HIGHLIGHTED TOPIC | Regulation of the Cerebral Circulation

Hypoxic regulation of the fetal cerebral circulation

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Pearce, William. Hypoxic regulation of the fetal cerebral circulation. J Appl Physiol 100: 731–738, 2006; doi:10.1152/japplphysiol.00990.2005.—Fetal cerebrovascular responses to acute hypoxia are fundamentally different from those observed in the adult cerebral circulation. The magnitude of hypoxic vasodilatation in the fetal brain increases with postnatal age although fetal cerebrovascular responses to acute hypoxia can be complicated by age-dependent depressions of blood pressure and ventilation. Acute hypoxia promotes adenosine release, which depresses fetal cerebral oxygen consumption through action of adenosine on neuronal A1 receptors and vasodilatation through activation of A2 receptors on cerebral arteries. The vascular effect of adenosine can account for approximately half the vasodilatation observed in response to hypoxia. Hypoxia-induced release of nitric oxide and opioids can account for much of the adenosine-independent cerebral vasodilatation observed in response to hypoxia in the fetus. Direct effects of hypoxia on cerebral arteries account for the remaining fraction, although the vascular endothelium contributes relatively little to hypoxic vasodilatation in the immature cerebral circulation. In contrast to acute hypoxia, fetal cerebral blood flow tends to normalize during acclimatization to chronic hypoxia even though cardiac output is depressed. However, uncompensated chronic hypoxia in the fetus can produce significant changes in brain structure and function, alteration of respiratory drive and fluid balance, and increased incidence of intracranial hemorrhage and periventricular leukomalacia. At the level of the fetal cerebral arteries, chronic hypoxia increases protein content and depresses norepinephrine release, contractility, and receptor densities associated with contraction but also attenuates endothelial vasodilator capacity and decreases the ability of ATP-sensitive and calcium-sensitive potassium channels to promote vasorelaxation. Overall, fetal cerebrovascular adaptations to chronic hypoxia appear prioritized to conserve energy while preserving basic contractility. Many gaps remain in our understanding of how the effects of acute and chronic hypoxia are mediated in fetal cerebral arteries, but studies of adult cerebral arteries have produced many powerful pharmacological and molecular tools that are simply awaiting application in studies of fetal cerebral artery responses to hypoxia.

cerebral arteries; neonate; high altitude; perivascular innervation; vascular endothelium

One of the most fundamental principles of cardiovascular regulation is that it should efficiently match each tissue’s blood flow with its metabolic demands. This principle applies not only to fully mature adult tissues but also to the immature tissues of the fetus in which oxygen consumption is typically high despite a low arterial PO2 (85). An important feature of this regulation in the fetus is that at the lower limits of oxygen availability, blood flow is centralized to favor the brain and heart at the expense of other organs and tissues (104). In extreme situations in which this regulation succumbs to overwhelming peripheral vasodilatation, hypotension ensues with resultant hypoxic-ischemic cerebral damage (52). Such damage is rarely fully reversible and often yields lifelong neurological morbidity that is graded with the severity and duration of the insult (48, 76, 102). Fortunately, long before these extremes are reached, the fetus can elicit a broad variety of vascular responses that help maintain cerebral homeostasis during low-oxygen conditions. Among these are the specialized mechanisms that mediate the short-term vasodilatory responses to acute hypoxia and the more long-term changes in artery structure and reactivity that enable the fetus to adapt to chronic hypoxia. The purpose of this review is to summarize the main features of these fetal cerebrovascular adjustments, with separate emphasis on responses to acute and chronic hypoxia.

Key characteristics of fetal cerebrovascular responses to acute hypoxia

Owing in large part to its rapid pace of growth and synthesis, the fetal brain exhibits greater rates of cerebral oxygen con-
sumption than measured in the adult brain. This active metabolism is closely coupled to oxygen delivery (61), even during periods of mild cerebral hypothermia (27). This coupling also includes a strong influence of oxygen delivery on oxygen consumption, because acute hypoxia elicits significant decreases in neuronal activity and cerebral metabolic rate (78) even though cellular oxygenation is not low enough to directly limit metabolism (39). This ability of hypoxia to inhibit cerebral metabolic rate appears to be the primary mechanism used by the llama fetus, which is extraordinarily well adapted to altitude hypoxia, when faced with an acute hypoxic challenge (69). In most fetal mammals, however, the response to acute hypoxia includes both an increase in blood flow to maintain oxygen delivery and an inhibition of oxidative metabolism (78).

