Adaptational responses to hypoxia

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WITH THE EVOLUTIONARY TRANSITION of life from water to land, adaptation of the organism to changing environmental conditions became critical for survival. One of the most dramatic life-threatening situations is a reduction in oxygen supply to the vital organs. Decreased tissue oxygenation may arise on such different occasions as exposure to low ambient oxygen, i.e., at high altitude, or during severe blood loss. Over the past two years, more than two dozen studies have appeared in the American Journal of Physiology (AJP)-Regulatory, Integrative and Comparative Physiology dealing with adaptational responses to acute and chronic hypoxemia. Articles include investigations on cardiovascular regulation (10, 20, 30), respiratory control (19, 26, 27), secretory mechanisms (2, 15, 16), and synaptic transmission (13).

Peripheral vasoconstriction and redistribution of the cardiac output toward the myocardial and cerebral circulations are among the potentially life-saving mechanisms that are activated during hypoxemia. Recent findings indicate that developing organisms depend primarily on adrenergic control of cardiovascular function with only minor contribution from the parasympathetic nervous system (9). With the use of the α-adrenergic antagonist phentolamine, it was shown that α1-adrenergic receptors in embryonic chicken play a major role in the adaptational response of the vasculature to hypoxia by maintaining basal vascular tone and by mediating the redistribution of the cardiac output away from the peripheral circulations (24). Differences between the fetal and adult organism in the distribution of blood flow during chronic hypoxic stress are reflected by the differential adaptation of adrenergic nerves to long-term hypoxic exposure. Thus stimulation-evoked norepinephrine release from cerebral and facial sheep arteries was higher during development compared with adult arteries (7). On the other hand, the capacity to release norepinephrine declined in fetal middle cerebral arteries after chronic hypoxia but was maintained in adult blood vessels (7).

The complex role of the nitric oxide (NO) system in the response to tissue hypoxemia is highlighted in several recent contributions. As outlined in a review article by Liang and Knox (21), NO is considered as a double-edged sword. For example, the proximal tubule in the kidney produces large quantities of NO in response to various stimuli, including hypoxia. Because NO usually inhibits sodium and fluid reabsorption by the proximal tubule, enhanced generation of NO may lower tubular oxygen consumption and thereby protect the kidney against hypoxic/ischemic injury. On the other hand, stimulation of NO production during hypoxia, presumably depending on macrophage-type inducible NO synthase, caused severe damage to proximal tubular cells.

Participation of the NO system in the hypoxic and hypercarbic drive to breathing was analyzed in the toad Bufo paracnemis (12). Chemoreception of CO2 and the breathing response to hypoxia in the amphibian brain involve signaling through the nucleus isthmi in the mesencephalon. Microinjection of the NO synthase inhibitor NG-nitro-L-arginine methyl ester (i-NAME) into the nucleus isthmi of B. paracnemis revealed that locally acting NO has an inhibitory effect on the tidal volume (Vt) when the respiratory drive is high such as under hypoxia or hypercarbia (12). Improved tissue oxygenation can result from NO-mediated hypoxic vasodilation. Recent findings indicate that the contribution of NO to hypoxia-induced vasorelaxation varies considerably between vascular beds in the developing organism. Thus inhibition of NO attenuated the increase in coronary blood flow and increased gastrointestinal vascular resistance during hypoxia but had no effect on hypoxic vasodilation in the brain (14).

Interestingly, altered signaling of NO appears to play a role also in the constriction of the ductus arteriosus after birth. As the full-term ductus constricts, oxygen concentration in its inner vessel wall falls to <0.2%. With the use of isolated rings of fetal lamb ductus arteriosus, it was shown recently that decreased responsiveness of the vascular wall to the vasodilatory action of endoge-
nous NO (and prostaglandins) prevents ductus arteriosus reopening despite the severe local tissue hypoxia (17). Furthermore, the strong inhibitory effects of NO and prostaglandins, in addition to a weaker intrinsic vascular tone, appear to be responsible for the smaller increment in tension of preterm compared with near-
term ductus arteriosus (18). As a consequence, the immature ductus arteriosus will fail to remodel completely after birth.

