Chronic hypoxia alters prejunctional $\alpha_2$-receptor function in vascular adrenergic nerves of adult and fetal sheep

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Chronic hypoxia alters prejunctional $\alpha_2$-receptor function in vascular adrenergic nerves of adult and fetal sheep. Am J Physiol Regulatory Integrative Comp Physiol 281: R926–R934, 2001.—The impact of development and chronic high-altitude hypoxia on the function of prejunctional $\alpha_2$-adrenoceptors was studied by measuring norepinephrine release in vitro from fetal and adult sheep middle cerebral and facial arteries. Blockade of prejunctional $\alpha_2$-adrenoceptors with idazoxan significantly increased stimulation-evoked norepinephrine release in normoxic arteries. This effect was eliminated after chronic hypoxia in cerebral arteries, with a tendency to decline in fetal facial arteries. After chronic hypoxia, the capacity to release norepinephrine declined in fetal middle cerebral arteries with a similar trend in facial arteries. Norepinephrine release was maintained in adult arteries. During development, stimulation-evoked norepinephrine release from middle cerebral and facial arteries was higher compared with adult arteries. In fetal arteries, adrenergic nerve function declined after chronic hypoxia. However, in adult arteries, adrenergic nerves adapted to chronic hypoxia by maintaining overall function. This differential adaptation of adrenergic nerves in fetal arteries may reflect differences in fetal distribution of blood flow in response to chronic hypoxic stress.

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SYMPATHETIC NERVES ORIGINATING from the superior cervical ganglia amply innervate cerebral blood vessels (5). These nerves do not appear to play a major role in the control of cerebral blood flow under normal conditions, inasmuch as autoregulatory mechanisms maintain overall cerebrovascular tone (5). However, cerebrovascular adrenergic nerves have been shown to influence cerebral blood flow in the case of hypertension or hypoxia (1, 5, 12, 33). Other reports have shown an increase in adrenergic nerve activity during physiological stress. During acute hypercapnia, plasma catecholamines rise, reflecting elevated sympathetic nerve activity that is believed to protect vital organs (heart and brain) from damage (8). Thus potentially damaging consequences of hypertensive or hypoxic stress in the cerebral vasculature and peripheral organs may be attenuated by sympathetic nerve activation, suggesting that sympathetic nerves play a “protective” role during physiological stress (5, 30).

Acute hypoxia in isolated rabbit thoracic aortic strips inhibits contractile responses to adrenergic nerve stimulation to a greater extent than responses to exogenously applied norepinephrine (18), and stimulation-evoked norepinephrine release declines during acute hypoxia (19). In contrast, acute exposure to hypoxia in conscious dogs elevates circulating catecholamines, suggesting that acute hypoxia may elevate adrenergic nerve activity in vivo (27). In humans, acute hypoxia during exercise has been shown to increase release of cardiac norepinephrine along with the cotransmitter neuropeptide Y (14).

It is well known that release of norepinephrine from sympathetic nerves is inhibited via feedback activation of $\alpha_2$-adrenoceptors and subsequent reduction of calcium influx through N-type calcium channels (7, 29). Activation of $\alpha_2$-adrenoceptors has been shown to reduce the consequences of stress during severe acute hypoxia (17). In another study using isolated atrial tissue from humans, acute anoxia resulted in a decline in the effect of the $\alpha_2$-adrenoceptor agonist UK-14304 as well as the antagonist yohimbine (25). Thus a decline in the function of prejunctional $\alpha_2$-adrenoceptors may be one mechanism for enhanced sympathetic nerve activity during acute hypoxic stress.

High-altitude hypoxia during pregnancy has been associated with an elevated incidence of cerebrovascular morbidity in the fetus. Infants exposed to hypoxia during the prenatal period show a higher incidence of intraventricular hemorrhage (16). Although there is evidence that sympathetic nerves may play a role in adaptation to chronic hypoxia, still very little is known about the effect of hypoxia on sympathetic nerve function. Long-term hypoxia has been shown to increase dopamine, but not norepinephrine, turnover in rat sympathetic ganglia (6). More recent studies in fetal and adult sheep showed that norepinephrine release is positively modulated by nitric oxide (NO) released from NO synthase (NOS)-containing nerves in the middle
cerebral artery (4, 24). During chronic hypoxia at high altitude, the function of NOS nerves declined. However, despite the loss of this positive modulation of sympathetic nerves, stimulation-evoked norepinephrine release was not altered by chronic hypoxia (4). These data suggest that sympathetic nerves may adapt to chronic hypoxic stress to maintain overall function. However, these studies on the effects of chronic hypoxia do not address the full range of mechanisms that can modulate norepinephrine release at the neuroeffector junction.

