxia chemosensitive include the nucleus tractus solitarius (NTS), the C1 sympathetic region, and the pre-Bötzinger complex. The hypoxic sensitivity of the NTS is a recent addition to the medullary oxygen-sensitive sites. Hypoxia was found to depolarize one-third of NTS neurons in a medullary slice of the rat brain stem (101). Of interest is that progesterone was found to modulate the responses of NTS neurons by increasing the excitability in hypoxia-depressed neurons and decreasing excitability in hypoxia-excited neurons. This seemingly paradoxical effect may provide some insight into how progesterone stabilizes breathing during hypoxia and, perhaps, why women are less likely to develop periodic breathing during sleep.

Much recent work has focused on the hypoxia-chemosensitive regions in the RVLM, the C1 sympahtoexcitatory region (97, 132), and the respiratory pre-Bötzinger complex (112, 126). The C1 region contains neurons that are important for the generation of tonic vasomotor tone and the integration of reflex changes in blood pressure (116), whereas the pre-Bötzinger complex is the putative site of respiratory rhythm generation (23, 119, 124). The anatomic juxtaposition of these two hypoxia-sensitive regions may suggest that they share a common oxygen-sensing mechanism but remain phenotypically and functionally distinct through differences in their expression of receptor types and neuromodulator as well as separate sympathetic and respiratory projections.

The C1 region was identified as an intrinsic oxygen-sensitive site as a result of a number of observations. First, hypoxia increases sympathetic activity in the absence of peripheral chemoreceptors, suggesting a central site of excitation (147). Second, although hypothalamic and thalamic oxygen-sensitive regions could increase sympathetic activity through projections to sympathoexcitatory neurons in the C1 region, the C1 region also increases its activity during cerebral ischemia (51) and systemic hypoxia (132). That the C1 region is directly excited by hypoxia has been established by microinjecting sodium cyanide to produce local hypoxia, which resulted in an increase in tonic sympathetic nerve activity (86) that is dose dependent and reversible (131, 132) and specific to hypoxia and not hypercapnia and acidosis (132).

The pre-Bötzinger complex, located just rostral to the C1 region, is also directly excited by local hypoxia (126). Microinjection of a glutamate analog or sodium cyanide into the pre-Bötzinger complex produces respiratory excitation in the form of augmented respiratory bursts (gasp or sigh-like) (125, 126). The survival value of ascribing an oxygen sensitivity to the pre-Bötzinger complex is likely due to its ability to elicit gasps and sighs. Gasping is a highly effective gas-exchange pattern essential for autoreuscitation (50), and failure to gasp has been implicated in sudden infant death syndrome (40). Spontaneous sighs, which are a common feature of normal respiration occurring during both wakefulness and sleep (62, 107, 139), are modified by various afferent inputs (5, 8, 22, 42, 121), especially hypoxia (134). Of interest is that, during sleep, the majority of sighs are associated with electroencephalographic signs of arousal (107, 149), which in the context of obstructive sleep apnea syndrome (OSAS) may be important for breaking an apnea. The pre-Bötzinger complex may also receive projections from rostral brain sites, some of which may have oxygen-chemosensitive properties. For example, the increase in respiratory frequency that occurs with hypoxic activation of the caudal hypothalamus could represent a projection from that region to the pre-Bötzinger complex. Of interest along these lines is that microinjection of sodium cyanide into the paraventricular nucleus of the rat increased frequency of “yawning,” assessed as a large inspiration with mouth opening (68). If “yawning” is another form of augmented breaths, it again suggests that an oxygen-chemosensitive network exists within the brain stem that is capable of regulating the activity of the respiratory rhythm generator.

