Adenosine $A_{2A}$ receptors mediate cardiovascular responses to hypoxia in fetal sheep

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Koos, Brian J., and Takatsugu Maeda. Adenosine $A_{2A}$ receptors mediate cardiovascular responses to hypoxia in fetal sheep. Am J Physiol Heart Circ Physiol 280: H83–H89, 2001.—Nonselective adenosine (ADO) receptor antagonists block hypoxia-induced bradycardia and hypertension in fetal sheep. This study was designed to determine the ADO receptor subtype that is involved in these cardiovascular responses. In chronically catheterized fetal sheep (>0.8 term), fetal hypoxemia was induced by having the ewe breathe a hypoxic gas mixture (9% O$_2$-3% CO$_2$-88% N$_2$) for 1 h. Intra-arterial infusion of ZM-241385, an antagonist highly selective for ADO $A_{2A}$ receptors, to eight fetuses during normoxia significantly increased mean arterial pressure (MAP) from 42.5 ± 2.0 to 46.1 ± 2.0 mmHg without altering heart rate (HR). Infusion of a selective antagonist of ADO $A_1$ receptors [1,3-dipropyl-8-cyclopentylxanthine (DPCPX)] elevated MAP and HR only after the infusion was terminated, although administration of the vehicle for ZM-241385 or DPCPX had no effect on MAP or HR. Isocapnic hypoxia with infusion of DPCPX or the vehicle for DPCPX or ZM-241385 produced a transient fall in HR, a rise in MAP, and a decrease in plasma volume. In contrast, ADO $A_{2A}$ receptor blockade abolished the hypoxia-induced bradycardia and hypertension and blunted the decline in plasma volume. We conclude that fetal ADO $A_{2A}$ receptors: 1) modulate AP during normoxia, and 2) mediate cardiovascular responses during acute O$_2$ deficiency.

arterial pressure; autonomic nervous system; blood flow; fetus; heart rate

ACUTE HYPOXIA PRODUCES a transient bradycardia in near-term (>0.8 term) fetal sheep (6, 27). This fall in heart rate (HR) can be abolished by elimination of vagal influences on the heart through muscarinic blockade or vagotomy (16) or by bilateral denervation of the carotid bodies (1, 15). The baroreceptors have minimal involvement in the response because the bradycardia is evoked even when the rise in arterial pressure (AP) is eliminated by autonomic blockade (28) or transection of the lumbar spinal cord (5). Thus the fall in HR appears to be a reflex triggered by hypoxic excitation of the carotid chemoreceptors. During prolonged O$_2$ deficiency, HR rises toward control levels as a result of the increase in plasma catecholamine concentrations (18) and probably other factors.

Acute reductions in arterial partial pressure of O$_2$ (PaO$_2$) also elevate fetal mean AP (MAP). This hypertension, resulting primarily from constriction of the femoral arteries, can be eliminated by bilateral denervation of the carotid bodies (15). Although a number of factors increase vascular resistance during hypoxia, peripheral chemoreceptor-mediated stimulation of the lumbar sympathetic nerves appears to be the major factor.

We have reported that adenosine (ADO) receptor blockade abolishes hypoxia-induced bradycardia and hypertension in fetal sheep (22). These results indicate that elevated fetal ADO concentrations resulting from acute O$_2$ deficiency (23) have a critical role in eliciting these responses. The ADO receptor antagonists [8-phe-nyltheophylline (8-PT) and 8-p-sulphophenyltheophylline (8-SPT)] used in these studies blocked both ADO $A_1$ and $A_2$ receptors. This study was designed to determine the ADO receptor subtype that mediates these cardiovascular responses.

METHODS

Twenty-nine pregnant ewes (Rambouillet-Columbia cross) underwent surgery under halothane anesthesia at ~120 days of gestation (~0.8 term). Polyvinyl catheters were inserted in the right brachiocephalic artery, external jugular vein, and carotid artery of the fetus, and another was placed in the amniotic sac (27). Tetracycline (15 mg/kg im) was injected into the ewe before surgery, and ampicillin (500 mg) was injected into the amniotic sac after the procedure and on the first postoperative day. Buprenorphine HCl (0.006 mg/kg im) was administered to the ewe immediately after surgery to control postoperative pain.