Mounting evidence suggests that sympathetic nerve function is important for survival during acute hypoxia and possibly for adaptation to chronic hypoxic stress. Thus we set out to study the effects of chronic hypoxia on sympathetic nerve function in fetal and adult middle cerebral and facial arteries of sheep. Two discrete parameters controlling stimulation-evoked norepinephrine release were investigated. First, we used the α2-adrenoceptor antagonist idazoxan to examine the impact of development and chronic hypoxia on prejunctional α2-adrenergic modulation of norepinephrine release. Second, adrenergic uptake blockers, deoxycorticosterone (Doc) and cocaine (Coc), were used to study the impact of development and chronic hypoxia on the function of norepinephrine reuptake. Using norepinephrine release in vitro as an index of adrenergic nerve function along with selective pharmacological agents enables further investigation of the impact of chronic hypoxia on function of an important control mechanism in the cerebral circulation.

**METHODS**

Sixteen pregnant and sixteen nonpregnant ewes of mixed breed were obtained from a single supplier (Nebeker Ranch, Lancaster, CA). These animals were randomly separated into control normoxic (8 pregnant and 8 nonpregnant) and long-term hypoxic groups (8 pregnant and 8 nonpregnant). Animals in the control group remained at Nebeker Ranch (718 m). At 30 days gestation, animals in the hypoxic group (pregnant and nonpregnant) were transported to the Barcroft Laboratory, White Mountain Research Station (Bishop, CA; altitude 3,820 m). At 138–142 days gestation, pregnant and nonpregnant normoxic and hypoxic animals were transported to the Department of Perinatal Biology at Loma Linda University where they underwent immediate study.

In the case of hypoxic ewes awaiting study, immediately after arrival at the Department of Perinatal Biology, a non-occlusive tracheal catheter was surgically implanted (11) so that N2 gas could be administered to maintain the arterial PO2 at ~60 Torr. Arterial blood gases in the adults were maintained (in mM) 75 NaH2PO4, 500 sodium dodecyl sulfate, 0.025 EDTA, 20% acenitoline, and 5% methanol. The following formula was used to calculate the amount of norepinephrine in the injected sample: pg NE = (NE peak Ht sample/NE peak Ht standard)×100 pg DHBA×(DHBA peak Ht standard/DHBA peak Ht sample), where NE is norepinephrine and Ht is peak height. Recovery varied from 85 to 98%.
To quantify the tissue norepinephrine content, arteries were homogenized at the end of each experiment in 0.1 N perchloric acid followed by centrifugation. A 300-μl aliquot of the supernatant was taken, and norepinephrine was extracted in a similar manner as the perfusate. Norepinephrine content was used to calculate stimulation-evoked fractional norepinephrine release: fractional NE release = pg NE released/pg NE tissue content \( \times \) number of stimulation pulses.

**Statistical analysis.** The impact of development and hypoxia on norepinephrine content and release was analyzed by two-way ANOVA and Fisher’s protected least-significant difference test. Effect of treatments within the groups was analyzed by Student’s paired t-test. The level of significance chosen was \( P < 0.05 \).

**Drugs used.** Coc, Doc, and L-NAME were obtained from Sigma Chemicals (St. Louis, MO). Idazoxan was obtained from Research Biochemicals (Natick, MA).