The ability to increase cerebral perfusion in response to acute hypoxia appears early in fetal development and has been demonstrated at less than 0.7 gestation (65), although there is some doubt that at this age the extent of vasodilatation is able to totally compensate for decreased arterial oxygen content (42). Similarly, the use of Doppler techniques has enabled demonstration of hypoxic cerebral vasodilatation in premature human infants (34) as well as in fetal lambs, in utero (66).

Across all of these responses to acute hypoxia, one consistent feature is that the magnitude of the response is age dependent and peaks in the early postnatal period (15).

Another important feature of hypoxic vasodilatation in the fetal brain is that it is highly heterogeneous both among different brain regions and among adjacent tissue compartments (17, 60). As shown in studies of adult brain, hypoxic vasodilatation in the fetal brain is most robust in the brain stem (26). The fetal brain stem is also more resistant to hypoxic damage than other brain areas and initiates a robust neovascularization in response to hypoxia (118). One consequence of the strong brain stem vasodilator response to acute hypoxia is that the increased flow can depress CO2 in the cisterna and thereby transiently depress ventilation (33, 45). This effect also appears to be age dependent and becomes more pronounced as sensitivity to CO2 increases with postnatal age (15). In multiple species, acute hypoxia can also precipitate hypotension, and, again, the magnitude of this response is age dependent with the greatest effect in the early postnatal period (15, 103, 133). This effect appears to be mediated in part by chemoreceptor-mediated bradycardia, but aside from this influence there appears to be little participation of the carotid chemoreflexes in fetal responses to acute hypoxia (51, 60), although these reflexes are fully developed in the adult (56).

TISSUE MEDIATORS OF ACUTE HYPOXIC CEREBRAL VASODILATATION IN THE FETUS

Coupling between blood flow and metabolism depends heavily on a negative feedback loop between tissue production of vasodilator metabolites and the level of contractile tone in the arteries and arterioles supplying the tissue. In this context, one of the most important molecules signaling an increase in metabolic demand relative to oxygen delivery is adenosine. As shown in a broad variety of studies, tissue adenosine release mediates a significant fraction of the cerebral vasodilatation produced by hypoxia (94) through action on adenosine A2 receptors (18), and this response is fully developed by 0.6 gestation in most species (65). In addition, release of cerebral adenosine also helps mediate hypoxic inhibition of fetal breathing movements (62) and neonatal ventilation (116). Interestingly, adenosine also appears to mediate hypoxic depression of fetal cerebral metabolism through action on adenosine A1 receptors (19). Clearly, in the fetus as in the adult (95), adenosine is a critically important mediator of cerebrovascular homeostasis during acute hypoxic insults, as summarized in Fig. 1.

Despite adenosine’s importance in hypoxic cerebral vasodilatation, it is not the only mediator of this response. Pharmacological antagonism of adenosine A2 receptors inhibits only about half the increase in fetal cerebral blood flow produced by acute hypoxia (19), indicating a role for other mechanisms. Although hypoxia can increase cerebral PGE2 levels, it has no significant effect on prostacyclin or thromboxane release (84), suggesting that prostanoids play at best a modest role in hypoxic cerebral vasodilatation in the immature brain (67).

Other possible mediators include vasopressin, but the role of this molecule appears to be highly dependent on both brain region and species (47, 107). Hypoxia may also increase cerebrospinal fluid levels of pituitary adenylate cyclase-activating peptide that, in turn, have been associated with release of vasodilator opioids (126). Other evidence suggests that hypoxia may promote release of opioids such as methionine enkephalin linked to production of nitric oxide and cGMP (5, 125). Regardless of whether the source of this nitric oxide is from neurons (126) or the vascular endothelium, the accumulated evidence suggests important interactions between nitric oxide, cGMP, and opioid release during acute hypoxia in the immature brain (7) (see Fig. 1). How opioids contribute to hypoxic cerebral vasodilatation in the adult brain, however, has not been well studied and remains controversial.