In an effort to maintain adequate tissue oxygenation, the vasculature frequently responds to hypoxia with a decrease in local resistance. In contrast, hypoxic vasoconstriction is a characteristic of mammalian pulmonary vascular smooth muscle. Recent findings indicate that the capacity of vascular segments to constrict under hypoxia is a phylogenetically old mechanism. By comparing the effect of low oxygen on the tension of isolated vessel rings from the dorsal aorta of different primitive vertebrates, it was shown that the antecedent of hypoxic pulmonary vasoconstriction might be operating in cyclostomes (25). Notably, removal of the endothelium was without effect, suggesting that hypoxic vasoconstriction is an intrinsic feature of the vascular smooth muscle cells (25). In a related study, hypoxic vasoconstriction of dorsal aortas from sea lamprey was found to correlate with an increase in cytosolic Ca2+/Ca2+ exchange is used during hypoxic vasoconstriction in hagfish (28). Major novel insights into the ionic mechanisms of hypoxic vasoconstriction came from studies on frog skin, an important vertebrate respiratory organ. Cutaneous vasoconstriction in Xenopus laevis in response to hypoxia was enhanced with the L-type Ca2+-channel opener Bay K 8644 and could be mimicked with the K+-channel antagonist 4-aminopyridine (23). The effect of 4-aminopyridine was blocked by the L-type Ca2+-channel antagonist nifedipine, which also inhibited hypoxic vasoconstriction (23). These results indicate that, similar to hypoxia-induced increase in pulmonary vascular resistance, hypoxic vasoconstriction in amphibian tissues may involve a reduction in membrane K+ conductance with subsequent depolarization of vascular smooth muscle cells and influx of Ca2+ through L-type Ca2+ channels.

The concept that exposure to hypoxia elicits a drop in body temperature is not new, but considerable advances have been made over the past few years in elucidating the underlying mechanisms. In particular, it was shown by intracerebroventricular microinjection of the adenosine receptor antagonist aminophylline that adenosine is a central mediator of hypoxia-induced hypothermia (6). Notably, prolonged exposure of rats to an inspiratory oxygen concentration of 10% completely disrupted the circadian rhythms of both the body temperature and the level of activity (3, 4). This discovery has major implications with regard to endocrine and metabolic regulation as it raises the interesting possibility that the circadian clock is directly sensitive to changes in the local oxygen tension.

As reviewed in an article by Bissonnette (5), the typical respiratory response to acute hypoxia in the fetus and newborn consists in an initial increase in ventilation, which is followed by a decline below baseline levels, particularly in preterm neonates. Recent progress in this area indicates that, in addition to temporal changes in platelet-derived growth factor–β expression in the brain stem (1), GABA in the nucleus tractus solitarii has a pivotal role in hypoxic ventilatory depression (29). Thus an in vivo microdialysis technique was used to demonstrate increased extracellular GABA concentrations in the nucleus tractus solitarii of conscious rats during hypoxia-induced respiratory decline. This GABA increase was dependent on normal innervation of the carotid bodies. In the same study, local injection of GABA antagonists into the nucleus tractus solitarii significantly attenuated ventilatory depression during hypoxia (29).

This article would be incomplete without referring to the beneficial effect that hypoxia can have under certain conditions. Studies with mammals and birds demonstrated that exposure to brief periods of oxygen deprivation protects the myocardium against ischemia-reperfusion injury. Several studies have recently appeared in AJP-Regulatory, Integrative and Comparative Physiology indicating that hypoxic/ischemic preconditioning also exists in other vertebrates, including fish (11, 22) and amphibians (8). Thus preconditioning appears to represent a fundamental mechanism of cardioprotection that developed early in the evolution of vertebrates. It seems that enhanced expression of heat shock proteins (8) and increased antioxidant enzyme capacity (22) during brief episodes of tissue hypoxia play a central role in this process.

REFERENCES


