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Hypoxia-Induced Changes in Neuronal Network Properties

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Abstract

Because of their high energetic demand, neurons within the mammalian central nervous system are extremely sensitive to changes in partial pressure of oxygen. Faced with acute hypoxic conditions, an organism must follow a complex and highly dynamic emergency plan to secure survival. Behavioral functions that are not immediately essential for survival are turned off, and critical behaviors (such as breathing) undergo a biphasic response. An augmentation of breathing is initially adaptive, whereas prolonged hypoxic conditions are better served by an energy-saving mode. However, the hypoxic response of an organism depends on many additional factors. Environmental conditions, the animal's age and health, and the pattern (continuous vs intermittent) and duration (chronic vs acute) of hypoxia greatly determine the specific course of a hypoxic response. Different forms of hypoxia can cause pathology or be used as therapy. Therefore, it is not surprising that the hypoxic response of an organism results from widespread and highly diverse reconfigurations of neuronal network functions in different brain areas that are accomplished by diverse hypoxic changes at all levels of the nervous system (i.e., molecular, cellular, synaptic, neuronal, network). Hypoxia-induced changes in synaptic transmission are generally depressive and result primarily from presynaptic mechanisms, whereas changes in intrinsic properties involve excitatory and inhibitory alterations involving the majority of K^+, Na^+, and Ca^{2+} channels. This article reviews the response of the nervous system to hypoxia, accounting for all levels of integration from the cellular to the network level, and postulates that a better understanding of the diversity of cellular events is only possible if cellular and network events are considered in a functional and organismal context.

Index Entries: Hypoxia; synaptic properties; intrinsic properties; neuronal networks; respiratory network.

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Introduction

Because of its role as the final acceptor of electrons in the mitochondrial respiratory chain, allowing adenosine triphosphate (ATP) synthesis via oxidative phosphorylation, oxygen is essential for the homeostasis and survival of cells in aerobic organisms *(1).* A lack of oxygen can be detrimental and may eventually lead to the death of the organism. Therefore, many strategies have evolved to ensure adequate oxygen supply and to detect and respond to changes in oxygen levels. Although most cells have some ability to sense and respond to oxygen changes, this issue has been best studied in specialized oxygen-sensing cells, including carotid body chemoreceptors *(2–5),* pulmonary neuroepithelial bodies *(6,7),* adrenal chromaffin cells *(8),* vascular smooth muscle cells *(3,9,10),* and central neurons *(11–17).*

Hypoxia, a deficiency of oxygen reaching the tissues of the body, can be caused by a reduction in partial pressure of oxygen (PO_2) in the environment, inadequate oxygen transport, or the inability of tissues to use oxygen. Extreme environmental conditions such as those found at high altitudes or in the deep sea may lead to hypoxia; however, several species of animals survive in extreme conditions *(18–24).* Hypoxia is often associated with a diverse number of pathological conditions, such as those leading to insufficient blood flow to tissue (e.g., cerebrovascular hemorrhage, vascular occlusion, cardiac arrest, and bypass surgery) or respiratory dysfunction (obstruction of airway, lung dysfunction, or neural control failure).

In recent years, much progress has been made in unraveling the cellular and molecular events caused by hypoxia *(3–17).* These studies have revealed an overwhelming complexity and diversity, which unfortunately did not necessarily lead to a better understanding of how an organism responds to hypoxia. Neurons located within the same area of the nervous system can depolarize or hyperpolarize, and these membrane changes can be caused by activating and/or inactivating inward and outward currents involving many different ionic channels and receptors as well as second messenger systems. However, researchers have learned that there is no single unifying cellular mechanism to explain how the nervous system responds to hypoxia. In retrospect, this outcome may not be surprising.

An organism must respond to hypoxia in an adaptive manner. To be adaptive, however, there cannot be a single, stereotypic response to hypoxia. The way by which an organism responds to hypoxia depends on the type of hypoxic conditions (acute vs chronic, intermittent vs continuous) as well as on the health and the age of the organism—to name just a few factors. To generate these adaptive responses, neuronal functions must be regulated in a heterogeneous manner. Consider acute hypoxia: those functions that are not immediately essential for survival must be turned off to save metabolic energy, whereas functions that are critical for the immediate survival must be maintained. Heterogeneous is also the timecourse of these regulatory processes. It may be advantageous to initially augment autonomic functions that enhance oxygen supply and reduce oxygen consumption. During prolonged hypoxia, however, oxygen conservation becomes more important than trying to enhance oxygen supply that may remain absent for longer time. We suggest that cellular responses to hypoxia must be considered in this functional context. The overwhelming cellular heterogeneity and inconsistency might be understood only when considered in the context of a network and behavioral function. Several experimental approaches have been used to unravel the molecular and cellular mechanisms underlying the hypoxic responses of neuronal networks, including the use of in vivo and in vitro preparations *(14,25–34).* Functional in vitro slice preparations have proved to be particularly useful, because these preparations allow a rigorous combination of cellular and systems level approaches *(14,25,30,31,35–43).*

The goal of this article is not to provide a complete description of the cellular responses of

the nervous system; rather, this article focuses on a discussion of cellular responses in the context of network functions. We conclude that to understand how the nervous system responds to hypoxia, more studies integrating cellular and systems level approaches are needed. However, this is not an easy task, because the hypoxic response of the mammalian brain is extremely heterogeneous. For example, the response to acute hypoxia is considerably different from the response to chronic hypoxia. Moreover, the response to acute, severe hypoxia is not the same as the response to mild, chronic hypoxia, which is not the same as the response to intermittent hypoxia. These types of hypoxia can be associated with specific environmental changes (such as those that occur during an ascent to high altitude) or pathological conditions (such as heart failure, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, or hypoventilation syndrome). Adaptations of the nervous system to chronic hypoxia are most profound in organisms living under extreme hypoxic conditions *(18–24).* Hypoxia-tolerant organisms have developed special ways to deal with hypoxia, such as the reduction of metabolic rate and the downregulation of ion channel activity ("channel arrest"). These strategies may help preserve critical ion gradients and greatly diminished energy use (for review, *see* refs. *18–24*). These adaptations occur in long time frames compared with the "emergency" response of organisms that are not adapted to extreme conditions. Considering all these conditions would certainly exceed the scope of a single article. Therefore, this article discusses the emergency response of neuronal networks to acute, chronic, and intermittent hypoxia in three different sections.

The Response of the Mammalian Brain to Acute Hypoxia

General Considerations

There are numerous cardiorespiratory disorders that result in a sustained reduction of arterial PO_2 levels, such as chronic obstructive pulmonary disease *(44);* congestive heart failure *(45);* and obstructive sleep apnea, which affects approx 25% of adult males *(46).* Hypoxic conditions can also occur acutely (e.g., because of sudden drops in environmental PO_2 levels, stroke, or sudden heart failure). Occurring within seconds, one of the first manifestations of acute hypoxia is the loss of higher brain functions, such as those that give rise to consciousness and purposeful behavior. These behavioral effects are associated with the loss of electroencephalographic (EEG) activity and evoked EEG potentials *(26,47).* The time required to cause marked disruptions in behavioral functions (usually seconds) is much shorter than the time (usually minutes) required to observe histopathological changes *(26,48).* It is tempting to speculate that the occurrence of histopathological changes is delayed because of an early, adaptive shutdown of higher brain functions. However, the difference in timing clearly indicates that the earliest effects of oxygen deprivation include a rapid and reversible influence of oxygen on the cellular and molecular determinants of neuronal excitability, such as the synaptic and intrinsic membrane properties of neurons *(28).*

Disruptions of neuronal circuits are generally attributed to changes in intrinsic membrane and postsynaptic properties *(14,25,28,30, 35,49–51),* changes in synaptic transmission *(32–34,37),* and changes in the vesicular release machinery *(38,43).* In most cases, various cellular effects occur simultaneously and act in concert, resulting in a complex and heterogeneous response at the network level. Neural circuits and neurons throughout the brain express very diverse responses to hypoxia. Although most neurons stop generating action potentials in hypoxia, some neuronal populations are more hypoxia-resistant. The cessation of action potential generation might be one functionally important strategy to shut down neuronal networks to save metabolic energy or to prevent the detrimental consequences of hypoxia. Excessive calcium influx or excitatotoxicity caused by excessive glutamate release are

potentially detrimental mechanisms that are preventable by a shutdown of network functions. However, it would be equally detrimental to shut down entire neuronal networks. There are also neurons that need to be hypoxia-resistant. Some of these hypoxia-resistant neurons behave like classical oxygen chemosensors *(52).* These central oxygen sensors presumably monitor brain oxygen levels and, when activated, coordinate critical functions necessary for the survival of the whole organism (for review, *see* ref. *52*).

The hypoxic response of the brain is adapted to the hypoxic sensitivity that changes with age. Generally, newborn mammals are more resistant to hypoxia than adult mammals (*53–57;* for a review, *see* ref. *58*). In 1953, Hicks *(59)* reported that newborn rodents could resist hypoxia for nearly an hour without damage. Subsequent studies in different central nervous structures, such as the brain stem *(56,60),* the hippocampus *(55,61–63),* and the cerebral cortex *(64,65),* confirmed these results and showed that the neuronal components were less sensitive to hypoxia (for review, *see* refs. *12*, *66*, and *67*).

Why can certain neuronal networks be more or less sensitive? To understand the connection between oxygen consumption and neuronal network functions, it is critical to consider the metabolic constraints and demands of neuronal networks.

Metabolic Considerations As They Relate to the Hypoxic Response

Under normoxic conditions, most neuronal networks are continuously active and, therefore, require high oxygen supply. To maintain network activity it is essential to continuously control ionic gradients. These ionic gradients are a prerequisite for membrane excitability, and they change continuously throughout ongoing network activity (*28, 62, 64;* for a review, *see* ref. *66*). In fact, 50% of a neuron's energy is used to maintain ionic gradients and fluxes *(22,66).* This expenditure requires a high level of ongoing ATP production to compensate for the poor energy storage capacity of the brain through energy-rich molecules. To maintain high levels of ATP, neurons normally use both aerobic and anaerobic metabolism *(66,68,69).* During acute hypoxia, neuronal ATP levels fall sharply within seconds as a result of the inhibition of oxidative phosphorylation *(70,71).* Despite the hypoxia-induced drop in ATP production *(71),* cellular ATP demands of most mammalian cells and tissues tend to remain constant. This leads to an energy deficit that can be compensated only by anaerobic ATP supply pathways *(72–74).* However, the finite stores of fermentable substrate and the accumulation of deleterious end-products (e.g., H^+) limit anaerobic metabolism as a long-term solution to severe oxygen deprivation *(73,74).* Therefore, glycolytic capacity may be an important determinant of neuronal survival in prolonged hypoxia *(75)* and may partially account for differences in hypoxic tolerance between ages and subtypes of neurons *(76).* The capacity for central neurons to carry out anaerobic glycolysis depends on a variety of factors, including glucose supply, intracellular conditions (e.g., pHi), and the activity/expression level of glycolytic enzymes *(77,78).*

Anaerobic metabolism allows neural circuits to support some degree of hypoxic conditions by providing ATP and, therefore, helping maintain cell function. For example, some hypoxia-induced changes in synaptic transmission can be prevented by conditions favoring anaerobic metabolism *(79).* Moreover, elevated glucose concentrations protect against hypoxic neuronal damage in hippocampal slices *(79,80)* and glial damage in cultures *(81).* Lactic acidosis also can protect hippocampal slices against hypoxic neuronal damage *(82).* The respiratory network can support long periods of hypoxia during neonatal period, which is best explained by an efficient anaerobic metabolism *(83,84).*

However, the activation of anaerobic metabolism during hypoxia is limited in several ways. Most importantly, anaerobic metabolism leads to a pronounced decrease in pHi *(48,71,85).* Although the switch from aerobic to anaerobic

glycolysis reduces proton consumption because of a lowered ATP production, more protons are generated through the increased production of lactic acid *(86).* Therefore, a consequence of the increase in both lactic acid production and ATP consumption is a rise in hydrogen ion concentration. The rise in proton concentration inhibits glycolysis, thus reducing ATP production *(87).* This is additionally disadvantageous because low pH is detrimental for synaptic function, leading to the disruption of glutamate receptor activation *(88,89).* In the adult respiratory network, the rise in H^+ concentration has been associated with the hypoxic depression of respiratory activity *(84).*

Changes in Neuronal Intrinsic Properties to Acute Hypoxia Are Heterogeneous

Although most neurons are sensitive to hypoxia, there are significant differences between different neuronal types—even between those located within the same brain region *(11,14,35,65,90–96).* For example, hypoxia causes hippocampal neurons to stop action potential generation because of either a pronounced hyperpolarization or a depolarization leading to inactivation of transient channels *(25,35,50).* Conversely, some brain stem neurons involved in generating the respiratory rhythm become only slightly depolarized, enabling them to maintain cardiorespiratory functions during oxygen deprivation *(11,14,95–98).* However, even colocalized brain stem neurons may have strikingly different hypoxic responses *(14,99),* making such generalizations potentially misleading. We propose that the diversity of cellular responses in any given network or brain area can only be understood when considered in a functional context. Networks in different regions must be reconfigured in a behaviorally, developmentally, and metabolically specific manner to guarantee the survival of the entire organism. Although the organism may be able to afford a temporary loss of networks that control higher brain functions or digestive functions, respiratory and cardiovascular functions must be maintained. The differential response to hypoxia observed in different neuron types may be produced by differences in their intrinsic properties or differences in the oxygen-sensing mechanisms, which is discussed in the next two sections.

The hypoxic responses of the hippocampus and cerebral cortex have been extensively studied. Although most investigations have shown that hippocampal and neocortical neurons have a biphasic response to hypoxia (consisting of depolarization and hyperpolarization), there is disagreement regarding the order of these events. Some reports suggest that hypoxia or metabolic inhibition (by cyanide) causes hyperpolarization, which is preceded by an initial, transient depolarization *(25,35,39,49,100–104).* Other reports show that hypoxia produces an initial membrane hyperpolarization followed by a depolarization *(11,25,35,50,66,105,106).* Additionally, a minority of reports show that hippocampal and neocortical neurons only depolarize *(25,35,49,96,101,102,107–109).* Much of the apparent differences in the hypoxic responses of neurons may be explained by different activity states or different conditions of neurons and network functions. For example, in the hippocampal CA1 region, cyanide causes different responses, depending on the resting potential of the cells: hyperpolarization (or an initial depolarization followed by hyperpolarization) was generally observed in cells with less negative resting potentials, and depolarization was found in cells with more negative resting potentials *(110).* These changes in the resting membrane potential of hippocampal and neocortical neurons have been associated with changes in membrane input resistance *(11,35,39,49,50,90,101,104,107,108,111–115).* The heterogeneity of the responses of different types of neurons—even within the same structure—suggests that the cellular mechanisms underlying these membrane changes are not common and, perhaps, are only explained by their differential functional contributions. Therefore, it is impossible to generalize the hypoxic effects on neurons—particularly nuclei—because the neuronal elements in a given neuronal network may respond quite differently.

Considerations drawn for the neocortex also apply to other brain areas. Thalamo-cortical neurons respond to hypoxia with a depolarization accompanied by an increase in input conductance *(40).* Among locus coeruleus cells, one group of neurons hyperpolarized, whereas another group depolarized in hypoxia *(116).* As mentioned, functional considerations why some neurons depolarize, whereas others hyperpolarize are still missing. In a similarly diverse manner, two-thirds of the nucleus of the tractus solitarius neurons hyperpolarize, whereas the remaining neurons depolarize *(114).* Neurons from the sympathoexcitatory C1 region depolarize in hypoxia *(117).* Midbrain dopaminergic neurons hyperpolarize during a hypoxic stimulus *(118,119),* whereas striatal neurons depolarize *(120).* Neurons recorded in the caudal hypothalamus of rats, cats, and rabbits are excited by hypoxia both in vivo *(121,122)* and in vitro *(123,124).* Similarly to hippocampal and neocortical neurons, neurons of the substantia nigra *(125),* locus coeruleus *(126),* and dorsal vagal nucleus *(93)* respond to hypoxia in a biphasic manner—in this case, with an initial depolarization followed by a hyperpolarization.

The changes of specific ionic conductances underlying the membrane hyperpolarizations or depolarizations with their associated changes in input resistance are equally heterogeneous. The contribution of specific ion channels to a neuron's response can be inferred from electrophysiological studies, as discussed later. However, their contribution can also be inferred through a pharmacological approach. For example, in dorsal root ganglion neurons, the hyperpolarization observed during hypoxia is presumably caused by an increased K^+ conductance through Ca^{2+}-activated K^+ channels, because the hyperpolarization can be blocked by intracellular application of Ca^{2+} chelators *(127).* Other currents involved in the generation of a hyperpolarization are the ATP-sensitive K^+ currents (IK_{ATP}). In rat dorsal vagal neurons, blockers of ATP-sensitive K^+ channels, such as tolbutamide and glibenclamide, suppress anoxia-induced hyperpolarization, and activators of ATP-sensitive K^+ channels mimic the hypoxic response *(128,129).* Similar effects have been observed in hippocampal *(130)* and striatal neurons *(131).* Researchers have proposed that the activation of IK_{ATP} channels prevents detrimental Ca^{2+} increase in hippocampal neurons *(132)* and neuronal damage in neocortical neurons *(133).* Based on this pharmacological strategy, several ion channels have been identified that contribute to the hypoxic response. But are these channels directly sensitive to hypoxia, or are they indirectly activated (*see* next section).