MECHANISMS FOR SENSING HYPOXIA

The mechanisms for sensing hypoxia need to be considered with regard to whether the hypoxic exposure is acute, sustained, chronic (e.g., high altitude or chronic obstructive pul-
monary disease), or intermittent (e.g., OSAS or hypoventilation syndrome), with the latter capable of inducing long-term adaptive or maladaptive responses. The neuronal responses to hypoxia likely reflect neurophysiological changes due to changes in the function of ion channels, oxygen sensors (e.g., heme proteins), signaling pathways, neuromodulators, and genomic processes. Some of these topics have been recently reviewed (79, 93, 95, 102, 104); therefore, this review will only highlight those mechanisms that may be relevant for central oxygen sensitivity.

**Ion channels.** A number of ion channels are modulated by hypoxia in ways that can result in depolarization and increased excitability of cells, including $K^+$, $Ca^{2+}$, and $Na^+$ channels. This suggests that a diversity of oxygen-transducing mechanisms could exist dependent on the cell type and the complement of ion channels expressed in the cell. Observations made in carotid body glomus cells and pulmonary vascular smooth muscle cells suggest some conservation of oxygen chemotransduction, which may be transferable to oxygen-sensitive neurons in the brain. From studies in the carotid body, two major hypotheses of oxygen transduction have evolved: the “metabolic hypothesis,” which proposes a major role for the mitochondrial oxidative transport chain, and the “membrane hypothesis,” which proposes a central role for an ion channel that either directly senses oxygen or has its conductance regulated by a membrane-bound protein. These two hypotheses of oxygen transduction in the carotid body have been recently reviewed (109).

$K^+$ channels. The identification of an oxygen-sensitive $K^+$ channel offered strong support for the concept of a membrane-delimited oxygen-sensing process. Hypoxia (in the range of 120–70 Torr) decreases the $K^+$ current in isolated glomus cells (78), which presumably produces a depolarization, an opening of voltage-gated $Ca^{2+}$ channels, and an increase in intracellular $Ca^{2+}$, the release of neurotransmitters, and an activation of sensory afferent nerves. Hypoxic inhibition of $K^+$ channels has now been demonstrated in several other hypoxia-sensitive tissues, including the pulmonary vasculature (148), airway neuroepithelial bodies (151), H146 cells (99), adrenal chromaffin cells (140), PC-12 cells (153), and central neurons (63). In addition, the addition of $C_i$ hypoxia-chemosensitive neurons is also associated with a reduced $K^+$ current (145) and an increased $Ca^{2+}$ conductance (133).

There are a wide variety of $K^+$ channels that, when modulated by hypoxia, could lead to an increased excitability, including “leak” $K^+$ currents and $Ca^{2+}$-activated $K^+$ channels. For example, hypoxia has recently been shown to inhibit an acid-sensitive, voltage-independent leak $K^+$ current (TASK-1) in glomus cells (20). Leak currents are instantaneous open-rectifier currents, which influence both resting membrane potential and the duration of the action potential. The oxygen sensitivity of TASK-1 channels in the carotid body is presumably not mediated through an inhibition by acidosis but represents a unique regulation of this channel by oxygen. The mechanism that confers this unique oxygen sensitivity to TASK-1 channels is presently unknown, but recent theories have postulated roles for a membrane-bound protein (114) or metabolic signal (19) in ion channel regulation. TASK-1 channels are expressed in several brain regions, including the cerebellum, locus coeruleus, raphe nucleus, hypoglossal motor neurons, NTS, thalamus, and hypothalamus (6, 84, 123, 136, 137, 146). In addition to TASK-1 channels, TASK-3 channels are also abundant in the brain (137). Because inhibition of TASK-3 channels has been shown to abolish the reduction of $K^+$ current during hypoxia in H146 cells (54), TASK-3 channels could possibly play a role in the oxygen transduction of central chemosensors. However, whether these leak channels are important in the oxygen sensing of central oxygen-sensitive neurons has not been established.