**RESULTS**

**Effect of idazoxan on norepinephrine release.** As shown in Fig. 2, application of the \( \alpha_2 \)-adrenoceptor antagonist idazoxan significantly elevated norepinephrine release in all normoxic arteries studied: fetal and adult middle cerebral and facial arteries. In arteries from animals exposed to chronic hypoxia, the effect of idazoxan to increase stimulation-evoked norepinephrine release was markedly lower, and this was found in all arteries studied with the exception of adult fetal arteries. In middle cerebral arteries from hypoxic fetuses or adults, the application of idazoxan no longer significantly increased norepinephrine release (Fig. 2, A and B). In facial arteries from hypoxic fetuses, the enhancement of stimulation-evoked norepinephrine release by idazoxan was attenuated; however, the effect of idazoxan was still statistically significant (Fig. 2C). In contrast, in the adult facial artery, after chronic hypoxia the effect of idazoxan was not altered compared with arterial tissue from normoxic animals (Fig. 2D).

**Effect of uptake blockade.** When extraneuronal and neuronal uptake of norepinephrine was blocked with Doc and Coc, stimulation-evoked norepinephrine overflow was significantly elevated in all groups studied (Fig. 3). Chronic hypoxia did not appear to significantly influence the effectiveness of uptake blockade in fetal cerebral arteries or fetal and adult facial arteries (Fig. 3, A, C, and D). The effect of treatment with Doc and Coc tended to be greater in middle cerebral arteries from hypoxic, compared with normoxic, adults (Fig. 3B). However, this difference was not statistically significant.

The amount of norepinephrine uptake is, in part, dependent on the concentration of norepinephrine in the junctional cleft. Thus it is possible that changes with development or hypoxia in the effect of Doc and Coc may be due to changes in the amount of norepinephrine in the junctional cleft. Therefore, to determine more clearly the impact of development and hypoxia on norepinephrine uptake per se, we expressed this data as a ratio: the increase in norepinephrine release due to Doc and Coc divided by total norepinephrine release in the presence of Doc and Coc. This calculation allows the effect of uptake blockade to be corrected by the total amount of norepinephrine released. As shown in Fig. 4, when the data are expressed in this manner, a clearer pattern emerges.

First, in both fetal arteries, middle cerebral and facial, uptake of norepinephrine was significantly greater after chronic hypoxic exposure (Fig. 4). However, uptake of norepinephrine was not altered by chronic hypoxia in adult middle cerebral and facial arteries (Fig. 4). Furthermore, in fetal middle cerebral arteries from both normoxic and hypoxic animals, norepinephrine uptake was significantly lower compared with adult, suggesting that in middle cerebral arteries, uptake of norepinephrine increases with development (Fig. 4A). In contrast to the middle cerebral artery, uptake of norepinephrine was not significantly altered with development in facial arteries from normoxic or hypoxic animals (Fig. 4B).

**Fig. 1.** Representative data from 1 experiment in the middle cerebral artery illustrate the experimental protocol for measurement of stimulation-evoked norepinephrine release. Tissues were exposed throughout to 10 μM \( \beta \)-adrenoceptor antagonist idazoxan (Ida) for 20 min and activated again (S2) for 1 min. After S2, tissues were exposed to Doc and Coc (10 \( \times \) 10^6 M) and 10 \( \times \) 10^6 M idazoxan (Ida) for 20 min and then activated again for 1 min (S3).
Effect of development. As shown in Fig. 5, in normoxic animals there were no statistically significant developmental differences in vascular norepinephrine content in either middle cerebral or facial arteries. In contrast, there are distinct developmental differences in stimulation-evoked fractional norepinephrine release in both vessels. When extraneuronal and neuronal norepinephrine uptake were blocked, stimulation-evoked norepinephrine release was greater in both middle cerebral and facial arteries from normoxic fetuses compared with normoxic adults (Fig. 2, A and C). This effect of development persisted when idazoxan was added, so that stimulation-evoked norepinephrine release remained greater in normoxic fetal arteries compared with normoxic adult (Fig. 2, A and C).

Effect of hypoxia. Chronic hypoxia resulted in a tendency for norepinephrine content to be lower in both middle cerebral and facial arteries (Fig. 5). However, this only reached statistical significance in the adult middle cerebral artery. Stimulation-evoked norepinephrine release in the presence of both uptake and prejunctional $\alpha_2$-adrenoceptor antagonists can be taken as a measure of the total capacity of adrenergic nerves to release norepinephrine. Under these conditions, stimulation-evoked norepinephrine release from the hypoxic fetal middle cerebral artery was significantly lower compared with arteries from normoxic fetuses (Fig. 2A). In contrast to the fetus, despite the lack of effect of idazoxan on norepinephrine release, in the presence of idazoxan there was no statistically significant difference in stimulation-evoked norepinephrine release between adult middle cerebral arteries from hypoxic and normoxic animals (Fig. 2B).