Modulation of Ion Channels by Acute Hypoxia

The possibility that ion channels are directly regulated by oxygen tension was first described in chemoreceptive cells of the carotid body, where K^+ channels are inhibited by hypoxia *(134).* Since then, several other types of ion channels have been proposed as possible candidates for hypoxia modulation *(7,134–136),* but whether this modulation results from a direct effect on the ion channel itself or on auxiliary regulatory proteins remains uncertain (for a review, *see* ref. *135*). In the following sections, we discuss the effect of hypoxia on various ion channels. These hypoxic effects can be considered as building blocks that are used by functionally different neurons to generate a depolarization or hyperpolarization.

K^+ Channels

Both hypoxic depolarization and hyperpolarization have been associated with the modulation of different types of K^+ channels, including Ca^{2+}-dependent K^+ channels, ATP-dependent K^+ channels, and leak currents. As mentioned earlier, hypoxia produces a sharp fall in ATP concentration. This decrease causes the opening of the IK_{ATP}, thus leading to membrane hyperpolarization. Activation of IK_{ATP} by hypoxia has been reported in various neurons, such as cortical neurons *(137),* hippocampal neurons *(138,139),* neurons of the substantia nigra *(140),* dopaminergic midbrain neurons *(141),* dorsal vagal neurons *(142),* neu-

rons of the substantia gelatinosa *(143),* and medullary respiratory neurons *(144–146).* The correlation of the hypoxia-induced activation of this channel with the hyperpolarization has been established in several neurons throughout the brain *(39,107,129,138).* Hypoxia also produces an increase in intracellular Ca^{2+} that can open Ca^{2+}-dependent K^+ channels, which is another mechanism that can lead to a membrane hyperpolarization. This mechanism has been described for hippocampal pyramidal neurons *(25,101,104,112,147),* neocortical neurons *(16,148),* and neurons of the substantia nigra *(16).*

However, K^+ channels can also have the opposite effect. In the past few years, a group of "leak," or background, K^+ channels (the so-called two-pore domain K^+ channels) has been identified as a potential target for hypoxic modulation *(15,149–151).* The inhibition of these potassium channels has been associated with a hypoxia-induced depolarization *(15,152).*

Na^+ Channels

Na^+ channels are responsible for both action potential generation and pacemaker activity; the former is produced by the transient Na^+ current and the latter by the persistent Na^+ current (for a review, *see* ref. *153*). Hypoxia is known to modulate both currents, thus affecting neuronal excitability. Originally observed in myocytes *(154),* hypoxia increases the persistent Na^+ current in hippocampal neurons *(17,41,155),* whereas hypoxia increases both the persistent and the transient Na^+ current in hypothalamic neurons *(156).* The effect of hypoxia on the transient Na^+ current in hypothalamic neurons is not consistent with other reports of hippocampal, cortical, and respiratory neurons, where hypoxia depressed the transient Na^+ current *(42,157,158).* The differences observed regarding the effect of hypoxia on this current could be related with differences in neuronal type and/or Na^+ channel subunit composition.

Ca^{2+} Channels

Ca^{2+} channels are important for basic neuronal functions, such as neurotransmitter release, tonic and bursting firing, and spike adaptation. Therefore, the modulation of Ca^{2+} channels by hypoxia may produce dramatic changes in neuronal activity at the cellular and network levels. The effect of hypoxia on the L-type Ca^{2+} channel has been well-characterized. The L-type Ca^{2+} current increases during oxygen depletion in hypoxia-sensitive neurons in both the brain stem and hippocampus *(159–162).* Other reports in the rostral ventrolateral medulla and hippocampus described an increase in the whole-cell Ca^{2+} current, without specifying the calcium channel subtype *(161–163).* However, compared with other high-voltage activated Ca^{2+} channels, the L-type channel was about 3.5 times more sensitive to hypoxia *(161).* In respiratory neurons, some studies have shown an increase in calcium currents *(164),* whereas others have shown a decrease *(165).* This difference might be explained by the differential modulation of different calcium channel subtypes, a possibility that has not been well-described.

Finally, some other ionic mechanisms are affected by hypoxia. The hyperpolarization-activated current is increased by hypoxia in thalamic neurons *(40,166)* and is depressed in respiratory neurons *(167).* Additionally, the decline in intracellular ATP, which occurs within seconds of acute hypoxia, causes a reduction in the activity of the Na^+/K^+ ATPase, which is necessary for maintaining proper ionic gradients and, therefore, membrane potential. Inhibition of the Na^+/K^+ ATPase produced by hypoxia has been associated with a massive depolarization in some neurons *(11,168–170).*

Despite all the advances made, the hypoxic effects on particular ion channels are not well-integrated into a general understanding of how these changes alter the electrical behavior of particular neurons. However, it may be unrealistic to expect such a general understanding. As discussed earlier, hypoxia differentially alters the activity of several different ion channels in different types of neurons. Therefore, it is likely that the observed heterogeneity in the hypoxic responses may be

explained by different, and very specific, combinations of modulated ion channels in any given neuron.

Depression of Synaptic Transmission During Acute Hypoxia

One of the initial hypoxic responses produced in the majority of neural networks is a profound depression of synaptic transmission observed both in vitro *(29,30,171,172)* and in vivo *(32–34,173).* This general depression might reduce the overall number of active neurons in any given neuronal network. Most studies suggest that this synaptic depression results from a presynaptic mechanism *(55).* For example, under hypoxic conditions that virtually abolish the evoked excitatory potential, it is still possible to obtain a postsynaptic response by iontophoretic application of glutamate *(174).* Moreover, the amplitude of miniature excitatory postsynaptic currents is not modified during hypoxia *(174),* and hypoxia increases paired-pulse facilitation *(175);* the three evidences are strong indicatives of a presynaptic origin. These experiments indicate that the hypoxia-induced changes in synaptic transmission are likely to be presysnaptic. Conversely to the effects on intrinsic properties, the depression of synaptic transmission produced by hypoxia is consistent and can be observed in several brain areas, including the hippocampus *(25,32–34,175–177),* cerebral cortex *(178),* striatum *(179),* brain stem *(114, 180–182),* and spinal cord *(143,171,172).* The depression of synaptic transmission occurs in various neurotransmitter systems, such as glutamatergic *(175–177,183–185),* γ-aminobutyric acid (GABA)ergic *(179,183,185),* and cholinergic systems *(186,187).*

Three hypotheses have been proposed to explain the effects of hypoxia on synaptic transmission: (a) the inhibition of presynaptic Ca^{2+} currents *(50,51);* (b) the interference with the vesicular release machinery *(38,43);* and (c) the modulation of presynaptic receptors controlling neurotransmission *(33,34,37,113,176,188–192).* Although these possibilities are not necessarily exclusive, the third option appears to be supported by most evidence. Adenosine plays a major role in the depression of synaptic transmission during hypoxia. As a consequence of depleted intracellular ATP stores, the extracellular levels of adenosine rise markedly during hypoxia *(176,191–193).* This adenosine outflow temporally correlates with a hypoxic depression of the evoked excitatory potential *(176,192,194).* Several groups have found that adenosine acting on adenosine A1 receptors is responsible for about 50% of the hypoxic depression of synaptic transmission in hippocampal slices in vivo *(32–34)* and in vitro *(113,176,188–192).* Other neuromodulator systems have been implicated in the remaining 50%. For example, activation of the muscarinic M2 receptors *(175)* and metabotropic glutamatergic receptors (*195,196*) also contributes to the depression produced by hypoxia.

Changes in the Respiratory Network During Acute Hypoxia

Although hypoxia-induced changes have been studied in many neurons and networks, there are not many neuronal networks in which it is possible to relate hypoxic changes at the cellular level to changes at the level of a functional network. The response of the mammalian respiratory system to hypoxia is an exception, because this response can be studied in vivo and various in vitro preparations. The respiratory response to hypoxia is biphasic *(181, 197–204).* An initial increase in the frequency and amplitude of ventilation (augmentation) serves as an important mechanism to increase oxygen supply. If hypoxic conditions continue, then the augmentation is followed by a secondary decrease in frequency and amplitude (depression). This depression phase is believed to save metabolic energy during situations when oxygen levels are low. During prolonged hypoxic conditions, depression can terminate in a reversible cessation of ventilation (central apnea). If severe hypoxia continues, then breathing turns into gasping, which is characterized by rapidly rising inspirations

without subsequent expirations. Gasping is associated with a rise in heart rate and arousal. Therefore, gasping has been considered as an important arousal mechanism that may lead to autoresuscitation *(205–207).* If autoresuscitation fails, then terminal apnea follows, which is characterized by the irreversible arrest of breathing and, ultimately, death of the organism. Indeed, one of the leading hypotheses to explain sudden infant death syndrome (SIDS) is that children who die from SIDS have a disturbance in the mechanisms that generate gasps, thus leading to a failure to autoresuscitate *(208–210).*

Without ignoring the role of peripheral chemosensors (for a review, *see* ref. *211*), there is evidence that the biphasic respiratory response to hypoxia has a strong central nervous system component *(212,213).* In fact, first indication for a central hypoxic response came from in vitro experiments that clearly showed a biphasic respiratory response. This central hypoxic response was most convincingly demonstrated in in vitro spontaneously active respiratory rhythmic transverse slice preparations of mice *(14,99,144,182,214,215).* Although the biphasic pattern of the central hypoxic response is generally stereotyped and reproducible, there is some heterogeneity between different respiratory nuclei and animals of different ages.

Similarly to other mammalian networks, the respiratory network of neonates is very resistant to hypoxia *(214,216,217).* Respiratory movements were found to persist longer in intact neonatal rats than in rats older than 1 wk *(218,219,220,221).* Despite hypoxia-induced acidosis, the extracellular K^+ and Ca^{2+} concentrations remained almost unaffected, even during sustained periods of anoxia in in vitro preparations in newborn rats *(222–224)* and newborn rabbits *(204).* Additionally, the respiratory rhythm generated in in vitro preparations persists for several minutes and even hours under hypoxia in newborns *(214, 224–226).* In these neonatal preparations, anoxia did not significantly affect the amplitude of integrated hypoglossal nerve (XII) bursts, and rhythmic activity never ceased during the depression phase. These findings are consistent with the observation that the respiratory network in newborns is efficient at anaerobic metabolism *(83).*

In more mature animals, hypoxia maintained for long periods of time causes major metabolic disturbances contributing to the depression of amplitude and frequency of the respiratory network activity *(203,227).* Consistent with these observations, hypoxia results in the reversible suppression of inspiratory nerve activity in an arterially perfused brain stem preparation from adult rats *(228)* and in vivo adult cat *(181).* In slices obtained from postnatal mice older than 7 d, augmentation was accompanied by a significant increase in the amplitude of XII bursts, and during the subsequent depression a significant decrease. When the period of hypoxia was extended beyond a few minutes, this depression always led to the cessation of rhythmic activity in XII rootlets *(214).*

There are significant differences in the hypoxic response of the different respiratory nuclei. For example, the activity of phrenic, intercostal, and hypoglossal motoneurons (XII) significantly increases during the hypoxic augmentation *(215,229–231),* whereas a significant proportion of bulbospinal neurons in the ventral respiratory group (VRG) and the dorsal respiratory group show no change or exhibit a decrease in discharge frequency. However, there are also neurons within the VRG that increase their activity *(200,232).* Telgkamp and Ramirez *(215)* demonstrated significant differences in the hypoxic response between the presumed respiratory rhythm-generating network in the VRG and the hypoglossal motor nucleus in vitro. The amplitude of respiratory bursts was significantly increased only in the hypoglossus nucleus and not in the VRG, and there was a higher tonic excitation in the hypoglossus. This might be functionally adaptive. It is tempting to speculate that neurons involved in the generation of the respiratory rhythm (located within the VRG) go into an energy-saving (and possibly life-saving) mode,

and motor output simultaneously remains enhanced via a local modulatory action. However, this local hypoxic modulation of hypoglossal motoneurons is potentially dangerous, because it makes motoneurons particularly vulnerable to hypoxic conditions *(95,180,233).* However, there are significant differences, even regarding motor nuclei. Hypoglossal motoneurons are particularly sensitive and produce a stronger depolarization and increase in firing in response to hypoxia than other brain stem neurons *(11,56,215),* such as vagal motoneurons *(83,93,95).* The specific hypoxic depolarization of hypoglossal motoneurons is depicted in the network model (Fig. 1); these neurons are highlighted in gray. This network model is explained in the following paragraph.

Hypoxia-Induced Changes in the Respiratory Rhythm-Generating Network

To understand how hypoxia alters the respiratory network, it is critical to describe its network function under control conditions. Increasing evidence indicates that breathing is produced by rhythm-generating neuronal networks located within the brain stem *(181,225, 234–237)* in an area called the pre-Bötzinger complex (PBC; ref. *235*) and in another area rostral to the PBC, known as the para-facial respiratory group (*236,237*). The latter respiratory group appears to be primarily responsible for the generation of expiratory activity, whereas the PBC is primarily, but not exclusively, responsible for the generation of inspiration. Because the hypoxic effects on para-facial respiratory group neurons are still unknown and the control of inspiration is particularly important during hypoxia, this article focuses on the effects of hypoxia on the neurons in the PBC. As demonstrated in the network model (Fig. 1), the PBC contains several types of neurons, including expiratory, inspiratory, and postinspiratory neurons *(14,181,182, 225,238, 239).* These neurons are connected via reciprocal inhibition, which is critical for establishing the three phases of respiratory activity: inspiration, postinspiration, and expiration (Fig. 1A; ref. *240*). In the absence of synaptic inhibition, expiratory neurons lose their rhythmicity, postinspiratory neurons discharge in phase with inspiration, and inspiratory activity continues *(182,241,242).* Some of the respiratory neurons, including inspiratory and expiratory neurons, respond to hypoxia with an initial depolarization, followed by a persistent hyperpolarization *(99,216,225),* whereas other respiratory neurons maintain tonic firing during prolonged hypoxia without apparent change in membrane potential *(99,182,225).*

Various ion channels have been implicated in the generation of the hypoxic response of respiratory neurons. The amplitude of the L-type calcium current increases during hypoxia *(164).* IK_{ATP} is activated during hypoxia *(144,145),* and the hyperpolarizing effect of this current has been suggested to account for the respiratory depression *(145).* Other channels affected by hypoxia include Na^+ channels *(42)* and I_h currents *(167).* Hypoxia also affects synaptic transmission in the PBC. The most obvious effect is a suppression of synaptic inhibition, which was observed both *in vivo (181)* and in vitro *(182,243).* The depression of synaptic inhibition has two consequences: expiratory neurons cease to discharge rhythmically *(99)* and postinspiratory neurons fire in phase with inspiration (ref. *182; see also* Fig. 1B). There is an additional effect on glutamatergic transmission. In some inspiratory neurons there is a reduction of phasic excitation *(216,225).* This was not always the case, however, as synaptic drive onto other inspiratory neurons was unaltered *(216,225).* This evidence suggests that there must be a hypoxia-resistant component of synaptic excitatory transmission that may be critically involved in the generation of gasping. However, the cellular mechanisms underlying this hypoxia resistance remain to be determined.

Using the transverse slice preparation of mice, progress was made in understanding how these diverse modulatory effects at the ion channel and synaptic level lead to the hypoxic response at the network level.