Pressure transducers (Argon Medical, Dallas, TX) were used to measure fetal arterial and amniotic fluid pressures, and the AP was corrected by subtracting the amniotic pressure. A cardiotachometer, triggered by the AP pulse, determined fetal HR. Fetal HR and AP were recorded on a Grass poly-graph (model 7E), and these signals were also sampled at 100 Hz by microcomputer with minute averages stored on disk.

Normoxia

Experiments began at least 4 days after surgery. The ADO receptor antagonist was infused intra-arterially to the fetus

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to determine the cardiovascular effects of selective receptor blockade in the basal state. In other experiments the vehicle alone was infused to control for vehicle effects on HR and AP. Experiments were carried out on separate days to minimize the potential for carryover effects, and the order of infusion was varied. Fetal arterial blood gases and pH were measured during the control period, 10, 30, and 60 min during the infusion, and 10 and 30 min after the infusion was stopped.

**ADO A\textsubscript{1} Receptor Blockade**

1,3-Dipropyl-8-cyclopentylxanthine (DPCPX), an ADO receptor antagonist with high selectivity for the A\textsubscript{1} receptor, was dissolved (2.5 mg/ml) in 0.04 M 2-hydroxypropyl-β-cyclodextrin and 0.2 N NaOH (50:50 vol/vol). DPCPX was infused into the right brachiocephalic trunk at 1.2 mg·min\textsuperscript{-1}·kg fetal weight\textsuperscript{-1} for 10 min and subsequently at 0.24 mg·min\textsuperscript{-1}·kg\textsuperscript{-1} for 50 min. As also increases fetal HR (21, 24), was infused into the right brachiocephalic artery at 1.3 mg·min\textsuperscript{-1}·kg\textsuperscript{-1} for 5 min and subsequently at 0.036 mg·min\textsuperscript{-1}·kg\textsuperscript{-1} for 55 min. An ADO receptor agonist with a high degree of selectivity for the A\textsubscript{2A} receptor, CGS-21680 produces a fetal tachycardia which also increases fetal HR (21, 24), was infused into the external jugular vein at 0.008 mg·min\textsuperscript{-1}·kg\textsuperscript{-1} for 3 min and then at 0.003 mg·min\textsuperscript{-1}·kg\textsuperscript{-1} for 57 min. This infusion rate, which produced a pronounced bradycardia, was used to test the extent of ADO A\textsubscript{1} receptor blockade produced by simultaneous infusion of DPCPX.

**ADO A\textsubscript{2A} Receptor Blockade**

An ADO receptor blocker with high selectivity for the A\textsubscript{2A} receptor, 4-(2-[7-amin0-2-(2-furyl)[1,2,4]triazolo[2,3-a]1,5,3]triazin-5-ylamino)ethylphenol (ZM-241385, Zeneca Pharmaceuticals), was dissolved (10 mg/10 ml) in polyethylene glycol 400 and 0.1 N NaOH (50:50 vol/vol) and diluted with saline to a total volume of 30 ml. ZM-241385 was infused into the right brachiocephalic artery at 1.3 mg·min\textsuperscript{-1}·kg\textsuperscript{-1} for 5 min and subsequently at 0.056 mg·min\textsuperscript{-1}·kg\textsuperscript{-1} for 55 min. An ADO receptor agonist with a high degree of selectivity for the A\textsubscript{2A} receptor, CGS-21680 produces a fetal tachycardia which is independent of the baroreflex (21, 24). These results indicate that stimulation of A\textsubscript{2A} receptors increases HR (21) and that this cardiovascular response might be used to determine A\textsubscript{2A} receptor activation. Because the long-lasting effects of CGS-21680 limit its use as a testing agent, ADO, which also increases fetal HR (21, 24), was infused into the external jugular artery (14 mg·min\textsuperscript{-1}·kg\textsuperscript{-1}) to test A\textsubscript{2A} receptor blockade during simultaneous infusion of ZM-241385. In other experiments ADO was infused for 1 h during simultaneous administration of DPCPX to determine whether DPCPX would blunt the ADO-induced rise in fetal HR. These latter studies provided information on the relative selectivity of DPCPX for the A\textsubscript{1} receptor.