DIRECT VASCULAR EFFECTS OF ACUTE HYPOXIA IN FETAL CEREBRAL ARTERIES

The brain parenchyma includes many different cell types, and each of these can release a different combination of vasoactive factors in response to hypoxia. In addition to the vasodilator molecules mentioned above, hypoxia can also stimulate some fetal cells to release contractile neurotransmitters such as serotonin and other monoamines (16, 54). The net result is that hypoxia initiates a dramatic and regionally heterogeneous change in the interstitial milieu that may not only promote vasodilatation but may also attenuate vasodilatation to some receptor agonists, such as N-methyl-D-aspartate (8). The reasons for this complexity arise not only from the mixtures of cerebral cell types that vary from region to region but also from the arteries and arterioles whose reactivity is labile and varies with age, artery size, and region.

One of the most important causes of hypoxia-induced changes in vasoreactivity is the direct effect of hypoxia on endothelial function. Endothelial vasodilator capacity is typically depressed in fetal cerebral arteries (99), and the endothelium contributes relatively little to hypoxic vasodilatation in the fetus (132). This may be due in part to the fact that oxygen is a key reactant in the synthesis of nitric oxide but is of limited availability in the fetus, where oxygen tensions well below 40 Torr are normal (55, 124). However, postnatal maturation imparts an increasing capacity for both pharmacologically induced and shear-induced endothelium-
dependent vasodilatation (123), and, correspondingly, the endothelial contribution to hypoxic vasodilatation increases throughout early postnatal life and becomes quite prominent in adult cerebral arteries (97, 132). Although there is some evidence that endothelial release of prostanoids may mediate some of the endothelium's contribution to hypoxic vasodilatation (83), other more extensive evidence attributes the main endothelial contribution of hypoxic vasodilation to endothelial release of nitric oxide (31, 50). This interpretation is not universal (46), but it suggests that hypoxia-induced release of nitric oxide from the endothelium and subsequent cGMP formation is an important, if variable and age-dependent, component of the fetal cerebral response to acute hypoxia (31, 50) (see Fig. 1).

Apart from the endothelium, hypoxia also exerts multiple direct effects on vascular smooth muscle (95). Immature cerebral arteries produce less active stress than adult arteries and are less resistant to the direct effects of acute hypoxia (96). An important consequence of these vascular characteristics is that the smaller and more peripheral cerebral arteries relax quickly and completely in response to hypoxia, whereas the larger and more proximal arteries, including the common carotid, maintain tone much better and play a more important role in the gradual adjustments of cerebrovascular resistance to hypoxia (40, 96). At the level of the smooth muscle, acute hypoxia can alter membrane potential and calcium influx in fetal smooth muscle (30) (see Fig. 1), although these responses have not been directly determined in fetal cerebral arteries. Hypoxia can also depress the density and binding affinity of G protein-coupled receptors for contractile agonists (3) but does not appear to directly influence the coupling of these receptors to inositol trisphosphate formation in fetal carotid arteries (2). Acute hypoxia also has been reported to activate calcium-sensitive potassium channels in neonatal pial arteries through a nitric oxide-independent mechanism (6). Within the adventitia of the artery wall, acute hypoxia may also promote the release of vasodilator sensory neuropeptides (49) but may also inhibit release of nitric oxide (91) from perivascular nerves in adult cerebral arteries. Without doubt, acute hypoxia exerts multiple direct effects on arteries, in vitro, but many of these effects await examination in arteries isolated from the fetal cerebral circulation.