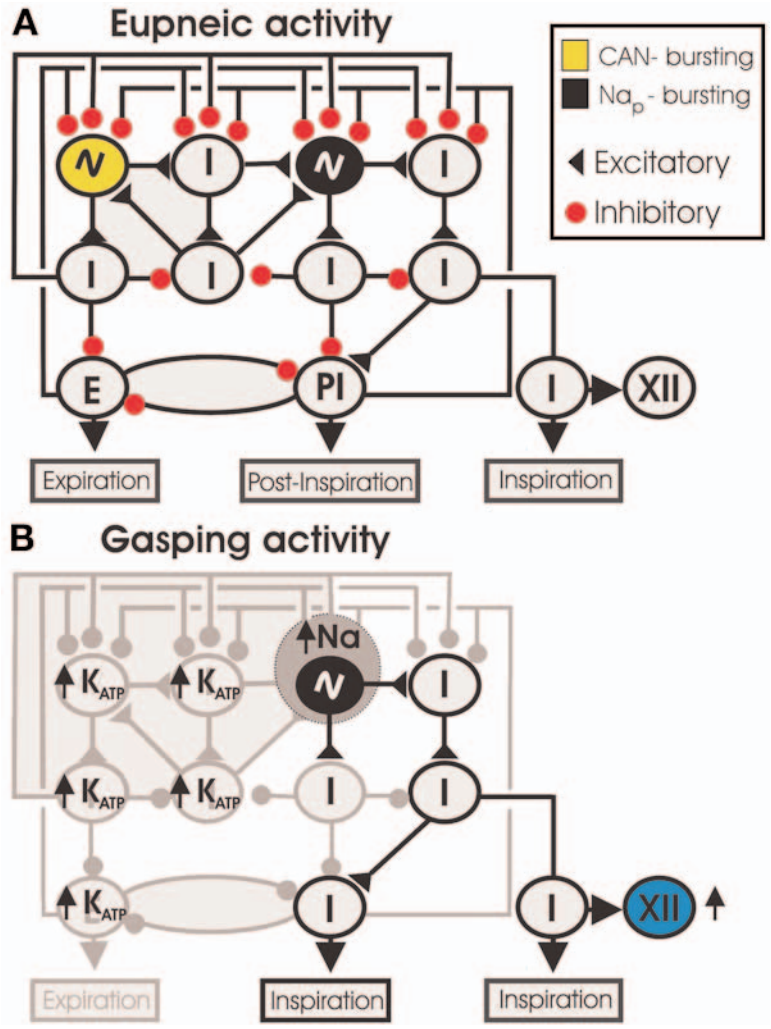

Fig. 1. Model of the respiratory network proposed for two states: **(A)** under normoxic and **(B)** hypoxic conditions. The two states represent eupneic and gasping activity, respectively. **(A)** The respiratory network contains a kernel of inspiratory neurons with heterogeneous pacemaker properties (light gray, black circles) that are connected via excitatory connections. Pacemakers are influenced by concurrent inhibition derived from inspiratory (I), expiratory (E), and postinspiratory neurons (PI). Inhibitory connections from inspiratory onto expiratory neurons play a critical role in establishing the different phases of respiratory activity. Inhibitory connections onto inspiratory neurons influence the kernel of pacemaker neurons, thereby playing a role in respiratory rhythm generation. **(B)** During hypoxia, major portions of the respiratory shut down, as indicated by the light grey outlines of the majority of circles and connections. The only neurons remaining under these conditions are the cadmium-insensitive pacemaker neurons (black circle) driving the remainder of the respiratory network. Under these conditions, the respiratory rhythm is driven by pacemaker neurons. The network also drives motoneurons that have their local hypoxic modulation. For example, hypoglossal (XII) motoneurons are strongly depolarized during hypoxia (gray circle).

As mentioned earlier, the slice preparation generates a biphasic hypoxic response. During the transition from normoxia into hypoxia, the respiratory network undergoes a drastic reconfiguration (Fig. 1; ref. *182*). Respiratory neurons without pacemaker properties hyperpolarize

(Fig. 1B). This was demonstrated by synaptically isolating inspiratory and expiratory nonpacemaker neurons *(99).* The reduction in the number of active nonpacemaker neurons might explain the synaptic depression observed at the network level. Specifically, the loss of synaptic inhibition could be explained by the cessation of activity in neurons that make synaptic inhibitory connections (Fig. 1B). As depicted in the network model (Fig. 1B), the loss of synaptic inhibition leads to the loss of expiratory phases and the reconfiguration of postinspiration into inspiration. Although the properties of nonpacemaker neurons might explain the reconfiguration of respiratory phases, to understand how gasping is generated, it also is critical to consider the properties of the so-called "pacemaker neurons," which are neurons that possess the intrinsic ability to generate regular bursts of activity *(28).*

Under normoxic conditions, the respiratory network contains a kernel of pacemaker neurons that is connected via excitatory glutamatergic connections (Fig. 1A; refs. *235* and *244*). There are at least two types of neurons among these pacemaker neurons, and these can be differentiated by their electrophysiological properties *(14,99,238,239,245).* Both types of pacemakers play a major role in the generation of the normal respiratory motor pattern under normoxic conditions *(14,245).*

Following in vitro characterization, one type of pacemaker neurons was presumably found to generate bursts through a mechanism based on a Ca^{2+}-activated cationic current (ICAN) (Fig. 1A, light gray); the other type generated bursting based on the persistent tetrodotoxin-sensitive Na^+ current (Fig. 1A, black). Both types of pacemaker neurons are differentially modulated by hypoxia. The neurons that rely on ICAN lose the ability to burst intrinsically during prolonged hypoxia (Fig. 1B, longer than 3 min). The other type of pacemaker neurons, which rely on the persistent sodium current, continues to burst throughout long periods of hypoxia (Fig. 1B).

We have proposed that these neurons play a critical role in generating gasping activity because blocking the persistent Na^+ current with riluzole abolishes fictive gasping in vitro *(14).* The cessation of activity in nonpacemaker neurons and ICAN-dependent pacemaker neurons can be hypothesized to result from the activation of the IK_{ATP} current, whereas the maintenance of bursting in persistent-sodium-dependent pacemaker neurons results from the hypoxic activation of sodium channels (Fig. 1B). Regarding the model proposed in Fig. 1, it is also interesting to note that the respiratory rhythm under control conditions depends on a heterogeneous population of pacemaker neurons as well as network properties (Fig. 1A), whereas under hypoxic conditions, the respiratory rhythm critically depends on the persistent-sodium-dependent pacemaker neurons driving the respiratory rhythm during gasping (Fig. 1B). This dependence on just one population of respiratory neurons and on only on major ionic mechanism (the persistent sodium current) makes the respiratory network particularly vulnerable during hypoxia, which may explain why some children die of SIDS because of the failure to gasp *(14).* It would be interesting to learn whether similar reconfigurations also occur in other neuronal networks, such as the neocortex, in which some neurons cease to discharge early and others remain active—even during prolonged exposure to severe hypoxia. Considering the differential sensitivity of neurons in the context of an adaptive network reconfiguration might be the only way to understand why the responses of individual neurons are so heterogeneous and network-dependent.

Long-Lasting Effects of Hypoxia

In addition to the remarkable adaptive properties of neural networks to short-term hypoxia, neural networks also demonstrate long-term adaptations that greatly outlast the acute hypoxic exposure. For example, clinical data suggest that oxygen deprivation during early development may provoke irreversible structural and functional modifications (for

review, *see* refs. *246–248*). As described earlier, during the initial stages of hypoxia, neurons exhibit alterations in synaptic transmission and intrinsic membrane properties. Consequently, there are detrimental changes in the neuronal intracellular environment, such as a rise in intracellular Ca^{2+} concentration, an attenuation of ATP levels, and changes in pH, which may alter the activity of those neurons and the activity of neuronal networks in the long term (for review, *see* ref. *48*).

In hippocampal CA1 neurons, spontaneous neuronal activity and excitability is increased after return to control oxygen levels, both in vivo *(249,250)* and in vitro *(183,251–253).* Other studies have found a long-term increase in synaptic transmission associated with an enhancement of postsynaptic *N*-methyl-D-aspartate (NMDA)-receptor-mediated responses. Together with presynaptic changes, these postsynaptic changes may at least partly explain the increase in excitability of pyramidal neurons *(183,251–254).* The NMDA-mediated responses in the CA1 region of the rat hippocampus remained potentiated for 1 h after an anoxic-aglycemic episode *(251,252).* Some authors have referred to this long-term increase of synaptic transmission as hypoxia-induced long-term potentiaton *(251, 252,255),* which has also been reported in the corticostriatal synapse *(256).*

Another long-lasting effect of hypoxia is neuronal damage. In hypoxia-sensitive structures such as the cerebral cortex, cerebellum, striatum, and hippocampus, damage typically is produced after several minutes of oxygen deprivation *(87,257).* A critical factor in the induction of hypoxic brain injury is a network process called spreading depression-like depolarization (*SDLD;* refs. *258* and *259*). SDLD is characterized by rapid and nearly complete depolarization of a sizable population of brain cells, accompanied by a massive redistribution of ions between intra- and extracellular compartments. This depolarization propagates slowly as a regenerative wave through brain tissue *(259–263).* Several studies have suggested that SDLD is produced by the cooperative action of overactivated persistent Na^+ current and NMDA-receptor-controlled current (for a review, *see* ref. *264*). In the CA1 region of the rat hippocampus, SDLD is accompanied by both a negative shift of the extracellular dendritic cell potential (meaning a massive depolarization) and a sharp decrease in light transmittance, which is correlated with cellular swelling *(265).* This swelling has been confirmed in brain slices by measurements of extracellular volume *(266–268),* extracellular resistance *(269,270),* optical properties of brain tissue *(271,272),* and intracellular volume *(273).* Both SDLD and neuronal swelling contribute to neuronal damage *(266,274–276).*

Neuronal death, which is caused by decreased or interrupted oxygen delivery, has also been attributed to changes in intracellular pH, decreased ATP levels, free radical production, increases in intracellular Na^+ and Ca^{2+} concentrations, and membrane depolarization (for a review, *see* ref. *48*). The dramatic increase in intracellular Ca^{2+} *(277–281)* appears to play the most important role in excitotoxic cell damage associated with hypoxia *(282–286).* Ionotropic glutamate receptors are key players in this damaging hypoxia-induced Ca^{2+} influx *(285,287–291).*

Additionally, the influx of Na^+ appears to be an important factor in hypoxia-induced injury. Sodium channel blockers, such as tetrodotoxin and lidocaine, as well as extracellular solutions containing a low Na^+ concentration protect neurons from ischemic damage. These pharmacological experiments suggest that voltage-gated Na^+ channels play an early and important role in oxygen-sensing and cell damage *(291–297).* Researchers recently demonstrated that Na^+ entry via voltage-dependent Na^+ channels during hypoxia led to apoptotic cell death *(298).*

Effects of Chronic Hypoxia on Neural Networks

As mentioned earlier, chronic hypoxia may occur under certain environmental conditions as a result of insufficient blood flow (cerebrovascular hemorrhage, brain tumor, vascular

occlusion, cardiac arrest, or bypass surgery) or respiratory dysfunction (obstruction of airway, lung dysfunction, or neural control failure). Despite its importance, there have been fewer studies on the effects of chronic hypoxia regarding alteration at the neuronal and network levels compared to studies of acute hypoxia. The temporal characteristics of chronic hypoxia (e.g., intermittent vs continuous hypoxia) influence how neurons and networks adapt to chronic hypoxia. Chronic hypoxia typically alters protein expression, including significant changes in ion channel expression (for a review, *see* ref. *299*). The regulation of gene expression largely results from the activation of a hypoxia-sensitive transcription factor called hypoxia-inducible factor (HIF)-1 (refs. *300* and *301*). HIF-1 is a heterodimer of HIF-1a and HIF-1b, which are basic helix–loop–helix proteins of the PAS family. HIF-1b is expressed constitutively in all cells. It does not respond to changes in oxygen tension, but it is essential for hypoxia-induced transcriptional changes mediated by the HIF-1 heterodimer (for a review, *see* ref. *302*).

Oxygen levels directly regulate the expression of the HIF-1a component in a dose-dependent manner, with a gradual increase as PO_2 decreases from 20 to 5% and a pronounced increase as PO_2 falls below 5% *(302,303).* The dynamics of the onset and decay of HIF-1a expression are quite rapid. For example, the decay of HIF-1a after re-oxygenation of lung tissue occurs within 1 min *(304).* Such rapid dynamics enable short bouts of intermittent hypoxia to produce adaptations at the level of gene transcription that, in turn, promotes angiogenesis, erythropoiesis, and glycolysis. Although no data currently exist to clearly indicate whether tissues respond differentially to continuous or intermittent hypoxia, it appears reasonable to expect that HIF-1 expression is a critical determinant in initiating and reversing the adaptive and/or maladaptive responses to intermittent hypoxia. The gene expression modulated by these transcription factors could change the density and distribution of neuronal membrane proteins, such as ion channels and transporters, and thereby alter cell function (ref. *305;* for a review, *see* ref. *302*). Past investigations have shown that prolonged hypoxia selectively upregulates glycolytic and related enzymes (e.g., lactate dehydrogenase, pyruvate kinase, hexokinase) but not nonglycolytic cytoplasmic enzymes (e.g., fatty acyl-CoAsynthetase, cytoplasmic malate dehydrogenase, and glucose-6-phosphate dehydrogenase) in mammalian cells *(78,306,307).* There are also direct changes in ion channels—for example, chronic hypoxia increases the expression of L-type and Ca^{2+}-activated K^+ channels *(299).* Chronic hypoxia causes Na^+ channel messenger RNA and saxitoxin binding (a Na^+ channel blocker) to decrease in adult rat brains and to increase in fetal brains *(305,308).*

Effects of Intermittent Hypoxia on Neuronal Networks

Intermittent hypoxia is broadly defined as repeated episodes of hypoxia interspersed with episodes of normoxia *(309).* This type of hypoxic pattern is observed in obstructive sleep apnea (OSA), a clinical syndrome characterized by repeated episodes of upper airway obstruction during sleep—now recognized as a highly prevalent public health problem causing substantial cardiovascular and neurocognitive morbidities *(310–314).* OSA is characterized by episodic airway obstructions during sleep, often occurring more than 60 times per hour, with significant desaturations of hemoglobin to levels as low as 50%. These events are associated not only with hypoxia but also hypercapnia. The frequent arousals also lead to significant sleep fragmentation *(311–314).* Patients with OSA exhibit substantial memory and executive functional losses, have increased circulating markers of oxidative stress and inflammation, and develop regional gray matter loss *(311–314).*

Chronic intermittent hypoxia significantly increases right ventricular heart mass, likely associated with pulmonary vascular remodeling and pulmonary hypertension *(315–319).*

There are also detrimental effects on normal development, especially in the fetus. It is well-established that intermittent hypoxia significantly decreases fetal growth *(320,321).* It has long-term consequences, including hypertension, cerebral and coronary vascular problems, developmental and neurocognitive deficits, and neurodegeneration caused by the cumulative effects of persistent bouts of hypoxia (for a review, *see* ref. *309*). In animal models, intermittent hypoxia leads to neurodegeneration, inflammation, and impaired spatial learning. This has been demonstrated in the Morris water maze, even in the absence of significant sleep fragmentation *(322–326).* Intermittent hypoxia induces a sustained (more than 3 h) hyperexcitability of CA1 pyramidal neurons accompanied with epileptiform activity, which depends on activation of L-type Ca^{2+} channels and NMDA receptors *(327).* The hypoxia-induced activity was also associated with a time-dependent expression of the inducible nitric oxide synthase. An increased expression of inducible nitric oxide synthase may play a critical role in the early pathophysiological events leading to intermittent-hypoxia-mediated neurobehavioral deficits *(325).* Relevant to SIDS, both prenatal and early postnatal intermittent hypoxia adversely affect gasping and related survival mechanisms *(206,328,329).*

Despite the detrimental effects of intermittent hypoxia, protocols of intermittent hypoxia have also been used in humans because of their beneficial effects. For example, intermittent hypoxic training has been shown to have a significant anti-arrhythmic effect in acute myocardial ischemia in conscious animals *(330,331),* and intermittent hypoxia prevents experimental atherosclerosis in rabbits *(332).* Intermittent hypoxia is an effective stimulus for erythropoietin (a hormone that stimulates red blood cell formation) production in both humans *(333–335)* and rats *(336).* In the respiratory network, intermittent hypoxia produces a long-lasting increase in normoxic ventilation *(337–339),* a phenomenon discussed in the following section.

Long-Term Facilitation of the Respiratory Output

The respiratory network exhibits long-lasting alterations in rhythmic activity that depends on the characteristics of the hypoxic stimulus. After termination of a single hypoxic episode, the isolated respiratory network responds with a short-term frequency increase *(340),* and the whole animal responds with a short-term frequency decline *(341).* On the other hand, an exposure to brief (3–5 min), repetitive episodes of hypoxia causes an increase in respiratory frequency as well as an increase in the amplitude of integrated motor neuronal bursts both in vivo and in vitro (refs. *339* and *340–348;* for a review, *see* ref. *349*). These changes persist for more than 90 min and are collectively referred as long-term facilitation (LTF; refs. *340, 349,* and *350*). The details of this form of plasticity vary with preparation *(339,345),* animal strain *(349),* age *(351,352),* and experimental conditions *(347).* However, it appears that changes in motor neuron burst amplitude result from a direct modulation at the level of the motor nuclei *(338,339),* whereas the frequency effects result from direct changes in the respiratory network *(340).* This differential modulation is depicted in the network model in Fig. 2. This model proposes that the frequency modulation, which can be observed even in the isolated respiratory network (Fig. 2B; ref. *340*), is generated by a direct modulation of the pacemaker kernel within the PBC (Fig. 2A, gray circle), whereas the amplitude modulation results from a direct effect at the level of the motor nuclei (Fig. 2A, light gray circle).