**Hypoxia**

One hour of isocapnic hypoxia was induced in the fetus by having the ewe breathe a hypoxic gas mixture (8% O\textsubscript{2}-3% CO\textsubscript{2}-89% N\textsubscript{2}) from a plastic bag (27). An ADO receptor antagonist or its vehicle was infused during hypoxia. Fetal blood for blood gas analysis was withdrawn during the control period, 10, 30, and 60 min during hypoxia, and 10 and 30 min after fetal blood gases had been restored to normal.

Arterial blood gases and pH were determined using blood gas electrodes (model 1304, Instrumentation Laboratories, Lexington, MA) with measurements corrected to fetal temperature (39.5°C). Hb and O\textsubscript{2} saturation were determined using an OSM-2 Hemoximeter (Radiometer, Copenhagen, Denmark).

**Statistical Analysis**

Minute averages of HR and MAP were analyzed using repeated-measures ANOVA with post hoc comparison by Tukey’s least-significant difference criterion. Differences were significant at \( P < 0.05 \). Values are means ± SE.

**RESULTS**

**Normoxia**

**Test of ADO A\textsubscript{1} receptor blockade.** CPA administration to seven fetuses reduced HR from the control of 170 ± 4 to 121 ± 5 beats/min within 10 min of the start of the administration of the A\textsubscript{1} receptor agonist; HR remained at this low rate until the infusion was terminated. CPA did not significantly alter MAP. Infusion of DPCPX, the ADO A\textsubscript{1} receptor antagonist, prevented the CPA-induced bradycardia (control, 171 ± 7 beats/min; CPA, 173 ± 9 beats/min), indicating that the appropriate dose of DPCPX was used in these experiments to block A\textsubscript{1} receptors. DPCPX did not alter MAP (control, 42.7 ± 2.6 mmHg; DPCPX + CPA, 43.9 ± 2.3 mmHg).

**ADO A\textsubscript{1} receptor blockade.** DPCPX was administered to eight fetuses. During the control period, fetal PaO\textsubscript{2}, arterial partial pressure of CO\textsubscript{2} (PaCO\textsubscript{2}), and pH averaged 24.8 ± 1.6 Torr, 47.5 ± 1.1 Torr, and 7.331 ± 0.009, respectively. DPCPX reduced fetal PaO\textsubscript{2} by ~3 mmHg after 10 min of infusion, but no other measurements were significantly altered. Infusion of the vehicle alone did not alter fetal arterial blood gases or pH. DPCPX infusion did not significantly alter fetal HR; however, the average HR increased significantly by about 35 beats/min after the infusion was terminated (Fig. 1). MAP also was not affected by the infusion, but it rose by nearly 5 mmHg within 30 min after the infusion had been stopped. Administration of the vehicle alone did not cause significant cardiovascular changes.

**Test of ADO A\textsubscript{2A} receptor blockade.** In seven fetuses, ADO was infused intra-arterially for 60 min with simultaneous administration of ZM-241385 or vehicle. In control studies (vehicle infusion) ADO significantly increased fetal HR within 20 min after starting the infusion (control, 182 ± 7 beats/min; ADO, 199 ± 8 beats/min) to a maximum rate of 219 ± 10 beats/min after 40 min of ADO administration. MAP did not significantly change from the control of 43.5 ± 2.7 mmHg. With simultaneous infusion of ZM-241385 and ADO, fetal HR was 165 ± 6 and 161 ± 5 beats/min after 20 and 40 min of infusion, respectively, which was virtually the same as control (161 ± 10 beats/min). MAP was not significantly altered during ZM-241385 and ADO administration. These results indicate that the dose of ZM-241385 used in this study was sufficient to block ADO A\textsubscript{2A} receptors.

In six fetuses DPCPX was infused during 1 h of ADO administration. Mean fetal HR increased from a control of 157 ± 5 beats/min to a maximum of 201 ± 2 beats/min after 60 min of ADO infusion. This maximum value was ~32% less (\( P < 0.05 \)) than the highest rate (control, 157 ± 7 beats/min; ADO, 222 ± 9 beats/
min) observed with infusion of ADO and the DPCPX vehicle after 60 min.