Fig. 1. Summary of combined effects of acute hypoxia, chronic hypoxia, and maturation on cerebrovascular tone. This diagram summarizes the main effects of acute and chronic hypoxia discussed in the accompanying text. For reference, corresponding effects of postnatal maturation are also shown. The effects of each influence are indicated by the enclosed abbreviations defined at the top of the figure (A−, A+, C−, C+, M−, and M+). Circled − signs indicate inhibition. This diagram is not intended to be comprehensive but rather is given as an overview of known sites of action of hypoxia on the pathways governing cerebrovascular tone. sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; PKG, cyclic guanosine monophosphate-activated protein kinase; PG(EP), prostaglandin/E-prostanoid; BK, large conductance calcium-sensitive potassium channel; KATP, ATP-sensitive potassium channel; eNOS, endothelial nitric oxide synthetase; COX, cyclooxygenase; NE, norepinephrine; NO, nitric oxide.
EFFECTS OF CHRONIC HYPOXIA ON THE FETAL BRAIN

Chronic hypoxia produces a pattern of responses very different from those elicited by acute hypoxia. With sustained hypoxia, plasma hemoglobin concentrations rise and blood flows to most fetal organs tend to normalize but with sustained reductions in oxygen delivery to most organs other than the brain and heart (14). Fetal cardiac output is typically depressed by moderate chronic hypoxia, but cerebral blood flow is maintained, as is the vasodilatory response to acute hypoxia (55). Much of this compensation for chronic hypoxia appears to be facilitated by the maternal circulation (20). In contrast, maternal pathologies such as placental insufficiency (90) and hypertension (35) can cause chronic fetal hypoxia, in which cases the fetal compensations for chronic hypoxia can be quite heterogeneous. Chronic fetal hypoxia has been associated with low birth weights (92, 121) and a variety of changes in brain structure, neuronal density, and function (88, 90, 105) as well as a broad range of cerebral pathologies, including increased incidence of intracranial hemorrhage (130) and periventricular leukomalacia (113). Acclimatization to chronic hypoxia during fetal life has also been suggested to have an adverse influence on adult cardiovascular health (9).

Given the range and diversity of clinically relevant fetal responses to chronic hypoxia, a broad variety of studies have focused on how fetal cerebral tissues alter their characteristics in response to chronic hypoxia. Thus chronic hypoxia has been shown to upregulate pontine adenosine receptors (63), suggesting modulation of hypoxia’s ability to inhibit cerebral metabolism. Chronic hypoxia has also been shown to stimulate hypothalamic production of vasopressin and oxytocin (57) and release of atrial and brain natriuretic peptides (59), indicating important potential changes in fetal fluid balance during chronic hypoxia. Other studies have revealed that expression of the enzyme ornithine decarboxylase increases upon exposure to hypoxia with a time to peak response of ~4 h (72, 93). Owing to the key role of ornithine decarboxylase in polyamine synthesis related to growth and differentiation, these studies indicate a fundamental response at the cellular level that may help individual cerebral cells adapt to the demands of chronic hypoxia. Other studies have revealed that chronic hypoxia stimulates the synthesis of the vasodilator adrenomedullin in the fetal cerebral cortex (53), suggesting a mechanism whereby the fetal brain may help maintain adequate oxygen delivery under low-oxygen conditions. The vasodilator peptide calcitonin gene-related peptide also appears to play an important role in fetal adjustments to chronic hypoxia (115), although the exact role of this peptide in the cerebral circulation remains largely unexamined. Without doubt, chronic hypoxia brings about a diverse sequence of adjustments in neuronal and glial protein expression and regulation within the fetal brain (see Fig. 1). How these changes are coordinated and how they influence overall cerebrovascular regulation remain largely unknown.

EFFECTS OF CHRONIC HYPOXIA ON FETAL CEREBRAL ARTERIES

Aside from hypoxic changes in the cerebral parenchyma, it is also clear that chronic hypoxia dramatically alters the composition and reactivity of fetal cerebral arteries. The vasculature of the immature brain is highly plastic and can respond with robust increases in capillary density in response to hypoxia (112). Both vascular endothelial growth factor and erythropoietin are important components of the endocrine response to chronic hypoxia, and in turn these bring about multiple changes of significance for cardiovascular and cerebrovascular regulation (81). Chronic hypoxia increases protein content in fetal cerebral arteries, depresses the magnitude of depolarization-induced contractions, and also depresses the densities of several receptor types that drive contraction in these arteries (71, 120). In turn, inositol trisphosphate mobilization and receptor density are also depressed by chronic hypoxia (131).