It was recently proposed that a protein kinase C-induced stimulation of IK_{ATP} channels in the mitochondria of respiratory neurons was responsible for the hypoxic facilitation of rhythmic activity *(353).* Respiratory LTF can be produced by intermittent hypoxia *(339,340)*—or the physiological surrogate—electrical stimulation of the carotid sinus nerves *(342,343).* Interestingly, LTF is elicited by hypoxia only when presented in an episodic

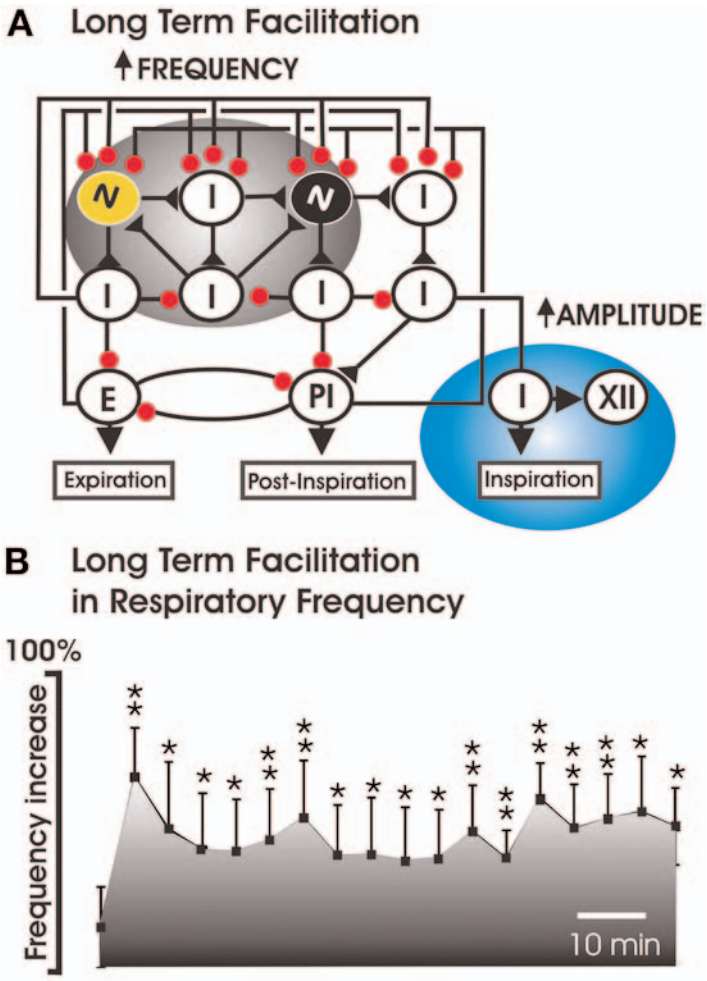

Fig. 2. The respiratory network assumes a different state following intermittent hypoxia. **(A)** Intermittent hypoxia triggers long-term facilitation (LTF), resulting in an increased respiratory frequency that is presumably controlled by the respiratory kernel of pacemaker neurons (large, gray-shaded circle), and enhance respiratory amplitude that is presumably controlled by local modulation of the motor nuclei (large, light gray circle). **(B)** Intermittent hypoxia leads to an increase in respiratory frequency (ordinate) lasting for more than 90 min (abscissa). This form of LTF was observed in the isolated respiratory network of mice, indicating a central neuronal origin. (Modified from ref. *340*.)

pattern *(347)*, demonstrating strong pattern sensitivity similar to other models of plasticity. LTF is serotonin-dependent, because it is abolished by serotonin receptor antagonists or serotonin depletion *(342–344)*. The long-term effects involve protein synthesis because inhibitors of protein synthesis also abolish LTF *(354)*.

A protein critical for this plasticity is brain-derived neurotrophic factor, which is both necessary and sufficient to induce LTF *(355)*. As mentioned earlier, LTF shows very interesting age and gender differences. Compared to 3- to 4-mo-old male Sprague Dawley rats *(347)*, LTF is attenuated in the phrenic nerve and nearly abolished in the hypoglossal nerve

of 12- to 14-mo-old male rats *(351).* Conversely, LTF increases with age in female rats and is influenced by the estrus cycle *(352).* The age and gender dependence of LTF resembles the age and gender dependence of OSA observed in humans *(356),* suggesting a possible link. Although intermittent hypoxia elicits unique forms of respiratory plasticity in neonates *(357,358),* LTF has not been studied in this age group. The study of LTF during development is important, because serotonin-dependent plasticity has been associated with various respiratory disorders of the newborn *(359,360).* Although much has been learned regarding how intermittent hypoxia affects the motor output, the mechanism that leads to the long-term frequency modulation remains unknown *(340),* although a modulation of pacemaker activity is the most likely target for this form of plasticity.

Interestingly, LTF is susceptible to even further plasticity, a phenomenon that is generally referred to as metaplasticity. Bilateral cervical dorsal rhizotomy increases both hypoxia-induced phrenic LTF and serotonin terminal density near phrenic motoneurons *(338),* and chronic intermittent hypoxia augments phrenic LTF *(361).*

Conclusions and Perspectives

Oxygen is essential for the homeostasis and survival of cells in all aerobic organisms. Therefore, it is not surprising that evolution has produced diverse strategies to ensure adequate oxygen supply, including various strategies to sense and to respond to changes in oxygen levels. The diversity of strategies in the hypoxic response of the mammalian nervous system may correspond to the relative evolutionary age of a given brain structure.

As mentioned earlier, one of the first manifestations of hypoxia is the loss of higher brain functions, such as those that give rise to consciousness and purposeful behavior. These higher brain functions are generated by the most "recent" brain structures, such as cortex and hippocampus. The disruption of network activity associated with higher brain functions could be interpreted as an adaptation to maintain the activity of the evolutionary older networks associated with survival (e.g., respiratory network) and to shut down the activity of the evolutionary younger networks that are not immediately necessary for survival. This strategy could allow the brain to switch some networks into an energy-saving mode and to maintain vital networks in a functional mode. However, as illustrated in this article, the situation is not so simple. Substantial reconfigurations occur even in those networks that are critical for survival. During hypoxia, the respiratory network assumes a new and very different configuration in which many neuronal elements are shut down, and the rhythm is maintained by a subpopulation of hypoxia-tolerant pacemaker neurons that generate gasping (Fig. 1).

The situation may be similar in other neuronal networks (i.e., irrespective of evolutionary age or necessity for survival). For example, it is surprising that some neurons in the neocortex are much more hypoxia-tolerant than hypoglossal motoneurons *(96,180),* although hypoglossal motoneurons are critical for survival because they control upper airway potency, whereas neocortical neurons are "only important" for higher brain functions. Perhaps these hypoxia-tolerant neocortical neurons maintain neocortical functions in an energy-saving mode, much like the respiratory network that goes into a gasping mode. However, such functional considerations have not been rigorously addressed for networks located in neocortex, hippocampus, and other areas involved in higher brain functions. Currently, we only know that the neural responses in these areas are extremely heterogeneous. Therefore, future studies need to better integrate findings obtained at the cellular level with those at the level of the network and associated behavior. This integrative approach is an important step to better understand how the brain adapts to hypoxia. Functional slice preparations from various different areas

become increasingly available and will facilitate such integrative studies.

Another important research avenue aims at better understanding of the long-term adaptations of neuronal networks following a hypoxic exposure. In the past, much research has focused on the well-known irreversible and ultimately detrimental structural and functional modifications produced by hypoxia (for review, *see* refs. *246–248*). However, there are also long-term changes that remodel neuronal networks, resulting in a new network state that is possibly protective and more resistant to subsequent hypoxic exposures. This article mentioned two long-term changes associated with hypoxia: the long-term potentiation (LTP) observed in hippocampus and the LTF observed in the respiratory network. Although both types of plasticity may be adaptive, careful analysis is necessary to investigate the benefit of these forms of plasticity. Recent evidence has demonstrated that hypoxic LTP may occlude the induction of "physiological" LTP *(362).* The hypoxic LTP may also increase network excitability, leading possibly to epileptic activity *(363).* If persistent, the intermittent pattern necessary to induce LTF may have detrimental effects on other networks associated with cognition *(312,322–326).*

Intermittent hypoxia is also known to diminish the induction of LTP *(364).* Therefore, it will be very important to dissect and differentiate the effects of intermittent hypoxia on different neuronal networks and their associated functions. However, there is great potential that these types of hypoxic exposures are extremely beneficial. It has been suggested that LTF may lead to new therapeutic strategies for treating breathing disorders, such as respiratory insufficiency after spinal cord injury *(365).* Intermittent hypoxia is well-known as a preconditioning stimulus not only in the mammalian nervous system but also other organ systems *(366).* We conclude that hypoxia is a very powerful modulator of neuronal network activity that can produce short-lasting changes in the millisecond range as well as long-lasting effects that can persist throughout a life span. Hypoxia is associated with several pathological conditions and triggers remarkable adaptations to extreme conditions. Hypoxia has very heterogeneous effects on neuronal networks. This heterogeneity appears to be the result of a complex interplay of hypoxic effects that simultaneously alter neuronal metabolism, intrinsic membrane properties, and synaptic transmission within each neuronal network. The study of the hypoxic modifications of the cellular components, together with the systematic analysis of alterations evoked in several vital neuronal circuits, has important clinical implications for the treatment of various neurological diseases associated with oxygen deficiency.

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References

1. Gnaiger E. (2001) Bioenergetics at low oxygen: dependence of respiration and phosphorylation on oxygen and adenosine diphosphate supply. *Respir. Physiol.* **128,** 277–297.
2. Gonzalez C., Almaraz L., Obeso A., and Rigual R. (1994) Carotid body chemoreceptors: from natural stimuli to sensory discharges. *Physiol. Rev.* **74,** 829–898.
3. Lopez-Barneo J., Pardal R., and Ortega-Saenz P. (2001) Cellular mechanism of oxygen sensing. *Annu. Rev. Physiol.* **63,** 259–287.
4. Peers C. (1997) Oxygen-sensitive ion channels. *Trends Pharmacol. Sci.* **18,** 405–408.
5. Prabhakar N. R. (2000) Oxygen sensing by the carotid body chemoreceptors. *J. Appl. Physiol.* **88,** 2287–2295.
6. Fu X. W., Wang D., Nurse C. A., Dinauer M. C., and Cutz E. (2000) NADPH oxidase is an O2 sensor in airway chemoreceptors: evidence from K+ current modulation in wild-type and

oxidase-deficient mice. *Proc. Natl. Acad. Sci. USA* **97,** 4374–4379.
7. Youngson C., Nurse C., Yeger H., and Cutz E. (1993) Oxygen sensing in airway chemoreceptors. *Nature.* **365,** 153–155.
8. Thompson R. J. and Nurse C. A. (1998) Anoxia differentially modulates multiple K+ currents and depolarizes neonatal rat adrenal chromaffin cells. *J. Physiol.* **512,** 421–434.
9. Archer S. L., Huang J., Henry T., Peterson D., and Weir E. K. (1993) A redox-based O2 sensor in rat pulmonary vasculature. *Circ. Res.* **73,** 1100–1112.
10. Archer S. L., Souil E., Dinh-Xuan A. T., et al. (1998) Molecular identification of the role of voltage-gated K+ channels, Kv1.5 and Kv2.1, in hypoxic pulmonary vasoconstriction and control of resting membrane potential in rat pulmonary artery myocytes. *J. Clin. Invest.* **101,** 2319–30.
11. Haddad G. G. and Jiang C. (1993) O2 deprivation in the central nervous system: on mechanisms of neuronal response, differential sensitivity and injury. *Prog. Neurobiol.* **40,** 277–318.
12. Haddad G. G. and Jiang C. (1997) O2-sensing mechanisms in excitable cells: role of plasma membrane K+ channels. *Annu. Rev. Physiol.* **59,** 23–42.
13. Henrich M., Hoffmann K., Konig P., et al. (2002) Sensory neurons respond to hypoxia with NO production associated with mitochondria. *Mol. Cell. Neurosci.* **20,** 307–322.
14. Peña F., Parkis M. A., Tryba A. K., and Ramirez J. M. (2004) Differential contribution of pacemaker properties to the generation of respiratory rhythms during normoxia and hypoxia. *Neuron* **43,** 105–117.
15. Plant L. D., Kemp P. J., Peers C., Henderson Z., and Pearson H. A. (2002) Hypoxic depolarization of cerebellar granule neurons by specific inhibition of TASK-1. *Stroke* **33,** 2324–2328.
16. Jiang C. and Haddad G. G. (1994) A direct mechanism for sensing low oxygen levels by central neurons. *Proc. Natl. Acad. Sci. USA* **91,** 7198–7201.
17. Hammarstrom A. K. and Gage P. W. (2000) Oxygen-sensing persistent sodium channels in rat hippocampus. *J. Physiol.* **529,** 107–118.
18. Lutz P. L. and Nilsson G. E. (1997) Contrasting strategies for anoxic brain survival—glycolysis up or down. *J. Exp. Biol.* **200,** 411–419.
19. Bickler P. E. and Buck L. T. (1998) Adaptations of vertebrate neurons to hypoxia and anoxia: maintaining critical Ca2+ concentrations. *J. Exp. Biol.* **201,** 1141–1152.
20. Bickler P. E., Donohoe P. H., and Buck L. T. (2002) Molecular adaptations for survival during anoxia: lessons from lower vertebrates. *Neuroscientist* **8,** 234–242.
21. Hochachka P. W. and Lutz P. L. (2001) Mechanism, origin, and evolution of anoxia tolerance in animals. Comp. *Biochem. Physiol. B. Biochem. Mol. Biol.* **130,** 435–459.
22. Hochachka P. W. (1986) Balancing conflicting metabolic demands of exercise and diving. *Fed. Proc.* **45,** 2948–2952.
23. Hopfl G., Ogunshola O., and Gassmann M. (2003) Hypoxia and high altitude. The molecular response. *Adv. Exp. Med. Biol.* **543,** 89–115.
24. Hourdez S. and Weber R. E. (2005) Molecular and functional adaptations in deep-sea hemoglobins. *J. Inorg. Biochem.* **99,** 130–141.
25. Leblond J. and Krnjevic K. (1989) Hypoxic changes in hippocampal neurons. *J. Neurophysiol.* **62,** 1–14.
26. Bachevalier J. and Meunier M. (1989) Cerebral ischemia: are the memory deficits associated with hippocampal cell loss? *Hippocampus.* **6,** 553–560.
27. Hara H., Sukamoto T., and Kogure K. (1993) Mechanism and pathogenesis of ischemia-induced neuronal damage. *Prog. Neurobiol.* **40,** 645–670.
28. Ramirez J. M., Tryba A. K., and Pena F. (2004) Pacemaker neurons and neuronal networks: an integrative view. *Curr. Opin. Neurobiol.* **14,** 665–674.
29. Lipton P. and Whittingham T. S. (1979) The effect of hypoxia on evoked potentials in the in vitro hippocampus. *J. Physiol.* **287,** 427–438.
30. Luhmann H. J. and Heinemann U. (1992) Hypoxia-induced functional alterations in adult rat neocortex. *J Neurophysiol.* **67,** 798–811.
31. Cummins T. R., Agulian S. K., and Haddad G. G. (1993) Oxygen tension clamp around single neurons in vitro: a computerized method for studies on O2 deprivation. *J. Neurosci. Methods* **46,** 183–189.
32. Fowler J. C., Gervitz L. M., Hamilton M. E., and Walker J. A. (2003) Systemic hypoxia and the depression of synaptic transmission in rat hippocampus after carotid artery occlusion. *J. Physiol.* **550,** 961–972.
33. Gervitz L. M., Lutherer L. O., Davies D. G., Pirch J. H., and Fowler J. C. (2001) Adenosine induces initial hypoxic-ischemic depression of synaptic transmission in the rat hippocampus