Large-conductance $Ca^{2+}$-activated $K^+$ channels are also inhibited by hypoxia in carotid body glomus cells (103, 114), and hypoxia reduces the activity of small-conductance $Ca^{2+}$-activated $K^+$ channels (SK2 subtype) in adrenal chromaffin cells, suggesting that closure of SK2 channels may initiate $Ca^{2+}$ influx and catecholamine secretion in the adrenal medulla (67). These voltage-gated $K^+$ channels have an oxidoreductase active site that may couple cellular redox regulation to channel gating (2). Other possible ways that hypoxia may alter $K^+$ conductance would be through activation of ATP-activated $K^+$ channels (64) or modulation of G-protein-coupled inward-rectifying $K^+$ channels by neuromodulators, e.g., 5-hydroxytryptamine (7).

$Ca^{2+}$ channels. Voltage-gated $Ca^{2+}$ channels are the primary means of $Ca^{2+}$ influx into the cell and hence are critical for the myriad cellular functions that are $Ca^{2+}$ dependent. In general, the activation of these $Ca^{2+}$ channels is regulated by changes in membrane potential, mediated principally by changes in $K^+$ channel activity. Nevertheless, some evidence suggests that $Ca^{2+}$ channels may be directly sensitive to changes in the level of $O_2$. For example, although an early study suggested that voltage-gated $Ca^{2+}$ channels in carotid body glomus cells are inhibited by hypoxia (88), presumably through a reduction in low-voltage-activated $Ca^{2+}$ channels, a more recent study has shown that L-type $Ca^{2+}$ currents are increased via a protein kinase C-dependent mechanism (130). Activation of L-type $Ca^{2+}$ channels in brain stem neurons has also been shown. In this case, hypoxia-induced glutamate release in medullary tissue slices of mice was found to bind to metabotropic receptors of inspiratory neurons, activating L-type channels (85). It was suggested (85) that blocking L-type $Ca^{2+}$ channels in mouse medullary slice preparations could block the excitation of inspiratory neurons. Some indirect support for a hypoxic activation of $Ca^{2+}$ current in the hypoxia-sensitive neurons in the RVLM comes from studies that used patch-clamp recordings in dissociated neurons (66, 82).

$Na^+$ channels. The classical voltage-activated $Na^+$ current is characterized as a tetrodotoxin-sensitive, rapidly activated inward current that inactivates slowly within tens of milliseconds. There is evidence in cortical neurons, which are depressed by hypoxia, that this transient $Na^+$ current is reduced during hypoxia due to an increased probability of inactivation (26). This response could be considered protective since it would lead to a decreased load on the $Na^+$-$K^+$-ATPase and a reduction in energy consumption. The use of whole cell patch-clamp recordings has led to the discovery of a persistent $Na^+$ current that is small in amplitude (1–4% of total $Na^+$ current amplitude), activated at more negative membrane potentials, and resistant to inactivation (24). Although the current is small, it can produce significant increases in intracellular $Na^+$ concentration if activated for several seconds. Increased intracellular $Na^+$ concentration during hypoxia has been shown to precede an increase in intracellular $Ca^{2+}$ concentration (39), an
observation that has led to the proposal that it contributes to the increase in intracellular Ca$^{2+}$ concentration by reversing the Na$^+$/Ca$^{2+}$ exchanger (53). Direct recordings of the persistent Na$^+$ current from inside-out patches of hippocampal neurons has shown that hypoxia (in the range of 45–0 Torr) and sodium cyanide increase the current by ~20-fold (52). The proposal that activation of the persistent Na$^+$ current leads to cell damage during anoxia would make it seem counterintuitive to propose its importance as part of the oxygen-sensing mechanism for central oxygen-sensitive neurons, but it may be one of degree and duration of the hypoxia. It is difficult to come to any conclusion regarding the importance of this current in the chemotransduction of hypoxia because there is limited information on the effect of hypoxia on Na$^+$ currents in oxygen-sensitive neurons. However, hypoxia has been shown to enhance both the rapidly inactivating and persistent Na$^+$ currents in acutely dissociated caudal hypothalamic neurons, which may suggest their importance in the excitation of these neurons during acute hypoxia (61). Because the persistent Na$^+$ current is important for intrinsic pacemaker activity in neurons, it is not surprising that it is present in neurons in the pre-Bötzinger complex (30, 118), the site of respiratory rhythm generation and oxygen sensitivity. Likewise, the intrinsic pacemaker activity and chemosensitivity of the C1 sympathoexcitatory region would also suggest a prominent role for the persistent Na$^+$ current.