At the same time, in distal branches of fetal middle cerebral arteries, hypoxia enhances the affinity of 5-HT receptors for serotonin in the neonate (114). Also in fetal middle cerebral arteries, chronic hypoxia appears to attenuate the ability of ATP-sensitive and calcium-sensitive potassium channels to promote relaxation (70). In ovine cerebral arteries, chronic hypoxia downregulates the ability of calcium to promote myosin phosphorylation, but this effect is more than offset by an upregulated ability of phosphorylated myosin to produce force (see Fig. 1). The net effect of these changes is to yield increased myofilament calcium sensitivity in fetal cerebral arteries (89). This upregulated calcium sensitivity may help to preserve the ability of the arteries to contract but with smaller, and possibly more energetically efficient, changes in cytosolic calcium. However, the combination of depressed overall contractility together with decreased potassium channel reactivity indicates that the hypoxic fetus is more delicately balanced between contraction and relaxation than in the normoxic state. Taken together, these adaptations to chronic hypoxia appear prioritized to conserve energy while preserving basic contractility. This untested hypothesis seems a reasonable focus for future investigations of the molecular mechanisms whereby hypoxia is sensed and initiates changes in gene transcription and protein expression leading to hypoxic cerebrovascular adaptation. Equally important, it is clear that cerebral arteries respond very differently to chronic hypoxia in adult and fetal brain, and the mechanistic basis for these marked differences remains largely unexplored.

In many cerebral arteries, the interface between the adventitial and medial layers is supplied by a broad variety of perivascular nerves that exert motor, sensory, and trophic influences on the smooth muscle and endothelium constituents of the artery wall. Not surprisingly, chronic hypoxia changes the function of at least some of these nerves. Chronic hypoxia depresses the function of nitric oxide releasing nerves in the middle cerebral artery, and because these nerves can facilitate norepinephrine release from adrenergic nerves, overall norepinephrine release decreases in chronically hypoxic fetal cerebral arteries (22, 23) (see Fig. 1). This response, which is due to a decrease in the expression of neuronal nitric oxide synthase (nNOS) in the perivascular nitridergic innervation (82), is a unique feature of the fetal response to chronic hypoxia and is absent in adult cerebral arteries. Typically, the adrenergic neurovascular apparatus is less efficient at initiating contraction in fetal compared with adult middle cerebral arteries (98), but chronic hypoxia appears to upregulate the ability of adrenergic stimulation to initiate contraction in fetal cerebral arteries (41, 73, 74). This effect, combined with the reduced norepinephrine release produced by hypoxic acclimatization in fetal arteries, suggests important changes in synaptic structure...
and/or function (such as reduced synaptic cleft width or reduced reuptake efficiency) that enable a smaller mass of norepinephrine to yield a stronger contraction, despite postsynaptic downregulation. Again this is a largely untested hypothesis worthy of further examination. In parallel, the effects of chronic hypoxia on other neurovascular motor systems seem ripe for exploration, as do the effects of chronic hypoxia on the important trophic influences these nerves exert on artery phenotype and vasoreactivity. In many respects, our understanding of the effects of chronic hypoxia on the function of the adrenergic, cholinergic, and peptidergic innervation of fetal cerebral arteries is still in its infancy and remains an attractive area for future work.

At the endothelial surface of cerebral arteries, chronic hypoxia also induces several important effects. It has long been recognized that intrapartum hypoxia disturbs the permeability of the blood-brain-barrier in human neonates (109). Chronic hypoxia has also been shown to depress endothelium-dependent vasodilatation in fetal, but not adult, cerebral arteries (71). This effect is highly conserved across species and has even been demonstrated in chicken embryos (108). The loss of endothelial vasodilatory capacity can be attributed to hypoxic depression of endothelial nitric oxide synthase mRNA and protein levels in the fetal brain (1) (see Fig. 1) and is thus similar to the effect of chronic hypoxia on nNOS levels in the perivascular nerves of fetal cerebral arteries (82). In contrast, the effects of chronic hypoxia on the expression of nNOS within the cerebral parenchyma appear to be more variable and species dependent (38), with some studies reporting an upregulation (1) and others reporting a downregulation (24, 25). Certainly, nitric oxide is not the only vasoactive substance released from the cerebral endothelium, but the effects of chronic hypoxia on these pathways remain largely unexamined.