in vivo. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **280,** R639–R645.
34. Gervitz L. M., Davies D. G., Omidvar K., and Fowler J. C. (2003) The effect of acute hypoxemia and hypotension on adenosine-mediated depression of evoked hippocampal synaptic transmission. *Exp. Neurol.* **182,** 507–517.
35. Fujiwara N., Higashi H., Shimoji K., and Yoshimura M. (1987) Effects of hypoxia on rat hippocampal neurones in vitro. *J. Physiol.* **384,** 131–151.
36. Jiang C. and Haddad G. G. (1992) Differential responses of neocortical neurons to glucose and/or O2 deprivation in the human and rat. *J. Neurophysiol.* **68,** 2165–2173.
37. Katchman A. N. and Hershkowitz N. (1993) Adenosine antagonists prevent hypoxia-induced depression of excitatory but not inhibitory synaptic currents. *Neurosci Lett.* **159,** 123–126.
38. Katchman A. N. and Hershkowitz N. (1993) Early anoxia-induced vesicular glutamate release results from mobilization of calcium from intracellular stores. *J. Neurophysiol.* **70,** 1–7.
39. Fujimura N., Tanaka E., Yamamoto S., Shigemori M., and Higashi H. (1997) Contribution of ATP-sensitive potassium channels to hypoxic hyperpolarization in rat hippocampal CA1 neurons in vitro. *J. Neurophysiol.* **77,** 378–385.
40. Erdemli G. and Crunelli V. (1998) Response of thalamocortical neurons to hypoxia: a whole-cell patch-clamp study. *J Neurosci.* **18,** 5212–5224.
41. Hammarstrom A. K. and Gage P. W. (1998) Inhibition of oxidative metabolism increases persistent sodium current in rat CA1 hippocampal neurons. *J Physiol.* **510,** 735–741.
42. Mironov S. L. and Richter D. W. (1999) Cytoskeleton mediates inhibition of the fast Na+ current in respiratory brainstem neurons during hypoxia. *Eur J Neurosci.* **11,** 1831–1834.
43. Kulik A., Trapp S., and Ballanyi K. (2000) Ischemia but not anoxia evokes vesicular and Ca(2+)-independent glutamate release in the dorsal vagal complex in vitro. *J. Neurophysiol.* **83,** 2905–2915.
44. Hida W., Tun Y., Kikuchi Y., Okabe S., and Shirato K. (2002) Pulmonary hypertension in patients with chronic obstructive pulmonary disease: recent advances in pathophysiology and management. *Respirology* **7,** 3–13.
45. Naughton M. T. and Bradley T. D. (1998) Sleep apnea in congestive heart failure. *Clin. Chest Med.* **19,** 99–113.
46. Lanfranchi P. and Somers V. K. (2001) Obstructive sleep apnea and vascular disease. *Respir. Res.* **2,** 315–319.
47. Rossen R., Kabat H., and Anderson J. P. (1943) Acute arrest of cerebral circulation in man. *Arch. Neurol. Psych.* **50,** 510–528.
48. Lipton P. (1999) Ischemic cell death in brain neurons. *Physiol. Rev.* **79,** 1431–1568.
49. Hansen A. J., Hounsgaard J., and Jahnsen H. (1982) Anoxia increases potassium conductance in hippocampal nerve cells. *Acta. Physiol. Scand.* **115,** 301–310.
50. Krnjevic K. and Leblond J. (1989) Changes in membrane currents of hippocampal neurons evoked by brief anoxia. *J Neurophysiol.* **62,** 15–30.
51. Young J. N. and Somjen G. G. (1992) Suppression of presynaptic calcium currents by hypoxia in hippocampal tissue slices. *Brain Res.* **21,** 70–76.
52. Neubauer J. A. and Sunderram J. (2004) Oxygen-sensing neurons in the central nervous system. *J. Appl. Physiol.* **96,** 367–374.
53. Duffy T. E., Kohle S. J., and Vannucci R. C. (1975) Carbohydrate and energy metabolism in perinatal rat brain: relation to survival in anoxia. *J. Neurochem.* **24,** 271–276.
54. Ferriero D. M., Arcavi L. J., Sagar S. M., McIntosh T. K., and Simon R. P. (1988) Selective sparing of NADPH-diaphorase neurons in neonatal hypoxia-ischemia. *Ann. Neurol.* **24,** 670–676.
55. Cherubini E., Ben-Ari Y., and Krnjevic K. (1989) Anoxia produces smaller changes in synaptic transmission, membrane potential, and input resistance in immature rat hippocampus. *J. Neurophysiol.* **62,** 882–895.
56. Haddad G. G. and Donnelly D. F. (1990) O2 deprivation induces a major depolarization in brain stem neurons in the adult but not in the neonatal rat. *J. Physiol.* **429,** 411–428.
57. Jiang C., Agulian S., and Haddad G. G. (1991) O2 tension in adult and neonatal brain slices under several experimental conditions. *Brain Res.* **568,** 159–164.
58. Singer D. (1999) Neonatal tolerance to hypoxia: a comparative-physiological approach. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **123,** 221–234.
59. Hicks S. P. (1953) Developmental brain metabolism; effects of cortisone, anoxia, fluoroac-

etate, radiation, insulin, and other inhibitors on the embryo, newborn, and adult. *AMA Arch. Pathol.* **55,** 302–327.
60. Ballanyi K., Kuwana S., Volker A., Morawietz G., and Richter D. W. (1992) Developmental changes in the hypoxia tolerance of the in vitro respiratory network of rats. *Neurosci. Lett.* **148,** 141–144.
61. Choi D. W. and Rothman S. M. (1990) The role of glutamate neurotoxicity in hypoxic-ischemic neuronal death. *Annu. Rev. Neurosci.* **13,** 171–182.
62. Friedman J. E. and Haddad G. G. (1993) Major differences in Ca2+i response to anoxia between neonatal and adult rat CA1 neurons: role of Ca2+o and Na+o. *J. Neurosci.* **13,** 63–72.
63. Kawai S., Yonetani M., Nakamura H., and Okada Y. (1989) Effects of deprivation of oxygen and glucose on the neural activity and the level of high energy phosphates in the hippocampal slices of immature and adult rat. *Brain Res. Dev. Brain Res.* **48,** 11–18.
64. Bickler P. E., Gallego S. M., and Hansen B. M. (1993) Developmental changes in intracellular calcium regulation in rat cerebral cortex during hypoxia. *J. Cereb. Blood. Flow. Metab.* **13,** 811–819.
65. Luhmann H. J., Kral T., and Heinemann U. (1993) Influence of hypoxia on excitation and GABAergic inhibition in mature and developing rat neocortex. *Exp. Brain Res.* **97,** 209–224.
66. Hansen A. J. (1985). Effect of anoxia on ion distribution in the brain. *Physiol. Rev.* **65,**101–148
67. Ben-Ari Y. (1992) Effects of anoxia and aglycemia on the adult and immature hippocampus. *Biol. Neonate.* **62,** 225–230.
68. Kasischke K. A., Vishwasrao H. D., Fisher P. J., Zipfel W. R., and Webb W. W. (2004) Neural activity triggers neuronal oxidative metabolism followed by astrocytic glycolysis. *Science* **305,** 99–103.
69. Booth R. F., Patel T. B., and Clark J. B. (1980) The development of enzymes of energy metabolism in the brain of a precocial (guinea pig) and non-precocial (rat) species. *J. Neurochem.* **34,** 17–25.
70. Kreisman N. R., Sick T. J., LaManna J. C., and Rosenthal M. (1981) Local tissue oxygen tension-cytochrome a,a3 redox relationships in rat cerebral cortex in vivo. *Brain Res.* **218,** 161–174.
71. Erecinska M. and Silver I. A. (1994) Ions and energy in mammalian brain. *Prog. Neurobiol.* **43,** 37–71.
72. Hong S. S., Gibney G. T., Esquilin M., Yu J., and Xia Y. (2004) Effect of protein kinases on lactate dehydrogenase activity in cortical neurons during hypoxia. *Brain Res.* **1009,** 195–202.
73. Paschen W. and Djuricic B. (1995) Comparison of in vitro ischemia-induced disturbances in energy metabolism and protein synthesis in the hippocampus of rats and gerbils. *J. Neurochem.* **65,** 1692–1697.
74. Milusheva E. A., Doda M., Baranyi M., and Vizi E. S. (1996) Effect of hypoxia and glucose deprivation on ATP level, adenylate energy charge and [Ca2+]o-dependent and independent release of [3H]dopamine in rat striatal slices. *Neurochem. Int.* **28,** 501–507.
75. Marrif H. and Juurlink B. H. (1999) Astrocytes respond to hypoxia by increasing glycolytic capacity. *J. Neurosci. Res.* **57,** 255–260.
76. Ojala B. E., Page L. A., Moore M. A., and Thompson L. V. (2001) Effects of inactivity on glycolytic capacity of single skeletal muscle fibers in adult and aged rats. *Biol. Res. Nurs.* **3,** 88–95.
77. Dang C. V. and Semenza G. L. (1999) Oncogenic alterations of metabolism. *Trends Biochem. Sci.* **24,** 68–72.
78. Robin E. D., Murphy B. J., and Theodore J. (1984) Coordinate regulation of glycolysis by hypoxia in mammalian cells. *J. Cell. Physiol.* **118,** 287–290.
79. Tian G. F. and Baker A. J. (2000) Glycolysis prevents anoxia-induced synaptic transmission damage in rat hippocampal slices. *J. Neurophysiol.* **83,** 1830–1839.
80. Schurr A., West C. A., Reid K. H., Tseng M. T., Reiss S. J., and Rigor B. M. (1987) Increased glucose improves recovery of neuronal function after cerebral hypoxia in vitro. *Brain Res.* **421,** 135–139.
81. Callahan D. J., Engle M. J., and Volpe J. J. (1990) Hypoxic injury to developing glial cells: protective effect of high glucose. *Pediatr. Res.* **27,** 186–190.
82. Schurr A., West C. A., and Rigor B. M. (1988) Lactate-supported synaptic function in the rat hippocampal slice preparation. *Science* **240,** 1326–1328.
83. Ballanyi K., Volker A., and Richter D. W. (1996) Functional relevance of anaerobic metabolism in the isolated respiratory network of newborn rats. *Pflugers Arch.* **432,** 741–748.
84. LaManna J. C., Haxhiu M. A., Kutina-Nelson K. L., et al. (1996) Decreased energy metabolism in

brain stem during central respiratory depression in response to hypoxia. *J. Appl. Physiol.* **81,** 1772–1777.
85. Siesjo B. K., Katsura K., and Kristian T. (1996) Acidosis-related damage. *Adv. Neurol.* **71,** 209–233.
86. Fujiwara N., Abe T., Endoh H., Warashina A., and Shimoji K. (1992) Changes in intracellular pH of mouse hippocampal slices responding to hypoxia and/or glucose depletion. *Brain Res.* **572,** 335–339.
87. Pulsinelli W. A., Brierley J. B., and Plum F. (1982) Temporal profile of neuronal damage in a model of transient forebrain ischemia. *Ann. Neurol.* **11,** 491–498.
88. Giffard R. G., Monyer H., Christine C. W., and Choi D. W. (1990) Acidosis reduces NMDA receptor activation, glutamate neurotoxicity, and oxygen-glucose deprivation neuronal injury in cortical cultures. *Brain Res.* **506,** 339–342.
89. Tombaugh G. C. and Sapolsky R. M. (1990) Mild acidosis protects hippocampal neurons from injury induced by oxygen and glucose deprivation. *Brain Res.* **506,** 343–345.
90. Krnjevic K. (1993) Central cholinergic mechanisms and function. *Prog. Brain Res.* **98,** 285–292.
91. Martin L. J., Brambrink A. M., Lehmann C., et al. (1997) Hypoxia-ischemia causes abnormalities in glutamate transporters and death of astroglia and neurons in newborn striatum. *Ann. Neurol.* **42,** 335–348.
92. Crepel V., Krnjevic K., and Ben-Ari Y. (1992) Developmental and regional differences in the vulnerability of rat hippocampal slices to lack of glucose. *Neuroscience* **47,** 579–587.
93. Ballanyi K., Doutheil J., and Brockhaus J. (1996) Membrane potentials and microenvironment of rat dorsal vagal cells in vitro during energy depletion. *J. Physiol.* **495,** 769–784.
94. Ballanyi K., Kuwana S., Volker A., Morawietz G., and Richter D. W. (1992) Developmental changes in the hypoxia tolerance of the in vitro respiratory network of rats. *Neurosci. Lett.* **148,** 141–144.
95. Donnelly D. F., Jiang C., and Haddad G. G. (1992) Comparative responses of brain stem and hippocampal neurons to O2 deprivation: in vitro intracellular studies. *Am. J. Physiol.* **262,** L549–L554.
96. O'Reilly J. P., Jiang C., and Haddad G. G. (1995) Major differences in response to graded hypoxia between hypoglossal and neocortical neurons. *Brain Res.* **683,** 179–186.
97. Cowan A. I. and Martin R. L. (1992) Ionic basis of membrane potential changes induced by anoxia in rat dorsal vagal motoneurones. *J. Physiol.* **455,** 89–109.
98. Nolan P. C. and Waldrop T. G. (1996) Ventrolateral medullary neurons show age-dependent depolarizations to hypoxia in vitro. *Brain Res. Dev. Brain Res.* **91,** 111–120.
99. Thoby-Brisson M. and Ramirez J. M. (2000) Role of inspiratory pacemaker neurons in mediating the hypoxic response of the respiratory network in vitro. *J. Neurosci.* **20,** 5858–5866.
100. Cummins T. R., Donnelly D. F., and Haddad G. G. (1991) Effect of metabolic inhibition on the excitability of isolated hippocampal CA1 neurons: developmental aspects. *J. Neurophysiol.* **66,** 1471–1482.
101. Belousov A. B., Godfraind J. M., and Krnjevic K. (1995) Internal Ca2+ stores involved in anoxic responses of rat hippocampal neurons. *J. Physiol.* **486,** 547–556.
102. Hyllienmark L. and Brismar T. (1996) Effect of metabolic inhibition on K+ channels in pyramidal cells of the hippocampal CA1 region in rat brain slices. *J Physiol.* **496 (Pt 1),** 155–164.
103. Hyllienmark L. and Brismar T. (1999) Effect of hypoxia on membrane potential and resting conductance in rat hippocampal neurons. *Neuroscience* **91,** 511–517.
104. Erdemli G., Xu Y. Z., and Krnjevic K. (1998) Potassium conductance causing hyperpolarization of CA1 hippocampal neurons during hypoxia. *J. Neurophysiol.* **80,** 2378–2390.
105. Misgeld U. and Frotscher M. (1982) Dependence of the viability of neurons in hippocampal slices on oxygen supply. *Brain Res. Bull.* **8,** 95–100.
106. Reiner P. B., Laycock A. G., and Doll C. J. (1990) A pharmacological model of ischemia in the hippocampal slice. *Neurosci. Lett.* **119,** 175–178.
107. Zhang L. and Krnjevic K. (1993) Whole-cell recording of anoxic effects on hippocampal neurons in slices. *J. Neurophysiol.* **69,** 118–127.
108. Fung M. L. and Haddad G. G. (1997) Anoxia-induced depolarization in CA1 hippocampal neurons: role of Na+-dependent mechanisms. *Brain Res.* **762,** 97–102.
109. Rosen A. S. and Morris M. E. (1993) Anoxic depression of excitatory and inhibitory postsy-

naptic potentials in rat neocortical slices. *J. Neurophysiol.* **69,** 109–117.
110. Englund M., Hyllienmark L., and Brismar T. (2001) Chemical hypoxia in hippocampal pyramidal cells affects membrane potential differentially depending on resting potential. *Neuroscience* **106,** 89–94.
111. Godfraind J. M., Kawamura H., Krnjevic K., and Pumain R. (1971) Actions of dinitrophenol and some other metabolic inhibitors on cortical neurones. *J. Physiol.* **215,** 199–222.
112. Yamamoto S., Tanaka E., Shoji Y., Kudo Y., Inokuchi H., and Higashi H. (1997) Factors that reverse the persistent depolarization produced by deprivation of oxygen and glucose in rat hippocampal CA1 neurons in vitro. *J. Neurophysiol.* **78,** 903–911.
113. Zhu P. J. and Krnjevic K. (1997) Endogenous adenosine on membrane properties of CA1 neurons in rat hippocampal slices during normoxia and hypoxia. *Neuropharmacology* **36,** 169–176.
114. Pascual O., Morin-Surun M. P., Barna B., Denavit-Saubie M., Pequignot J. M., and Champagnat J. (2002) Progesterone reverses the neuronal responses to hypoxia in rat nucleus tractus solitarius in vitro. *J. Physiol.* **544,** 511–520.
115. Croning M. D., Zetterstrom T. S., Grahame-Smith D. G., and Newberry N. R. (1995) Action of adenosine receptor antagonists on hypoxia-induced effects in the rat hippocampus in vitro. *Br. J. Pharmacol.* **116,** 2113–2119.
116. Yang J. J., Chou Y. C., Lin M. T., and Chiu T. H. (1997) Hypoxia-induced differential electrophysiological changes in rat locus coeruleus neurons. *Life Sci.* **61,** 1763–1773.
117. Wang G., Zhou P., Repucci M. A., Golanov E. V., and Reis D. J. (2001) Specific actions of cyanide on membrane potential and voltage-gated ion currents in rostral ventrolateral medulla neurons in rat brainstem slices. *Neurosci. Lett.* **309,** 125–129.
118. Mercuri N. B., Bonci A., Calabresi P., Stratta F., and Bernardi G. (1994) Responses of rat mesencephalic dopaminergic neurons to a prolonged period of oxygen deprivation. *Neuroscience* **63,** 757–764.
119. Mercuri N. B., Bonci A., Johnson S. W., Stratta F., Calabresi P., and Bernardi G. (1994) Effects of anoxia on rat midbrain dopamine neurons. *J. Neurophysiol.* **71,** 1165–1173.
120. Calabresi P., Pisani A., Mercuri N. B, and Bernardi G. (1995) Hypoxia-induced electrical changes in striatal neurons. *J. Cereb. Blood Flow Metab.* **15,** 1141–1145.
121. Dillon G. H. and Waldrop T. G. (1993) Responses of feline caudal hypothalamic cardiorespiratory neurons to hypoxia and hypercapnia. *Exp. Brain Res.* **96,** 260–272.
122. Ryan J. W. and Waldrop T. G. (1995) Hypoxia sensitive neurons in the caudal hypothalamus project to the periaqueductal gray. *Respir. Physiol.* **100,** 185–194.
123. Dillon G. H. and Waldrop T. G. (1992) In vitro responses of caudal hypothalamic neurons to hypoxia and hypercapnia. *Neuroscience* **51,** 941–950.
124. Horn E. M., Dillon G. H., Fan Y. P., and Waldrop T. G. (1999) Developmental aspects and mechanisms of rat caudal hypothalamic neuronal responses to hypoxia. *J. Neurophysiol.* **81,** 1949–1959.
125. Watts A. E., Hicks G. A., and Henderson G. (1995) Putative pre- and postsynaptic ATP-sensitive potassium channels in the rat substantia nigra in vitro. *J. Neurosci.* **15,** 3065–3074.
126. Nieber K., Sevcik J., and Illes P. (1995) Hypoxic changes in rat locus coeruleus neurons in vitro. *J. Physiol.* **486,** 33–46.
127. Duchen M. R. (1990) Effects of metabolic inhibition on the membrane properties of isolated mouse primary sensory neurones. *J. Physiol.* **424,** 387–409.
128. Jiang C., Sigworth F. J., and Haddad G. G. (1994) Oxygen deprivation activates an ATP-inhibitable K+ channel in substantia nigra neurons. *J. Neurosci.* **14,** 5590–5602.
129. Mourre C., Ben Ari Y., Bernardi H., Fosset M., and Lazdunski M. (1989) Antidiabetic sulfonylureas: localization of binding sites in the brain and effects on the hyperpolarization induced by anoxia in hippocampal slices. *Brain Res.* **486,** 159–164.
130. Chung I., Zhang Y., Eubanks J. H., and Zhang L. (1998) Attenuation of hypoxic current by intracellular applications of ATP regenerating agents in hippocampal CA1 neurons of rat brain slices. *Neuroscience* **86,** 1101–1107.
131. Pisani A., Calabresi P., Centonze D., Marfia G. A., and Bernardi G. (1999) Electrophysiological recordings and calcium measurements in striatal large aspiny interneurons in response to combined O2/glucose deprivation. *J. Neurophysiol.* **81,** 2508–2516.
132. Wan Q., Yao H., and Wang F. (1999) Involvement of K(+) channels in the inhibitory effects