In fetal facial arteries treated with idazoxan, stimulation-evoked norepinephrine release tended to be lower in arteries from hypoxic, compared with normoxic, animals; however, this did not reach statistical significance (Fig. 2C). In the adult facial artery in the presence of idazoxan, norepinephrine release was unchanged by chronic hypoxia (Fig. 2D).

Basal norepinephrine release. Effects of treatments, development, and chronic hypoxia on basal norepinephrine release are shown in Table 1. There were no statistically significant effects of development or chronic hypoxia on basal, unstimulated norepinephrine release in any of the groups studied.

DISCUSSION

Successful adaptation to environmental stress such as chronic hypoxia appears to depend on sympathetic nerve reactivity (5). The fetus is exposed to a lowered $O_2$ environment and adapts in two ways: high cardiac output and high fetal oxygen consumption (22). When norepinephrine is infused into the fetus in utero to
simulate stress conditions, fetal oxygen consumption increases by redistribution of fetal blood flow to the placenta; this serves, in part, to maintain fetal blood gas levels (22).

The model of maternal and fetal hypoxia in this study (pregnant sheep maintained at 3,820 m) is thought to be one of moderate well-adapted hypoxia. There appears to be a “threshold” level of oxygen.
which depends on the oxygen level and duration of exposure (21). Beyond this threshold level of oxygen, detrimental effects can occur. During pregnancy at 3,820 m, adult and fetal arterial PO$_2$ values fall significantly, arterial pH remains unchanged, and hemoglobin rises to increase oxygen extraction (15). Hypoxic fetuses continue normal weight gains during gestation with near-term fetal weights comparable to control fetuses maintained at 718 m. Furthermore, fetal mortality, morbidity, and abortion do not increase during the hypoxic exposure period. Animals in this study were exposed to the same degree of hypoxic stress reported in previous studies, and arterial PO$_2$ values in adult and near-term fetuses were nearly equivalent to previously reported values (4, 15, 35). Thus this model serves as one of moderate chronic hypoxia in which adaptive responses can be successfully studied.

**Hypoxia and function of prejunctional α$_2$-adrenoceptors.** The most significant finding in this study is that chronic hypoxia caused a significant reduction in the effect of the α$_2$-adrenoceptor antagonist idazoxan in both fetal and adult middle cerebral as well as in the fetal facial artery. These data suggest that acclimatization at high altitude reduces negative feedback inhibition via α$_2$-adrenoceptors. Prejunctional α$_2$-adrenoceptors normally modulate stimulation-evoked norepinephrine release by decreasing calcium influx into sympathetic nerve terminals (7, 13, 29). Thus the current data suggest that during chronic hypoxia, cerebrovascular sympathetic nerves lose feedback modulation of stimulation-evoked calcium influx.

In contrast to these observations, in the adult facial artery, the effect of idazoxan to increase stimulation-evoked norepinephrine release is maintained after chronic hypoxia. Nevertheless, other studies have shown alterations in the expression or function of α$_2$-adrenoceptors in response to hypoxemia. In male humans at high altitude (>4,400 m) for 15 days, the expression of platelet α$_2$-adrenoceptors was reduced (36). In human atrial tissue and rat skeletal arterioles, modulation of stimulation-evoked norepinephrine release by prejunctional α$_2$-adrenoceptors and the contribution of postjunctional α$_2$-adrenoceptors to arteriolar tone declines during acute hypoxia (20, 25). Taken together, these data suggest that a decline in the function of pre- or postjunctional α$_2$-adrenoceptors during acute or prolonged hypoxia may be a common response to lowered arterial PO$_2$.