ADO A₂A receptor blockade. Fetal PaO₂, PaCO₂, and arterial pH during the control period in eight fetuses were 24.5 ± 1.2 Torr, 47.8 ± 1.8 Torr, and 7.334 ± 0.006, respectively. ZM-241385 did not cause significant changes in blood gases, although pH fell progressively during the infusion to a nadir of 7.308 ± 0.012 at the end of infusion. In vehicle experiments, the arterial blood gases and pH were normal during the control period and during infusion.

ZM-241385 did not significantly affect fetal HR, but the A₂A receptor antagonist raised fetal MAP by 3–4 mmHg (Fig. 2). The vehicle did not significantly affect either measurement.

Hypoxia

ADO A₁ receptor blockade. Eight fetuses received a continuous infusion of DPCPX during the hour in which fetal PaO₂ was reduced by ~9 mmHg (Fig. 3). This acute isocapnic hypoxia was associated with a fall in preductal arterial pH and a significant rise (~14%) in Hb concentration ([Hb]). Similar changes in fetal arterial blood gases, pH, and [Hb] were observed in fetuses in which only the DPCPX vehicle was infused during acute O₂ deficiency.

DPCPX infusion during hypoxia was associated with a transient fall in fetal HR and a sustained rise in MAP (Fig. 4). HR rose significantly upon termination of the infusion as observed for normoxic infusions (Fig. 1). Administration of the DPCPX vehicle during hypoxia also resulted in similar fetal cardiovascular responses.

ADO A₂A receptor blockade. ZM-241385 was infused to nine fetuses during hypoxia in which fetal PaO₂ fell by ~9 Torr (Fig. 5). Arterial pH progressively declined to 7.243 ± 0.024; however, PaCO₂ was little affected. Fetal [Hb] did not increase significantly until after 60 min of O₂ deficiency. Fetal HR, averaging 149 ± 4 beats/min during the control period, was not signifi-
cantly affected by hypoxia with ZM-241385 administration, and MAP also was not significantly altered (Fig. 6).

The PaO₂ was lowered to a similar degree in fetuses receiving the ZM-241385 vehicle; this hypoxia reduced arterial pH with minimal changes in PaCO₂. As observed in the DPCPX studies, this acute O₂ deficiency was associated with a significant increase in fetal [Hb], a transient bradycardia, and hypertension.

DISCUSSION

Heart Rate

ADO A₂A receptor blockade abolished the rapid fall in fetal HR that normally accompanies acute hypoxemia, although antagonism of ADO A₁ receptors failed to blunt the bradycardia. Thus activation of ADO A₂A receptors evokes this cardiovascular reflex. These receptors reside outside the blood-brain barrier because the hypoxia-induced bradycardia is eliminated by a nonselective ADO receptor antagonist (8-SPT) that poorly penetrates the brain (24). ADO A₂A receptors in carotid bodies may trigger the bradycardia because: 1) hypoxic stimulation of these chemoreceptors elicits a rapid fall in fetal HR (1, 15), 2) ADO excites the peripheral arterial chemoreceptors in fetal sheep (20), and 3) the carotid bodies of postnatal animals express ADO A₂A receptor mRNA (39). However, continuous intravascular infusion of ADO or an ADO A₂A receptor agonist in normoxic fetuses evokes tachycardia that is independent of the baroreflex by activating ADO A₂A receptors in the brain and myocardium (21, 24). Thus the chronotropic effects of ADO may depend on the level of fetal oxygenation and on ADO A₂A receptors in tissues other than or in addition to the carotid bodies.

The area postrema, which lies outside the blood-brain barrier, has ADO receptors that modulate cardiovascular responses. For example, microinjections of ADO in the area postrema of anesthetized rats lowers HR and AP, and nonselective blockade of ADO receptors in this locus blunts the cardiodepressor effects of ADO.
ANG II (29). These findings indicate that ADO A2A or A1 receptors within the area postrema have the potential to modulate autonomic responses triggered by hypoxic excitation of the carotid bodies.