of adenosine on anoxia-induced [Ca(2+)](i) increase in cultured rat hippocampal CA1 neurons. *Biol. Signals Recept.* **8,** 309–315.
133. Garcia de Arriba S., Franke H., Pissarek M., Nieber K., and Illes P. (1999) Neuroprotection by ATP-dependent potassium channels in rat neocortical brain slices during hypoxia. *Neurosci. Lett.* **273,** 13–16.
134. Lopez-Barneo J., Lopez-Lopez J. R., Urena J., and Gonzalez C. (1988) Chemotransduction in the carotid body: K+ current modulated by PO2 in type I chemoreceptor cells. *Science* **241,** 580–582.
135. Lopez-Barneo J. (1994) Oxygen-sensitive ion channels: how ubiquitous are they? *Trends Neurosci.* **17,** 133–135.
136. Fearon I. M., Palmer A. C., Balmforth A. J., Ball S. G., Varadi G., and Peers C. (1999) Modulation of recombinant human cardiac L-type Ca2+ channel alpha1C subunits by redox agents and hypoxia. *J. Physiol.* **514,** 629–637.
137. Fleidervish I. A., Gebhardt C., Astman N., Gutnick M. J., and Heinemann U. (2001) Enhanced spontaneous transmitter release is the earliest consequence of neocortical hypoxia that can explain the disruption of normal circuit function. *J. Neurosci.* **21,** 4600–4608.
138. Zawar C. and Neumcke B. (2000) Differential activation of ATP-sensitive potassium channels during energy depletion in CA1 pyramidal cells and interneurones of rat hippocampus. *Pflugers Arch.* **439,** 256–262.
139. Shan H. Q. and Cheng J. S. (2000) Effect of adenosine on adenosine triphosphate-sensitive potassium channel during hypoxia in rat hippocampal neurons. *Neurosci. Lett.* **286,** 45–48.
140. Yamada K., Ji J. J., Yuan H., et al. (2001) Protective role of ATP-sensitive potassium channels in hypoxia-induced generalized seizure. *Science.* **292,** 1543–1546.
141. Guatteo E., Federici M., Siniscalchi A., Knopfel T., Mercuri N. B., and Bernardi G. (1998) Whole cell patch-clamp recordings of rat midbrain dopaminergic neurons isolate a sulphonylurea- and ATP-sensitive component of potassium currents activated by hypoxia. *J. Neurophysiol.* **79,** 1239–1245.
142. Kulik A., Brockhaus J., Pedarzani P., and Ballanyi K. (2002) Chemical anoxia activates ATP-sensitive and blocks Ca(2+)-dependent K(+) channels in rat dorsal vagal neurons in situ. *Neuroscience* **110,** 541–554.
143. Park Y. K., Jung S. J., Yoo J. E., Kwak J., Lim W., and Kim J. (2003) Effect of acute hypoxia on ATP-sensitive potassium currents in substantia gelatinosa neurons of juvenile rats. *Pflugers Arch.* **446,** 600–606.
144. Mironov S. L., Langohr K., Haller M., and Richter D. W. (1998) Hypoxia activates ATP-dependent potassium channels in inspiratory neurones of neonatal mice. *J. Physiol.* **509,** 755–766.
145. Mironov S. L. and Richter D. W. (2000) Intracellular signalling pathways modulate K(ATP) channels in inspiratory brainstem neurones and their hypoxic activation: involvement of metabotropic receptors, G-proteins and cytoskeleton. *Brain Res.* **853,** 60–67.
146. Haller M., Mironov S. L., Karschin A., and Richter D. W. (2001) Dynamic activation of K(ATP) channels in rhythmically active neurons. *J. Physiol.* **537,** 69–81.
147. Nowicky A. V. and Duchen M. R. (1998) Changes in [Ca2+]i and membrane currents during impaired mitochondrial metabolism in dissociated rat hippocampal neurons. *J. Physiol.* **507,** 131–145.
148. Liu H., Moczydlowski E., and Haddad G. G. (1999) O(2) deprivation inhibits Ca(2+)-activated K(+) channels via cytosolic factors in mice neocortical neurons. *J. Clin. Invest.* **104,** 577–588.
149. Buckler K. J. (1997) A novel oxygen-sensitive potassium current in rat carotid body type I cells. *J. Physiol.* **498,** 649–662.
150. Buckler K. J., Williams B. A., and Honore E. (2000) An oxygen-, acid- and anaesthetic-sensitive TASK-like background potassium channel in rat arterial chemoreceptor cells. *J. Physiol.* **525,** 135–142.
151. Hartness M. E., Lewis A., Searle G. J., O'Kelly I., Peers C., and Kemp P. J. (2001) Combined antisense and pharmacological approaches implicate hTASK as an airway O(2) sensing K(+) channel. *J. Biol. Chem.* **276,** 26,499–26,508.
152. Campanucci V. A., Fearon I. M., and Nurse C. A. (2003) A novel O2-sensing mechanism in rat glossopharyngeal neurones mediated by a halothane-inhibitable background K+ conductance. *J. Physiol.* **548,** 731–743.
153. Crill W. E. (1996) Persistent sodium current in mammalian central neurons. *Annu. Rev. Physiol.* **58,** 349–362.
154. Ju Y. K., Saint D. A., and Gage P. W. (1996) Hypoxia increases persistent sodium current

in rat ventricular myocytes. *J. Physiol.* **497,** 337–347.
155. Hammarstrom A. K. and Gage P. W. (2002) Hypoxia and persistent sodium current. *Eur. Biophys J.* **31,** 323–330.
156. Horn E. M. and Waldrop T. G. (2000) Hypoxic augmentation of fast-inactivating and persistent sodium currents in rat caudal hypothalamic neurons. *J. Neurophysiol.* **84,** 2572–2581.
157. Cummins T. R., Jiang C., and Haddad G. G. (1993) Human neocortical excitability is decreased during anoxia via sodium channel modulation. *J. Clin. Invest.* **91,** 608–615.
158. O'Reilly J. P., Cummins T. R., and Haddad G. G. (1997) Oxygen deprivation inhibits Na+ current in rat hippocampal neurones via protein kinase C. *J. Physiol.* **503,** 479–488.
159. Kawai Y., Qi J., Comer A. M., Gibbons H., Win J., and Lipski J. (1999) Effects of cyanide and hypoxia on membrane currents in neurones acutely dissociated from the rostral ventrolateral medulla of the rat. *Brain Res.* **830,** 246–257.
160. Mazza E. Jr., Edelman N. H., and Neubauer J. A. (2000) Hypoxic excitation in neurons cultured from the rostral ventrolateral medulla of the neonatal rat. *J. Appl. Physiol.* **88,** 2319–2329.
161. Lukyanetz E. A., Shkryl V. M., Kravchuk O. V., and Kostyuk P. G. (2003) Action of hypoxia on different types of calcium channels in hippocampal neurons. *Biochim. Biophys. Acta.* **1618,** 33–38.
162. Lukyanetz E. A., Shkryl V. M., Kravchuk O. V., and Kostyuk P. G. (2003) Effect of hypoxia on calcium channels depends on extracellular calcium in CA1 hippocampal neurons. *Brain Res.* **980,** 128–134.
163. Sun M. K. and Reis D. J. (1994) Hypoxia-activated Ca2+ currents in pacemaker neurones of rat rostral ventrolateral medulla in vitro. *J. Physiol.* **476,** 101–116.
164. Mironov S. L. and Richter D. W. (1998) L-type Ca2+ channels in inspiratory neurones of mice and their modulation by hypoxia. *J Physiol.* **512,** 75–87.
165. Elsen F. P. and Ramirez J. M. (1997) Hypoxia reduces the amplitude of voltage dependent calcium currents in the isolated respiratory system of mice. *Soc. Neurosci.* **Abstr. 27,** 495.11
166. Erdemli G. and Crunelli V. (2000) Release of monoamines and nitric oxide is involved in the modulation of hyperpolarization-activated inward current during acute thalamic hypoxia. *Neuroscience* **96,** 565–574.
167. Mironov S. L., Langohr K., and Richter D. W. (2000) Hyperpolarization-activated current, Ih, in inspiratory brainstem neurons and its inhibition by hypoxia. *Eur. J. Neurosci.* **12,** 520–526.
168. Inoue M., Fujishiro N., and Imanaga I. (1999) Na+ pump inhibition and non-selective cation channel activation by cyanide and anoxia in guinea-pig chromaffin cells. *J. Physiol.* **519,** 385–396.
169. Lees G. J. (1991) Inhibition of sodium-potassium-ATPase: a potentially ubiquitous mechanism contributing to central nervous system neuropathology. *Brain Res. Brain Res. Rev.* **16,** 283–300.
170. Luhmann H. J. (1996) Ischemia and lesion induced imbalances in cortical function. *Prog. Neurobiol.* **48,** 131–166.
171. Jha A. and Deshpande S. B. (2003) Aglycemia and ischemia depress spinal synaptic transmission via inhibitory systems involving NMDA receptors. *Eur. J. Pharmacol.* **481,** 189–196.
172. Deshpande S. B. and Jha A. (2004) Aglycemia and ischemia depress monosynaptic and polysynaptic reflexes in neonatal rat spinal cord in vitro by involving different types of 5-hydroxytryptamine receptors. *Neurosci. Lett.* **372,** 167–172.
173. Xu Z. C. and Pulsinelli W. A. (1996) Electrophysiological changes of CA1 pyramidal neurons following transient forebrain ischemia: an in vivo intracellular recording and staining study. *J. Neurophysiol.* **76,** 1689–1697.
174. Hershkowitz N., Katchman A. N., and Veregge S. (1993) Site of synaptic depression during hypoxia: a patch-clamp analysis. *J. Neurophysiol.* **69,** 432–441.
175. Coelho J. E., de Mendonca A., and Ribeiro J. A. (2000) Presynaptic inhibitory receptors mediate the depression of synaptic transmission upon hypoxia in rat hippocampal slices. *Brain Res.* **869,** 158–165.
176. Frenguelli B. G., Llaudet E., and Dale N. (2003) High-resolution real-time recording with microelectrode biosensors reveals novel aspects of adenosine release during hypoxia in rat hippocampal slices. *J. Neurochem.* **86,** 1506–1515.
177. Pearson T. and Frenguelli B. G. (2004) Adenoceptor subtype-specific acceleration of the hypoxic depression of excitatory synaptic transmission in area CA1 of the rat hippocampus. *Eur. J. Neurosci.* **20,** 1555–1565.

178. Hentschel S., Lewerenz A., and Nieber K. (2003) Activation of A(3) receptors by endogenous adenosine inhibits synaptic transmission during hypoxia in rat cortical neurons. *Restor. Neurol. Neurosci.* **21,** 55–63.
179. Centonze D., Saulle E., Pisani A., Bernardi G., and Calabresi P. (2001) Adenosine-mediated inhibition of striatal GABAergic synaptic transmission during in vitro ischaemia. *Brain* **124,** 1855–1865.
180. Pierrefiche O., Bischoff A. M., Richter D. W., and Spyer K. M. (1997) Hypoxic response of hypoglossal motoneurones in the in vivo cat. *J. Physiol.* **505,** 785–795.
181. Richter D. W., Bischoff A., Anders K., Bellingham M., and Windhorst U. (1991) Response of the medullary respiratory network of the cat to hypoxia. *J. Physiol.* **443,** 231–256.
182. Lieske S. P., Thoby-Brisson M., Telgkamp P., and Ramirez J. M. (2000) Reconfiguration of the neural network controlling multiple breathing patterns: eupnea, sighs and gasps. *Nat. Neurosci.* **3,** 600–607.
183. Hammond C., Crepel V., Gozlan H., and Ben-Ari Y. (1994) Anoxic LTP sheds light on the multiple facets of NMDA receptors. *Trends Neurosci.* **17,** 497–503.
184. Hellweg R., von Arnim C. A., Buchner M., Huber R., and Riepe M. W. (2003) Neuroprotection and neuronal dysfunction upon repetitive inhibition of oxidative phosphorylation. *Exp. Neurol.* **183,** 346–354.
185. Rosen A. S. and Morris M. E. (1993) Anoxic depression of excitatory and inhibitory postsynaptic potentials in rat neocortical slices. *J. Neurophysiol.* **69,** 109–117.
186. Kasa P., Rakonczay Z., and Gulya K. (1997) The cholinergic system in Alzheimer's disease. *Prog. Neurobiol.* **52,** 511–535.
187. Porkka-Heiskanen T., Strecker R. E., Thakkar M., Bjorkum A. A., Greene R. W., and McCarley R. W. (1997) Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science* **276,** 1265–1268.
188. Fowler J. C. (1989) Adenosine antagonists delay hypoxia-induced depression of neuronal activity in hippocampal brain slice. *Brain Res.* **490,** 378–384.
189. Gribkoff V. K., Bauman L. A., and VanderMaelen C. P. (1990) The adenosine antagonist 8-cyclopentyltheophylline reduces the depression of hippocampal neuronal responses during hypoxia. *Brain Res.* **512,** 353–357.
190. Canhao P., de Mendonca A., and Ribeiro J. A. (1994) 1,3-Dipropyl-8-cyclopentylxanthine attenuates the NMDA response to hypoxia in the rat hippocampus. *Brain Res.* **661,** 265–273.
191. Dale N., Pearson T., and Frenguelli B. G. (2000) Direct measurement of adenosine release during hypoxia in the CA1 region of the rat hippocampal slice. *J. Physiol.* **526,** 143–155.
192. Pearson T., Currie A. J., Etherington L. A., et al. (2003) Plasticity of purine release during cerebral ischemia: clinical implications? *J. Cell. Mol. Med.* **7,** 362–375.
193. Zetterstrom T., Vernet L., Ungerstedt U., Tossman U., Jonzon B., and Fredholm B. B. (1982) Purine levels in the intact rat brain. Studies with an implanted perfused hollow fibre. *Neurosci. Lett.* **29,** 111–115.
194. Latini S., Bordoni F., Corradetti R., Pepeu G., and Pedata F. (1998) Temporal correlation between adenosine outflow and synaptic potential inhibition in rat hippocampal slices during ischemia-like conditions. *Brain Res.* **794,** 325–328.
195. de Mendonca A. and Ribeiro J. A. (1997) Contribution of metabotropic glutamate receptors to the depression of excitatory postsynaptic potentials during hypoxia. *Neuroreport* **8,** 3667–3671.
196. Doherty J. and Dingledine R. (1997) Regulation of excitatory input to inhibitory interneurons of the dentate gyrus during hypoxia. *J. Neurophysiol.* **77,** 393–404.
197. Cherniack N. S., Edelman N. H., and Lahiri S. (1971) The effect of hypoxia and hypercapnia on respiratory neuron activity and cerebral aerobic metabolism. *Chest* **59,** 29S.
198. Haddad G. G. and Mellins R. B. (1984) Hypoxia and respiratory control in early life. *Annu. Rev. Physiol.* **46,** 629–643.
199. Bureau M. A., Zinman R., Foulon P., and Begin R. (1984) Diphasic ventilatory response to hypoxia in newborn lambs. *J. Appl. Physiol.* **56,** 84–90.
200. St. John W. M. and Bianchi A. L. (1985) Responses of bulbospinal and laryngeal respiratory neurons to hypercapnia and hypoxia. *J. Appl. Physiol.* **59,** 1201–1207.
201. Fregosi R. F., Knuth S. L., Ward D. K., and Bartlett D. Jr. (1987) Hypoxia inhibits abdominal expiratory nerve activity. *J. Appl. Physiol.* **63,** 211–220.
202. Maruyama R., Yoshida A., and Fukuda Y. (1989) Differential sensitivity to hypoxic inhi-