FUTURE DIRECTIONS

As is common in fetal physiology, understanding and appreciation of the mechanisms that mediate the cerebrovascular effects of hypoxia lag far behind what is known in adult tissues, particularly in relation to the role of hypoxia-inducible factor (32, 58, 111). Thus many areas need work, and, to attract the scientific interest necessary to initiate and complete this work, it may be advantageous first to focus attention on the clinical causes, consequences, diagnosis, and treatment of chronic hypoxia in the fetus. As shown in many studies, humans can adapt successfully to chronic high-altitude hypoxia, but the mechanisms and long-term health consequences involved are unknown (9, 86). Perhaps more clinically relevant are the pathological causes of chronic fetal hypoxia, which include placental insufficiency (28, 79, 101), restricted uterine blood flow (20), and umbilical cord compression (80). At the behavioral level, greater attention also needs to be focused on the connections between maternal drug and alcohol abuse and fetal hypoxia (43, 129). Although the incidence of intrapartum fetal asphyxia is only about 2% (77), it would be of great value to obstetricians and neonatologists if the association between chronic fetal hypoxia and vulnerability to asphyxic insults were better defined (106). For neonates with persistent chronic hypoxia due to pulmonary insufficiency or cyanotic heart disease (13), there needs to be greater recognition of the fact that cardiopulmonary bypass and extracorporeal membrane oxygenation can precipitate multiple long-lasting disturbances of the cerebral circulation with potentially hypoxic consequences (36, 44).

Regarding the fetal consequences of chronic hypoxia, it has long been recognized that fetal hypoxemia is strongly associated with human intrauterine growth retardation (92). This growth retardation, in turn, may impart a compromised ability of the cerebral circulation to respond successfully to acute hypoxia and hypotension (11), although some studies suggest that in some cases growth retardation may involve a conditioning effect that enables the fetus to resist hypoxic cerebral damage in some species (119). These mechanisms are clearly worthy of further investigation, as they may provide clues to improved clinical strategies for management of cerebrovascular risk in the small-for-gestational-age infant. In parallel, there is a great abundance of promising opportunities to better understand how the fetal cerebral circulation responds to both acute and chronic hypoxia. In this context the three main categories of mechanisms include the effects of hypoxia on brain metabolism and production of vasoactive mediators, the direct effects of hypoxia on the smooth muscle and endothelium of cerebral arteries, and how hypoxia influences the motor, trophic, and sensory functions of the cerebrovascular perivascular innervation. Within each of these domains, there is tremendous opportunity for the application of molecular tools and genetic strains developed for studies of hypoxic adult arteries to studies of fetal cerebral arteries.

With greater understanding of the mechanisms whereby hypoxia influences cerebrovascular regulation, new opportunities should arise through which the subtle effects of fetal hypoxia could be more readily detected to identify the fetus at risk. To this end, Doppler methods are becoming increasingly useful for the detection of chronic hypoxia in utero (4, 10, 110) provided that the results are interpreted cautiously (64, 117). At the bedside, another promising tool for diagnosis is near-infrared spectroscopy, although again the results of such measurements must be interpreted carefully in relation to cerebral hypoxia (12, 37, 128). A more powerful tool is functional magnetic resonance imaging, which is impractical for routine use but offers great ability to assess fetal cerebral oxygenation and may help identify the at-risk neonate as well as the extent to which interventions are successful (122). Even more powerful but less practical is magnetic resonance spectroscopy (MRS), which offers unprecedented opportunities to measure concentrations of multiple compounds within the cerebral tissue and how these change in response to hypoxia (29, 75, 128). For example, proton and phosphorus MRS have demonstrated that hypoxia can dramatically increase the lactate-to-creatine ratio in cerebral tissue over a time course that correlates tightly with the time course of energy failure (100). Such measurements have prompted some to conclude that the use of MRS may revolutionize the detection of fetal cerebral injury (21). Hopefully, such advances will lead to development of more efficient therapies that avoid the undesirable cardiovascular and metabolic side effects of many conventional therapies used clinically to manage the posthypoxic fetus (68, 87).

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REFERENCES


invited review