The decline in function of these receptors in vascular sympathetic nerves during chronic hypoxic acclimatization could be viewed as an adaptation or a detrimental consequence of lowered oxygen tension. α$_2$-Adrenoceptor agonists have been shown to increase the latency for convulsion and death during severe hypoxia in mice and rats (17). Ornithine decarboxylase activity, a rapid indicator of acute hypoxic stress in the brain, was studied in newborn rats. The α$_2$-adrenoceptor antagonist phenoxybenzamine attenuated the rise in

![Image](https://example.com/image.png)

**Fig. 5.** Effect of development and chronic hypoxia on norepinephrine content in MCA and FA from fetal (A) and adult (B) normoxic and hypoxic sheep. Bars represent the means ± SE; n = 6 to 8 arteries from each group. *Significantly different from normoxic by 2-way ANOVA and Fisher’s PLSD test. Level of significance is P < 0.05.

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<tr>
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<th>Middle Cerebral Artery</th>
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<tr>
<td><strong>Fetal</strong></td>
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<td>Normoxic</td>
<td>0.9 ± 0.3</td>
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<tr>
<td>Hypoxic</td>
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<tr>
<td><strong>Adult</strong></td>
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<tr>
<td>Normoxic</td>
<td>0.6 ± 0.2</td>
<td>0.8 ± 0.3</td>
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<tr>
<td>Hypoxic</td>
<td>0.4 ± 0.1</td>
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Values are means ± SE of basal norepinephrine release in pg/pg content; n = 6–8 arteries from each group. Doc, deoxycorticosterone; Coc, cocaine; Ida, Idazoxan.
brain ornithine decarboxylase activity during acute hypoxic stress (30). Thus during acute hypoxia, modulation of central sympathetic nerves via prejunctional \(\alpha_2\)-adrenoceptors may be important to survival. However, acute hypoxia may not represent the best comparison for the current study, because the level of hypoxic stress at high altitude, although prolonged, is not necessarily severe.

**Hypoxia and function of adrenergic nerves.** When uptake of norepinephrine and negative feedback inhibition are blocked, stimulation-evoked norepinephrine release represents the capacity of the sympathetic nerves to release norepinephrine. Under these conditions, stimulation-evoked norepinephrine release is maintained after chronic hypoxia in adult middle cerebral arteries but declines after hypoxia in fetal middle cerebral arteries. Thus cerebrovascular sympathetic nerves in the fetus and adult respond to chronic hypoxia in a very different manner, with maintained adrenergic nerve function in the adult but a decline in function in the fetus.

A similar trend is seen in the fetal facial artery during hypoxia. When reuptake of norepinephrine and \(\alpha_2\)-adrenoceptors was blocked, there was a decline in stimulation-evoked norepinephrine release, which did not reach statistical significance. Again chronic hypoxia did not alter the capacity of the sympathetic nerves to release norepinephrine in adult facial arteries.

During chronic high-altitude hypoxia, norepinephrine content tended to decline in fetal and adult middle cerebral and facial arteries, reaching statistical significance in adult middle cerebral arteries. Despite the trend toward lower norepinephrine content in adult arteries, the capacity to release norepinephrine was maintained during chronic hypoxia. In the fetal middle cerebral artery, the small decrease in norepinephrine content cannot explain the >50% decline in stimulation-evoked norepinephrine release. Thus the decline in stimulation-evoked norepinephrine release in hypoxic fetal middle cerebral arteries would appear to be dependent on the sensitivity of the release mechanism itself.

**Effects of development.** In near-term normoxic fetal middle cerebral and facial arteries, blockade of prejunctional \(\alpha_2\)-adrenoceptors causes an increase in stimulation-evoked norepinephrine release that is approximately the same as the increase caused by idazoxan in arteries from the normoxic adult. Thus the function of vascular prejunctional \(\alpha_2\)-adrenoceptors appears to be similar in the near-term fetus and adult. The expression of prejunctional \(\alpha_2\)-adrenoceptors develops rapidly in utero and parallels sympathetic nerve innervation of the rat brain and sheep kidney and rat peripheral blood vessels during prenatal development (10, 34). However, little is known about the impact of development on function of prejunctional \(\alpha_2\)-adrenoceptors. Inhibition of stimulation-evoked contractile responses with an \(\alpha_2\)-adrenoceptor antagonist in rat iris arterioles in vitro was similar for animals near term and during postnatal development (10–21 days; Ref. 28). In renal cortical homogenates from near-term fetus, lamb, and adult, the density of \(\alpha_2\)-adrenoceptors is greatest in the near-term fetus and decreases in the lamb followed by a leveling in the adult (10). Despite the decline in \(\alpha_2\)-adrenoceptor expression during development, our data show robust function of \(\alpha_2\)-adrenoceptors in sympathetic nerves in the middle cerebral and facial arteries from the fetus and adult.