bition of respiratory processes in the anesthetized rat. *Jpn. J. Physiol.* **39,** 857–871.
203. Neubauer J. A., Melton J. E., and Edelman N. H. (1990) Modulation of respiration during brain hypoxia. *J. Appl. Physiol.* **68,** 441–451.
204. Trippenbach T., Richter D. W., and Acker H. (1990) Hypoxia and ion activities within the brain stem of newborn rabbits. *J. Appl. Physiol.* **68,** 2494–2503.
205. Kahraman L. and Thach B. T. (2004) Inhibitory effects of hyperthermia on mechanisms involved in autoresuscitation from hypoxic apnea in mice: a model for thermal stress causing SIDS. *J. Appl. Physiol.* **97,** 669–674.
206. Gozal D., Gozal E., Reeves S. R., and Lipton A. J. (2002) Gasping and autoresuscitation in the developing rat: effect of antecedent intermittent hypoxia. *J. Appl. Physiol.* **92,** 1141–1144.
207. Deshpande P., Khurana A., Hansen P., Wilkins D., and Thach B. T. (1999) Failure of autoresuscitation in weanling mice: significance of cardiac glycogen and heart rate regulation. *J. Appl. Physiol.* **87,** 203–210.
208. Harper R. M., Kinney H. C., Fleming P. J., and Thach B. T. (2000) Sleep influences on homeostatic functions: implications for sudden infant death syndrome. *Respir. Physiol.* **119,** 123–132.
209. Hunt C. E. (1992) The cardiorespiratory control hypothesis for sudden infant death syndrome. *Clin. Perinatol.* **19,** 757–771.
210. Poets C. F., Meny R. G., Chobanian M. R., and Bonofiglo R. E. (1999) Gasping and other cardiorespiratory patterns during sudden infant deaths. *Pediatr. Res.* **45,** 350–354.
211. Kara T., Narkiewicz K., and Somers V. K. (2003) Chemoreflexes: physiology and clinical implications. *Acta Physiol. Scand.* **177,** 377–384.
212. Solomon I. C. (2004) Ionotropic excitatory amino acid receptors in pre-Botzinger complex play a modulatory role in hypoxia-induced gasping in vivo. *J. Appl. Physiol.* **96,** 1643–1650.
213. Solomon I. C. (2005) Glutamate neurotransmission is not required for, but may modulate, hypoxic sensitivity of pre-Botzinger complex in vivo. *J. Neurophysiol.* **93,** 1278–1284.
214. Ramirez J. M., Quellmalz U. J., and Richter D. W. (1996) Postnatal changes in the mammalian respiratory network as revealed by the transverse brainstem slice of mice. *J. Physiol.* **491,** 799–812.
215. Telgkamp P. and Ramirez J. M. (1999) Differential responses of respiratory nuclei to anoxia in rhythmic brain stem slices of mice. *J. Neurophysiol.* **82,** 2163–2170.
216. Ballanyi K., Volker A., and Richter D. W. (1994) Anoxia induced functional inactivation of neonatal respiratory neurones in vitro. *Neuroreport* **6,** 165–168.
217. Richter D. W., Schmidt-Garcon P., Pierrefiche O., Bischoff A. M., and Lalley P. M. (1999) Neurotransmitters and neuromodulators controlling the hypoxic respiratory response in anaesthetized cats. *J. Physiol.* **514,** 567–578.
218. Fazekas J. F., Alexander F. A. D., and Himwich H. E. (1941). Tolerance of the newborn to anoxia. *J. Physiol. Lond.* **134,**282–287
219. Adolph E. F. (1969) Regulations during survival without oxygen in infant mammals. *Respir. Physiol.* **7,** 356–368.
220. Jacobi M. S. and Thach B. T. (1989) Effect of maturation on spontaneous recovery from hypoxic apnea by gasping. *J. Appl. Physiol.* **66,** 2384–2390.
221. Fewell J. E. and Wong V. H. (2002) Interleukin-1beta-induced fever does not alter the ability of 5- to 6-day-old rat pups to autoresuscitate from hypoxia-induced apnoea. *Exp. Physiol.* **87,** 17–24.
222. Brockhaus J., Ballanyi K., Smith J. C., and Richter D. W. (1993) Microenvironment of respiratory neurons in the in vitro brainstem-spinal cord of neonatal rats. *J. Physiol.* **462,** 421–445.
223. Voipio J. and Ballanyi K. (1997) Interstitial PCO2 and pH, and their role as chemostimulants in the isolated respiratory network of neonatal rats. *J. Physiol.* **499,** 527–542.
224. Volker A., Ballanyi K., and Richter D. W. (1995) Anoxic disturbance of the isolated respiratory network of neonatal rats. *Exp. Brain Res.* **103,** 9–19.
225. Ballanyi K., Onimaru H., and Homma I. (1999) Respiratory network function in the isolated brainstem-spinal cord of newborn rats. *Prog. Neurobiol.* **59,** 583–634.
226. Greer J. J. and Carter J. E. (1995) Effects of cyanide on the neural mechanisms controlling breathing in the neonatal rat in vitro. *Neurotoxicology* **16,** 211–215.
227. England S. J., Melton J. E., Douse M. A., and Duffin J. (1995) Activity of respiratory neurons during hypoxia in the chemodenervated cat. *J. Appl. Physiol.* **78,** 856–861.
228. Morawietz G., Ballanyi K., Kuwana S., and Richter D. W. (1995) Oxygen supply and ion homeostasis of the respiratory network in the

in vitro perfused brainstem of adult rats. *Exp. Brain Res.* **106,** 265–274.
229. Sears T. A. (1964) Investigations on respiratory motoneurones of the thoracic spinal cord. *Prog. Brain Res.* **12,** 259–273.
230. St. John W. M., Bartlett D. Jr. (1979) Comparison of phrenic motoneuron responses to hypercapnia and isocapnic hypoxia. *J. Appl. Physiol.* **46,** 1096–1102.
231. Hwang J. C., Bartlett D. Jr., and St. John W. M. (1983) Characterization of respiratory-modulated activities of hypoglossal motoneurons. *J. Appl. Physiol.* **55,** 793–798.
232. St John W. M. and Wang S. C. (1977) Alteration from apneusis to more regular rhythmic respiration in decerebrate cats. *Respir. Physiol.* **31,** 91–106.
233. Bergmann F. and Keller B. U. (2004) Impact of mitochondrial inhibition on excitability and cytosolic Ca2+ levels in brainstem motoneurones from mouse. *J. Physiol.* **555,** 45–59.
234. McCrimmon D. R., Ramirez J. M., Alford S., and Zuperku E. J. (2000) Unraveling the mechanism for respiratory rhythm generation. *Bioessays.* **22,** 6–9.
235. Smith J. C., Ellenberger H. H., Ballanyi K., Richter D. W., and Feldman J. L. (1991) Pre-Botzinger complex: a brainstem region that may generate respiratory rhythm in mammals. *Science* **254,** 726–729.
236. Onimaru H. and Homma I. (2003) A novel functional neuron group for respiratory rhythm generation in the ventral medulla. *J. Neurosci.* **23,** 1478–1486
237. Mellen N. M., Janczewski W. A., Bocchiaro C. M., and Feldman J. L. (2003) Opioid-induced quantal slowing reveals dual networks for respiratory rhythm generation. *Neuron* **37,** 821–826.
238. Peña F. and Ramirez J. M. (2002) Endogenous activation of serotonin-2A receptors is required for respiratory rhythm generation in vitro. *J. Neurosci.* **22,** 11,055–11,064.
239. Peña F. and Ramirez J. M. (2004) Substance P-mediated modulation of pacemaker properties in the mammalian respiratory network. *J. Neurosci.* **24,** 7549–7556.
240. Ogilvie M. D., Gottschalk A., Anders K., Richter D. W., and Pack A. I. (1992) A network model of respiratory rhythmogenesis. *Am. J. Physiol.* **263,** R962–R975.
241. Ramirez J. M. and Lieske S. P. (2003) Commentary on the definition of eupnea and gasping. *Respir. Physiol. Neurobiol.* **139,** 113–119.
242. Lieske S. P., Thoby-Brisson M., and Ramirez J. M. (2001) Reconfiguration of the central respiratory network under normoxic and hypoxic conditions. *Adv. Exp. Med. Biol.* **499,** 171–178.
243. Ramirez J. M., Quellmalz U. J., Wilken B., and Richter D. W. (1998) The hypoxic response of neurones within the in vitro mammalian respiratory network. *J. Physiol.* **507,** 571–582.
244. Koshiya N. and Smith J. C. (1999) Neuronal pacemaker for breathing visualized in vitro. *Nature* **400,** 360–363.
245. Del Negro C. A., Morgado-Valle C., Hayes J. A., et al. (2005) Sodium and calcium-mediated pacemaker neurons and respiratory rhythm generation. *J. Neurosci.* **25,** 446–453.
246. Hill A. (1991) Current concepts of hypoxic-ischemic cerebral injury in the term newborn. *Pediatr. Neurol.* **7,** 317–325.
247. Latchaw R. E. and Truwit C. E. (1995) Imaging of perinatal hypoxic-ischemic brain injury. *Semin. Pediatr. Neurol.* **2,** 72–89.
248. Roland E. H. and Hill A. (1995) Clinical aspects of perinatal hypoxic-ischemic brain injury. *Semin. Pediatr. Neurol.* **2,** 57–71.
249. Suzuki R., Yamaguchi T., Li C. L., and Klatzo I. (1983) The effects of 5-minute ischemia in Mongolian gerbils: II. Changes of spontaneous neuronal activity in cerebral cortex and CA1 sector of hippocampus. *Acta Neuropathol. (Berl).* **60,** 217–222.
250. Doolette D. J. and Kerr D. I. (1995) Hyperexcitability in CA1 of the rat hippocampal slice following hypoxia or adenosine. *Brain Res.* **677,** 127–137.
251. Crepel V., Hammond C., Chinestra P., Diabira D., and Ben-Ari Y. (1993) A selective LTP of NMDA receptor-mediated currents induced by anoxia in CA1 hippocampal neurons. *J. Neurophysiol.* **70,** 2045–2055.
252. Crepel V., Hammond C., Krnjevic K., Chinestra P., and Ben-Ari Y. (1993) Anoxia-induced LTP of isolated NMDA receptor-mediated synaptic responses. *J. Neurophysiol.* **69,** 1774–1778.
253. Gozlan H., Diabira D., Chinestra P., and Ben-Ari Y. (1994) Anoxic LTP is mediated by the redox modulatory site of the NMDA receptor. *J. Neurophysiol.* **72,** 3017–3022.
254. Hsu K. S. and Huang C. C. (1997) Characterization of the anoxia-induced long-term synaptic potentiation in area CA1 of the rat hippocampus. *Br. J. Pharmacol.* **122,** 671–681.
255. Lyubkin M., Durand D. M., and Haxhiu M. A. (1997) Interaction between tetanus long-term potentiation and hypoxia-induced potentia-

tion in the rat hippocampus. *J. Neurophysiol.* **78,** 2475–2482.
256. Calabresi P., Saulle E., Centonze D., Pisani A., Marfia G. A., and Bernardi G. (2002) Post-ischaemic long-term synaptic potentiation in the striatum: a putative mechanism for cell type-specific vulnerability. *Brain* **125,** 844–860.
257. Schmidt-Kastner R. and Freund T. F. (1991) Selective vulnerability of the hippocampus in brain ischemia. *Neuroscience* **40,** 599–636.
258. Vyskocil F., Kritz N., and Bures J. (1972) Potassium-selective microelectrodes used for measuring the extracellular brain potassium during spreading depression and anoxic depolarization in rats. *Brain Res.* **39,** 255–259.
259. Muller M. and Somjen G. G. (2000) Na(+) dependence and the role of glutamate receptors and Na(+) channels in ion fluxes during hypoxia of rat hippocampal slices. *J. Neurophysiol.* **84,** 1869–1880.
260. Leão A. A. P. (1947), Further observations on the spreading depression of activity in the cerebral cortex. *J Neurophysiol* **10,** 409–414.
261. Marshall W. H. (1959) Spreading cortical depression of Leao. *Physiol. Rev.* **39,** 239–279.
262. Nicholson C. (1984) Comparative neurophysiology of spreading depression in the cerebellum. *An. Acad. Bras. Cienc.* **56,** 481–494.
263. Somjen G. G., Aitken P. G., Czeh G. L., Herreras O., Jing J., and Young J. N. (1992) Mechanism of spreading depression: a review of recent findings and a hypothesis. *Can. J. Physiol. Pharmacol.* **70 Suppl,** S248–S254.
264. Somjen G. G. (2001) Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. *Physiol. Rev.* **81,** 1065–1096.
265. Bahar S., Fayuk D., Somjen G. G., Aitken P. G., and Turner D. A. (2000) Mitochondrial and intrinsic optical signals imaged during hypoxia and spreading depression in rat hippocampal slices. *J. Neurophysiol.* **84,** 311–324.
266. Hansen A. J. and Olsen C. E. (1980) Brain extracellular space during spreading depression and ischemia. *Acta Physiol. Scand.* **108,** 355–365.
267. Perez-Pinzon M. A., Tao L., and Nicholson C. (1995) Extracellular potassium, volume fraction, and tortuosity in rat hippocampal CA1, CA3, and cortical slices during ischemia. *J. Neurophysiol.* **74,** 565–573.
268. Sykova E., Svoboda J., Polak J., and Chvatal A. (1994) Extracellular volume fraction and diffusion characteristics during progressive ischemia and terminal anoxia in the spinal cord of the rat. *J. Cereb. Blood Flow Metab.* **14,** 301–311.
269. Chebabo S. R., Hester M. A., Jing J., Aitken P. G., and Somjen G. G. (1995) Interstitial space, electrical resistance and ion concentrations during hypotonia of rat hippocampal slices. *J. Physiol.* **487 (Pt 3),** 685–97.
270. Jing J., Aitken P. G., and Somjen G. G. (1994) Interstitial volume changes during spreading depression (SD) and SD-like hypoxic depolarization in hippocampal tissue slices. *J. Neurophysiol.* **71,** 2548–2551.
271. Kreisman N. R., LaManna J. C., Liao S. C., Yeh E. R., and Alcala J. R. (1995) Light transmittance as an index of cell volume in hippocampal slices: optical differences of interfaced and submerged positions. *Brain Res.* **693,** 179–186.
272. Turner D. A., Aitken P. G., and Somjen G. G. (1995) Optical mapping of translucence changes in rat hippocampal slices during hypoxia. *Neurosci. Lett.* **195,** 209–213.
273. Melzian D., Scheufler E., Grieshaber M., and Tegtmeier F. (1996) Tissue swelling and intracellular pH in the CA1 region of anoxic rat hippocampus. *J. Neurosci. Methods* **65,** 183–187.
274. Kreisman N. R., Soliman S., and Gozal D. (2000) Regional differences in hypoxic depolarization and swelling in hippocampal slices. *J. Neurophysiol.* **83,** 1031–1038.
275. Hossmann K. A. (1971) Cortical steady potential, impedance and excitability changes during and after total ischemia of cat brain. *Exp. Neurol.* **32,** 163–175.
276. Korf J., Klein H. C., Venema K., and Postema F. (1988) Increases in striatal and hippocampal impedance and extracellular levels of amino acids by cardiac arrest in freely moving rats. *J. Neurochem.* **50,** 1087–1096.
277. Astrup J., Siesjo B. K., and Symon L. (1981) Thresholds in cerebral ischemia - the ischemic penumbra. *Stroke* **12,** 723–725.
278. Choi D. W. (1988) Calcium-mediated neurotoxicity: relationship to specific channel types and role in ischemic damage. *Trends Neurosci.* **11,** 465–469.
279. Kass I. S. and Lipton P. (1982) Mechanisms involved in irreversible anoxic damage to the in vitro rat hippocampal slice. *J. Physiol.* **332:**459–472.
280. Roberts E. L. Jr. and Sick T. J. (1988) Calcium-sensitive recovery of extracellular potassium and synaptic transmission in rat hippocampal slices exposed to brief anoxia. *Brain Res.* **456,** 113–119.