Variable results have been reported for the effect of chronic hypoxia on the expression of Na$^+$ channels. Na$^+$ channel mRNA and saxitoxin binding (due to a decrease in binding sites, not affinity) have been shown to be decreased in adult rat brains exposed to chronic hypoxia (month) but increased in fetal brains (150). This was due to variable decreases in most brain regions with some exceptions (e.g., ventroposterior thalamic nuclei). In contrast, chronic hypoxia has been reported to induce Na$^+$ channels in PC-12 cells (128) and carotid body glomus cells (129). The presence or absence of neurotrophic factors may be important for explaining different effects of chronic hypoxia since the upregulation of Na$^+$ channels with chronic hypoxia may be dependent on neurotrophic factors (65, 75, 108), some of which may increase during hypoxia (135).

**Oxygen sensors.** Although differences in the relative proportions of these hypoxia-sensitive ion channels might help to explain the oxygen sensitivity of a neuron, most working hypotheses incorporate the notion that an oxygen sensor modulates ion channel activity. It seems likely that the mechanism of hypoxic sensitivity of these central cardiorespiratory neurons may be analogous to other oxygen-sensing organs such as the carotid body or pulmonary vasculature (79, 90, 91, 109, 152). In the carotid body, two recent hypotheses have gained prominence (73, 79, 109). The first theory proposes that there is a redox modulation of channels through changes in the ratio of redox couples. For example, if hypoxia increases the relative amounts of the reduced form of cytosolic glutathione and nicotinamide adenine dinucleotide (NADH), these could inhibit K$^+$ channels in carotid body glomus cells and pulmonary vascular smooth muscle cells. Although redox control of ion channel activity may contribute to the overall level of activity, these agents have not been regarded as O$_2$ sensors. Instead, the consensus is that the O$_2$ sensor involves heme-type oxygen-sensing protein (73) that is likely membrane bound (114). In support of this theory, Cross et al. (25) found a photometrically measurable heme signal that increased with hypoxia, a response that could be attenuated by inhibiting NAD(P)H oxidase. They suggested that this heme protein could contribute to chemoreception in the carotid body by regulating ion channel conductance through its ability to alter the production of H$_2$O$_2$, which changes protein conformation by inducing changes in the glutathione/GSSG redox system. Because cGMP levels decrease in the carotid body during hypoxia (143), another likely possibility is that the regulation of ion channel conductance is due to a heme protein linked to guanylyl cyclase. Two such proteins present in the carotid body are nitric oxide synthase (NOS) and heme oxygenase (HO). NOS, which is present in nerve endings, is important in efferent inhibition of the carotid body (144), whereas inhibition of HO with metalloporphyrins markedly increases the afferent activity of the carotid body (111). Recent work from our laboratory (83) has shown that HO is expressed in the C1 region and pre-Bötzinger complex of the RVLM. However, in contrast to its inhibitory function in the carotid body, results from our laboratory (27, 28) have shown that HO is necessary for the hypoxic excitation of these central medullary neurons.