In middle cerebral and facial arteries from normoxic animals, stimulation-evoked norepinephrine release is greater in the fetus compared with the adult when reuptake is blocked as well as during blockade of both reuptake and prejunctional \(\alpha_2\)-adrenoceptors. These data suggest that adrenergic nerve response to stimulation in the near-term fetus is greater compared with the adult. During in utero and postnatal development, density of adrenergic nerves in various tissues, including blood vessels, has been shown to increase and resembles the adult pattern by the sixth postnatal week (28). In the sheep, cerebrovascular sympathetic nerve function is greater in the fetus compared with the adult and increases further during parturition (4). In general, the data from this study support other studies demonstrating that the release of norepinephrine in the near-term fetus is greater than in the adult.

**Function of norepinephrine reuptake.** To effectively focus on the impact of development and chronic hypoxia on reuptake of norepinephrine per se, fractional norepinephrine release under drug-free conditions was subtracted from release in the presence of Doc and Coc. When the data were analyzed in this manner, it was clear that in the fetus, chronic hypoxia increased the reuptake of norepinephrine in both middle cerebral and facial arteries. In contrast, hypoxia did not alter reuptake of norepinephrine in the adult middle cerebral or facial artery. To our knowledge, there have been no previous studies on the impact of long-term high-altitude hypoxia on norepinephrine reuptake. Thus our finding that chronic hypoxia increases adrenergic reuptake in fetal arteries is novel.

In contrast to our data in adult arteries that show no effect of hypoxia on combined uptake and metabolism, two reports in the adult rat and dog show a decline in uptake during hypoxia. Five-day hypoxic exposure in the adult rat resulted in a decline in the uptake of \(^3\)Hnorepinephrine in right and left ventricles of the heart (23). Similarly, in the dog pulmonary artery, 14-day exposure to hypoxia significantly reduced the uptake of \(^3\)Hnorepinephrine (26). One possibility for the difference in the present report in adult sheep and the two discussed above is that the duration of hypoxia in our study is much greater compared with either 5 or 14 days. Overall, our data suggest that during chronic hypoxia, the function of extraneuronal and neuronal norepinephrine uptake mechanisms is maintained in the adult but increases in fetal arteries.

It is interesting that there is no significant developmental effect on norepinephrine reuptake in adrenergic nerves innervating the facial artery. This is in contrast to our findings in the fetal middle cerebral artery where reuptake of norepinephrine was signifi-
cantly smaller compared with the adult. These data suggest that the impact of development on the function of norepinephrine reuptake mechanisms may be dependent on the vascular model. Indeed, this is consistent with data in the right atrium and salivary glands showing that [3H]norepinephrine uptake is fully developed soon after birth (9). Our data in middle cerebral arteries are consistent with other studies showing that during near-term and postnatal development the function of reuptake mechanisms increases in nerve terminals in the iris, spleen, heart, and adrenal glands (2, 9).

In conclusion, in this model of well-adapted chronic hypoxia, the function of prejunctional α2-adrenoceptors declines compared with normoxic fetal and adult middle cerebral arteries, with a tendency to decline in fetal facial arteries as well. During chronic hypoxia, the capacity to release norepinephrine from fetal middle cerebral arteries declines but is maintained in adult arteries. A similar trend is seen in the facial artery. Furthermore, during development, stimulation-evoked norepinephrine release from middle cerebral and facial arteries is higher compared with adult. These data suggest that in fetal arteries, the function of adrenergic nerves declines during chronic hypoxia. However, in adult arteries, adrenergic nerves exhibit an adaptation to chronic hypoxia and maintain their overall function. This differential adaptation of adrenergic nerves in fetal arteries may possibly reflect differences in fetal distribution of blood flow in response to chronic hypoxic stress.

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