281. Siesjo B. K. (1992) Pathophysiology and treatment of focal cerebral ischemia. Part II: Mechanisms of damage and treatment. *J. Neurosurg.* **77,** 337–354.
282. Leist M. and Nicotera P. (1998) Calcium and neuronal death. *Rev. Physiol Biochem. Pharmacol.* **132,** 79–125.
283. Chow E. and Haddad G. G. (1998) Differential effects of anoxia and glutamate on cultured neocortical neurons. *Exp. Neurol.* **150,** 52–59.
284. Kristian T. and Siesjo B. K. (1996) Calcium-related damage in ischemia. *Life Sci.* **59,** 357–367.
285. Choi D. W. (1994) Calcium and excitotoxic neuronal injury. *Ann. NY Acad. Sci.* **747,** 162–171.
286. Tapia R., Medina-Ceja L., and Peña F. (1999) On the relationship between extracellular glutamate, hyperexcitation and neurodegeneration, in vivo. *Neurochem. Int.* **34,** 23–31.
287. Silver I. and Erecinska M. (1998) Oxygen and ion concentrations in normoxic and hypoxic brain cells. *Adv. Exp. Med. Biol.* **454,** 7–16.
288. Calabresi P., Centonze D., Pisani A., Cupini L., and Bernardi G. (2003) Synaptic plasticity in the ischaemic brain. *Lancet Neurol.* **2,** 622–629.
289. LoPachin R. M., Gaughan C. L., Lehning E. J., Weber M. L., and Taylor C. P. (2001) Effects of ion channel blockade on the distribution of Na, K, Ca and other elements in oxygen-glucose deprived CA1 hippocampal neurons. *Neuroscience.* **103,** 971–983.
290. Peña F. and Tapia R. (1999) Relationships among seizures, extracellular amino acid changes, and neurodegeneration induced by 4-aminopyridine in rat hippocampus: a microdialysis and electroencephalographic study. *J. Neurochem.* **72,** 2006–2014.
291. Peña F. and Tapia R. (2000) Seizures and neurodegeneration induced by 4-aminopyridine in rat hippocampus in vivo: role of glutamate- and GABA-mediated neurotransmission and of ion channels. *Neuroscience* **101,** 547–561.
292. Boening J. A., Kass I. S., Cottrell J. E., and Chambers G. (1989) The effect of blocking sodium influx on anoxic damage in the rat hippocampal slice. *Neuroscience* **33,** 263–268.
293. Haigney M. C., Lakatta E. G., Stern M. D., and Silverman H. S. (1994) Sodium channel blockade reduces hypoxic sodium loading and sodium-dependent calcium loading. *Circulation* **90,** 391–399.
294. Weber M. L. and Taylor C. P. (1994) Damage from oxygen and glucose deprivation in hippocampal slices is prevented by tetrodotoxin, lidocaine and phenytoin without blockade of action potentials. *Brain Res.* **664,** 167–177.
295. Fried E., Amorim P., Chambers G., Cottrell J. E., and Kass I. S. (1995) The importance of sodium for anoxic transmission damage in rat hippocampal slices: mechanisms of protection by lidocaine. *J. Physiol.* **489,** 557–565.
296. Friedman J. E. and Haddad G. G. (1994) Removal of extracellular sodium prevents anoxia-induced injury in freshly dissociated rat CA1 hippocampal neurons. *Brain Res.* **641,** 57–64.
297. Toner C. C. and Stamford J. A. (1997) Sodium channel blockade unmasks two temporally distinct mechanisms of striatal dopamine release during hypoxia/hypoglycaemia in vitro. *Neuroscience* **81,** 999–1007.
298. Banasiak K. J., Burenkova O., and Haddad G. G. (2004) Activation of voltage-sensitive sodium channels during oxygen deprivation leads to apoptotic neuronal death. *Neuroscience* **126,** 31–44.
299. Peers C. and Kemp P. J. (2004) Ion channel regulation by chronic hypoxia in models of acute oxygen sensing. *Cell Calcium* **36,** 341–348.
300. Semenza G. L. (2000) HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *J. Appl. Physiol.* **88,** 1474–1480.
301. Semenza G. L. (2000) Oxygen-regulated transcription factors and their role in pulmonary disease. *Respir. Res.* **1,** 159–162.
302. Sharp F. R. and Bernaudin M. (2004) HIF1 and oxygen sensing in the brain. *Nat. Rev. Neurosci.* **5,** 437–448.
303. Jiang B. H., Rue E., Wang G. L., Roe R., and Semenza G. L. (1996) Dimerization, DNA binding, and transactivation properties of hypoxia-inducible factor 1. *J. Biol. Chem.* **271,** 17,771–17,778.
304. Yu A. Y., Frid M. G., Shimoda L. A., Wiener C. M., Stenmark K., and Semenza G. L. (1998) Temporal, spatial, and oxygen-regulated expression of hypoxia-inducible factor-1 in the lung. *Am. J. Physiol.* **275,** L818–L826.
305. Xia Y., Fung M. L., O'Reilly J. P., and Haddad G. G. (2000) Increased neuronal excitability after long-term O(2) deprivation is mediated mainly by sodium channels. *Brain Res. Mol. Brain Res.* **76,** 211–219.
306. Hance A. J., Robin E. D., Simon L. M., Alexander S., Herzenberg L. A., and Theodore J. (1980) Regulation of glycolytic enzyme activity during chronic hypoxia by changes in rate-limiting enzyme content. Use of monoclonal

antibodies to quantitate changes in pyruvate kinase content. *J. Clin. Invest.* **66,** 1258–1264.
307. Ptashne K. A., Morin M. E., Hance A., and Robin E. D. (1985) Increased biosynthesis of pyruvate kinase under hypoxic conditions in mammalian cells. *Biochim. Biophys. Acta.* **844,** 19–23.
308. Xia Y. and Haddad G. G. (1999) Effect of prolonged O2 deprivation on Na+ channels: differential regulation in adult versus fetal rat brain. *Neuroscience.* **94,** 1231–1243.
309. Neubauer J. A. (2001) Physiological and pathophysiological responses to intermittent hypoxia. *J. Appl. Physiol.* **90,** 1593–1599.
310. Young A., Home M., Churchward T., Freezer N., Holmes P., and Ho M. (2002) Comparison of sleep disturbance in mild versus severe Parkinson's disease. *Sleep.* **25,** 573–577.
311. Montplaisir J., Bedard M. A., Richer F., and Rouleau I. (1992) Neurobehavioral manifestations in obstructive sleep apnea syndrome before and after treatment with continuous positive airway pressure. *Sleep.* **15,** S17–S19.
312. Beebe D. W. and Gozal D. (2002) Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *J. Sleep. Res.* **11,** 1–16.
313. Carpagnano G. E., Kharitonov S. A., Resta O., Foschino-Barbaro M. P., Gramiccioni E., and Barnes P. J. (2002) Increased 8-isoprostane and interleukin-6 in breath condensate of obstructive sleep apnea patients. *Chest.* **122,** 1162–1167.
314. Macey P. M., Henderson L. A., Macey K. E., et al. (2002) Brain morphology associated with obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* **166,** 1382–1387.
315. Belik J., Sienko A., and Light R. B. (1990) The effect of repeated intermittent hypoxia on pulmonary vasoconstriction in the newborn. *Can. J. Physiol. Pharmacol.* **68,** 355–362.
316. Irlbeck M., Iwai T., Lerner T., and Zimmer H. G. (1997) Effects of angiotensin II receptor blockade on hypoxia-induced right ventricular hypertrophy in rats. *J. Mol. Cell Cardiol.* **29,** 2931–2939.
317. McGuire M. and Bradford A. (1999) Chronic intermittent hypoxia increases haematocrit and causes right ventricular hypertrophy in the rat. *Respir. Physiol.* **117,** 53–58.
318. Nattie E. E., Bartlett D. Jr., and Johnson K. (1978) Pulmonary hypertension and right ventricular hypertrophy caused by intermittent hypoxia and hypercapnia in the rat. *Am. Rev. Respir. Dis.* **118,** 653–658.
319. Nattie E. E. and Doble E. A. (1984) Threshold of intermittent hypoxia-induced right ventricular hypertrophy in the rat. *Respir. Physiol.* **56,** 253–259.
320. Faridy E. E., Sanii M. R., and Thliveris J. A. (1988) Fetal lung growth: influence of maternal hypoxia and hyperoxia in rats. *Respir. Physiol.* **73,** 225–241.
321. Schwartz J. E., Kovach A., Meyer J., McConnell C., and Iwamoto H. S. (1998) Brief, intermittent hypoxia restricts fetal growth in Sprague-Dawley rats. *Biol. Neonate.* **73,** 313–319.
322. Gozal E., Row B. W., Schurr A., and Gozal D. (2001) Developmental differences in cortical and hippocampal vulnerability to intermittent hypoxia in the rat. *Neurosci Lett.* 2001 **305(3),** 197–201.
323. Row B. W., Kheirandish L., Neville J. J., and Gozal D. (2002) Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. *Pediatr. Res.* **52,** 449–453.
324. Li R. C., Row B. W., Gozal E., et al. (2003) Cyclooxygenase 2 and intermittent hypoxia-induced spatial deficits in the rat. *Am. J. Respir. Crit. Care Med.* **168,** 469–475.
325. Li R. C., Row B. W., Kheirandish L., et al. (2004) Nitric oxide synthase and intermittent hypoxia-induced spatial learning deficits in the rat. *Neurobiol. Dis.* **17,** 44–53.
326. Xu W., Chi L., Row B.W., et al. (2004) Increased oxidative stress is associated with chronic intermittent hypoxia-mediated brain cortical neuronal cell apoptosis in a mouse model of sleep apnea. *Neuroscience.* **126,** 313–323.
327. Godukhin O., Savin A., Kalemenev S., and Levin S. (2002) Neuronal hyperexcitability induced by repeated brief episodes of hypoxia in rat hippocampal slices: involvement of ionotropic glutamate receptors and L-type Ca(2+) channels. *Neuropharmacology.* **42,** 459–466.
328. Guntheroth W. G. and Kawabori I. (1975) Hypoxic apnea and gasping.*J. Clin. Invest.* **56,** 1371–1377.
329. Fewell J. E., Smith F. G., Ng V. K., Wong V. H., and Wang Y. (2000) Postnatal age influences the ability of rats to autoresuscitate from hypoxic-induced apnea. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **279,** R39–R46.
330. Meerson F. Z., Ustinova E. E., and Orlova E. H. (1987) Prevention and elimination of heart arrhythmias by adaptation to intermittent

high altitude hypoxia. *Clin. Cardiol.* **10,** 783–789.
331. Meerson F. Z., Ustinova E. E., and Manukhina E. B. (1989) Prevention of cardiac arrhythmias by adaptation to hypoxia: regulatory mechanisms and cardiotropic effect. *Biomed. Biochim. Acta.* **48,** S83–S88.
332. Kitaev M. I., Aitbaev K. A., and Liamtsev V. T. (1999) Effect of hypoxic hypoxia on development of atherosclerosis in rabbits Aviakosm. *Ekolog. Med.* **33,** 54–57.
333. Knaupp W., Khilnani S., Sherwood J., Scharf S., and Steinberg H. (1992) Erythropoietin response to acute normobaric hypoxia in humans. *J. Appl. Physiol.* **73,** 837–840.
334. Koistinen P. O., Rusko H., Irjala K., et al. (2000) EPO, red cells, and serum transferrin receptor in continuous and intermittent hypoxia. *Med. Sci. Sports Exerc.* **32,** 800–804.
335. Rutherford C. J., Schneider T. J., Dempsey H., Kirn D. H., Brugnara C., and Goldberg M. A. (1994) Efficacy of different dosing regimens for recombinant human erythropoietin in a simulated perisurgical setting: the importance of iron availability in optimizing response. *Am. J. Med.* **96,** 139–145.
336. Moore-Gillon J. C. and Cameron I. R. (1985) Right ventricular hypertrophy and polycythaemia in rats after intermittent exposure to hypoxia. *Clin. Sci.* **69,** 595–599.
337. Cao K. Y., Zwillich C. W., Berthon-Jones M., and Sullivan C. E. (1992) Increased normoxic ventilation induced by repetitive hypoxia in conscious dogs. *J. Appl. Physiol.* **73,** 2083–2088.
338. Kinkead R., Zhan W. Z., Prakash Y. S., Bach K. B., Sieck G. C., and Mitchell G. S. (1998) Cervical dorsal rhizotomy enhances serotonergic innervation of phrenic motoneurons and serotonin-dependent long-term facilitation of respiratory motor output in rats. *J. Neurosci.* **18,** 8436–8443.
339. Turner D. L. and Mitchell G. S. (1997) Long-term facilitation of ventilation following repeated hypoxic episodes in awake goats. *J. Physiol.* **499,** 543–550.
340. Blitz D. M. and Ramirez J. M. (2002) Long-term modulation of respiratory network activity following anoxia in vitro. *J. Neurophysiol.* **87,** 2964–2971.
341. Coles S. K. and Dick T. E. Neurones in the ventrolateral pons are required for post-hypoxic frequency decline in rats. *J. Physiol.* **497,** 79–94.
342. Millhorn D. E., Eldridge F. L., and Waldrop T. G. (1980) Prolonged stimulation of respiration by endogenous central serotonin. *Respir. Physiol.* **42,** 171–188.
343. Hayashi F., Coles S. K., Bach K. B., Mitchell G. S., and McCrimmon D. R. (1993) Time-dependent phrenic nerve responses to carotid afferent activation: intact vs decerebellate rats. *Am. J. Physiol.* **265,** R811–R819.
344. Fregosi R. F. and Mitchell G. S. (1994) Long-term facilitation of inspiratory intercostal nerve activity following carotid sinus nerve stimulation in cats. *J. Physiol.* **477,** 469–479.
345. Bach K. B. and Mitchell G. S. (1998) Hypercapnia-induced long-term depression of respiratory activity requires alpha2-adrenergic receptors. *J. Appl. Physiol.* **84,** 2099–2105.
346. Baker T. L. and Mitchell G. S. (2000) Episodic but not continuous hypoxia elicits long-term facilitation of phrenic motor output in rats. *J. Physiol.* **529,** 215–219.
347. Baker T. L., Fuller D. D., Zabka A. G., and Mitchell G. S. (2001) Respiratory plasticity: differential actions of continuous and episodic hypoxia and hypercapnia. *Respir. Physiol.* **129,** 25–35.
348. Babcock M., Shkoukani M., Aboubakr S. E., and Badr M. S. (2003) Determinants of long-term facilitation in humans during NREM sleep. *J. Appl. Physiol.* **94,** 53–59.
349. Fuller D. D., Bach K. B., Baker T. L., Kinkead R., and Mitchell G. S. (2000) Long term facilitation of phrenic motor output. *Respir. Physiol.* **121,** 135–146.
350. Powell F. L., Milsom W. K., and Mitchell G. S. (1998) Time domains of the hypoxic ventilatory response. *Respir. Physiol.* **112,** 123–134.
351. Zabka A. G., Behan M., and Mitchell G. S. (2001) Long term facilitation of respiratory motor output decreases with age in male rats. *J. Physiol.* **531,** 509–514.
352. Zabka A. G., Behan M., and Mitchell G. S. (2001) Time-dependent hypoxic respiratory responses in female rats are influenced by age and by the estrus cycle. *J. Appl. Physiol.* **91,** 2831–2838.
353. Mironov S. L., Hartelt N., and Ivannikov M. V. (2005) Mitochondrial K(ATP) channels in respiratory neurons and their role in the hypoxic facilitation of rhythmic activity. *Brain Res.* **1033,** 20–27.
354. Baker-Herman T. L. and Mitchell G. S. (2002) Phrenic long-term facilitation requires spinal serotonin receptor activation and protein synthesis. *J. Neurosci.* **22,** 6239–6246.
355. Baker-Herman T. L., Fuller D. D., Bavis R. W., et al. (2004) BDNF is necessary and sufficient

for spinal respiratory plasticity following intermittent hypoxia. *Nat. Neurosci.* **7,** 48–55.
356. Bixler E. O., Vgontzas A. N., Lin H. M., et al. (2001) Prevalence of sleep-disordered breathing in women: effects of gender. *Am. J. Respir. Crit. Care Med.* **163,** 608–613.
357. Gozal E. and Gozal D. (2001) Respiratory plasticity following intermittent hypoxia: developmental interactions. *J. Appl. Physiol.* **90,** 1995–1999.
358. Moss I. R. (2000) Respiratory responses to single and episodic hypoxia during development: mechanisms of adaptation. *Respir. Physiol.* **121,** 185–197.
359. Gaultier C. (2001) Abnormalities of the chemical control of breathing: Clinical correlates in infants and children. *Pediatr. Pulmonol.* **23,** 114–117.
360. Kinney H. C., Filiano J. J., and White W. F. (2001) Medullary serotonergic network deficiency in the sudden infant death syndrome: review of a 15-year study of a single dataset. *J. Neuropathol. Exp. Neurol.* **60,** 228–247.
361. Ling L., Fuller D. D., Bach K. B., Kinkead R., Olson E. B. Jr, and Mitchell G. S. (2001) Chronic intermittent hypoxia elicits serotonin-dependent plasticity in the central neural control of breathing. *J. Neurosci.* **21,** 5381–5388.
362. Youssef F. F., Addae J. I., McRae A., and Stone T. W. (2001) Long-term potentiation protects rat hippocampal slices from the effects of acute hypoxia. *Brain Res.* **907,** 144–150.
363. Levin S. and Godukhin O. (2005) Developmental changes in hyperexcitability of CA1 pyramidal neurons induced by repeated brief episodes of hypoxia in the rat hippocampal slices. *Neurosci. Lett.* **377,** 20–24.
364. Payne R. S., Goldbart A., Gozal D., and Schurr A. (2004) Effect of intermittent hypoxia on long-term potentiation in rat hippocampal slices. *Brain Res.* **1029,** 195–199.
365. Golder F. J. and Mitchell G. S. (2005) Spinal synaptic enhancement with acute intermittent hypoxia improves respiratory function after chronic cervical spinal cord injury. *J. Neurosci.* **25,** 2925–2932.
366. Beguin P. C., Joyeux-Faure M., Godin-Ribuot D., Levy P., and Ribuot C. (2005) Acute intermittent hypoxia improves rat myocardium tolerance to ischemia. *J. Appl. Physiol.,* **99,** 1064–1069.