**ADAPTATION OF CENTRAL OXYGEN SENSITIVITY**

Just as the peripheral chemoreceptors undergo adaptation in response to sustained or chronic hypoxia, it is likely that central oxygen sensors also adapt when subjected to sustained, chronic, or intermittent hypoxia. The net effects of these peripheral and central adaptations will ultimately determine the sympathetic and respiratory responses to chronic or intermittent hypoxia. The response to short-term sustained hypoxia is a respiratory decline, followed by enhanced respiratory and sympathetic activity if the hypoxia is sustained for days to years. If the hypoxia is intermittent, variable responses occur depending on the degree of hypoxia and the duration and frequency of the episodes. A great deal of data has been accumulated on the responses to sustained and chronic hypoxia in general, but little information is available on their effects on the central oxygen chemosensors. It does appear that these neurons adapt to chronic hypoxia because the sensitivity of RVLM neurons to hypoxia is enhanced after 4–5 days of chronic hypoxia (98). It seems likely that the specific nature of these adaptations will involve changes in signaling pathways (e.g., reactive oxygen species, mitogen-activated protein kinase), neuromodulators, and their receptors (e.g., opioids, nitric oxide, substance P, catecholamines, glutamate, GABA) and genomic effects with upregulation or downregulation of hypoxia-sensitive gene products (e.g., hypoxia inducible factor-1α, NF-κB, inducible NOS, HO-1).

**CLINICAL RELEVANCE AND FUTURE DIRECTIONS**

Considering the paucity of information regarding the cellular mechanisms of oxygen transduction in the central oxygen chemosensors, this field offers a broad range of research opportunities. The physiological and clinical relevance of such studies would go a long way toward enhancing our understanding of the role of the central oxygen chemosensors in the respiratory and sympathetic adaptations observed on ascent to high altitude or with the chronic sustained hypoxemia associated with cardiovascular and respiratory diseases (e.g., heart failure, chronic obstructive pulmonary disease) and chronic
OXYGEN-SENSING NEURONS IN THE CENTRAL NERVOUS SYSTEM

intermittent hypoxia associated with OSAS and hypoventila-
tion syndromes and infants at risk for sudden infant death.
Recently, there has been an intense focus on the chronic
intermittent hypoxia associated with OSAS because of its
potential for mediating many comorbid consequences such as
hypertension (35, 96, 106), increased sympathetic tone (21,
127), altered respiratory responses (92), and neurocognitive
deficits (43, 113, 115). Although the obstructive events pro-
duce hypoxemia as well as hypercapnia, arousals, and sleep
fragmentation, several studies have shown a major role for the
hypoxemia in mediating the consequences of obstructive sleep
apnea (36, 55, 76, 122, 141). For example, chronic intermittent
hypoxia alone can induce a persistent hypertension (18, 38)
due to elevated sympathetic tone (14, 37), enhance the sym-
pathetic and blood pressure responses to acute hypoxia and
hypercapnia (48, 56, 71), increase the sensitivity of the carotid
body (105, 110), increase the hypoxic ventilatory response (41,
45, 120), increase ventilatory long-term facilitation (77), de-
crease the duration of gasps (46), impair spatial learning (117),
decrease the excitability of hippocampal neurons (49), and
alter the expression of stress-related proteins in the CA1 region
of the hippocampus (47). Even short-term intermittent hypoxia
induces ventilatory (100) and phrenic (3, 4) long-term facili-
tation and reduces hypoxic ventilatory decline (44). These
results suggest that intermittent hypoxia produces adaptations in
the central nervous system that generally enhance the sen-
titivity of the sympathetic output, diminish the hippocampal
mechanisms associated with learning and memory, and pro-
duce increases or decreases in respiratory responses that are
likely to depend on the site of action in the respiratory neural
network. The neural site(s) responsible for the adaptive
changes in sympathetic and respiratory responses is not fully
known; however, the C1 sympathoexcitatory region and pre-
Bötzinger complex in the RVLM are likely potential sites of
adaptation. Future studies directed at dissecting the mechani-
cisms of central oxygen sensitivity acutely and examining how
sustained and intermittent hypoxia alter the sensitivity could
provide insights useful for developing novel therapeutic inter-
ventions for these syndromes.

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OXYGEN-SENSING NEURONS IN THE CENTRAL NERVOUS SYSTEM

Invited Review


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Invited Review

OXYGEN-SENSING NEURONS IN THE CENTRAL NERVOUS SYSTEM