CPA, an ADO A1 receptor agonist, lowered fetal HR as reported for another ADO analog [N6-(2-phenylisopropyl)adenosine (PIA)] with high selectivity for A1 receptors (38). The negative chronotropic effect of CPA most likely resulted from A1 receptor activation of the inwardly rectifying potassium channels in the sinoatrial node (36). Myocardial ADO A1 receptors do not appear to mediate the fall in HR associated with reductions in fetal PaO2 of ~10 Torr because fetal HR is maintained when the chemoreflexes are eliminated by bilateral cervical vagotomy or denervation of the carotid bodies. However, A1 receptors in the sinoatrial node may be involved in the negative chronotropic effects of more severe O2 deficiency when hypoxia has direct depressant effects on the myocardium.

The initial decline in HR was followed by a rise toward control even though the fetal PaO2 remained low. This increase in rate has been attributed to enhanced β-adrenergic receptor stimulation accompanying secretion of epinephrine by the adrenal medulla (18). ADO, which stimulates sympathetic activity in the fetus, increases plasma concentrations of epinephrine and norepinephrine (24); consequently the elevation in fetal ADO levels during hypoxia contributes to the rise in HR during sustained O2 deficiency.

Hypoxia in younger fetuses (<0.7 term) does not depress HR and may in fact cause tachycardia (6, 17). Because the carotid bodies respond to hypoxia at this gestational age (4), the response of younger fetuses may result from an immaturity of central control or efferent limb mechanisms.

In the newborn or adult, the tachycardia evoked by hypoxia results from increased ventilation because bradycardia occurs when respiration is controlled (12). This respiratory modulation of HR does not occur in the fetus because hypoxia inhibits breathing and because fetal breathing, being virtually isometric, does not activate the pulmonary stretch receptors (13).

Arterial Pressure

Fetal cardiovascular responses to hypoxia include increased vascular conductance in the brain, heart, and adrenals, and reduced conductance in the kidneys, lungs, spleen, gastrointestinal tract, and musculature (10). Fetal cardiac output, which is generally maintained during mild and moderate hypoxia, falls during severe hypoxia associated with metabolic acidemia and hypertension (10); thus the redistribution of cardiac output is essential for increasing O2 delivery to critical organs.

Hypoxic excitation of the carotid bodies initiates the changes in vascular resistance. For example, reflex vasoconstriction of the femoral arteries, which involves an α-adrenergic mechanism, largely accounts for the rise in AP (15), and this chemoreflex also contributes to the rapid increase in pulmonary vascular resistance (31). Reflex vasoconstriction is supported and maintained by vasoactive hormones that are released independently of the chemoreflexes, such as norepinephrine, cortisol, arginine vasopressin, and ANG II, and probably by changes in the local vascular control by ADO, nitric oxide, prostacyclin, thromboxane, and endothelin. ADO induces the release of norepinephrine (24), mediates the hypoxic secretion of arginine vasopressin (25), and modulates cortisol (9) and atrial natriuretic factor (34) responses to acute O2 deficiency. Thus ADO is a critical regulator of vascular resistance at the chemoreflexive, hormonal, and local levels.

The effects of hypoxia on MAP in fetal sheep depend on gestational age and the extent of O2 deficiency. Hypoxia (ΔPaO2 of approximately ~9 Torr), which generally has little effect on MAP in fetuses <0.85 term (6, 27), produces a progressive increase in MAP in older fetuses (6, 8, 22). This hypertensive response presumably reflects the maturation of central or effector mechanisms rather than a change in hypoxic sensitivity of the carotid chemoreceptors (4).

In this study the ADO A2A receptor antagonist abolished the hypoxia-induced rise in MAP, as previously reported for nonselective ADO receptor blockade (8, 22). These results indicate that activation of ADO A2A receptors is crucial to the increased peripheral resistance caused by acute reductions in fetal PaO2. These A2A receptors are likely involved in the reflex vasoconstriction of the femoral arteries (15) as well as the rise in circulating levels of vasoactive hormones (24, 25).

In postnatal animals, stimulation of ADO A2 receptors induces vasodilatation of the heart (3), brain (11), lungs (32), renal medulla (40), and other tissues through endothelium-dependent and endothelium-independent mechanisms. These studies, which have been performed in isolated organs or anesthetized animals, determined local effects but not systemic responses involving the intact autonomic nervous system. For example, in unanesthetized fetal sheep, intravascular infusion of a potent ADO A2A receptor agonist (CGS-21680) does not alter MAP because the vasodilatory effects are offset by a rise in sympathetic activity and a direct effect on the myocardium (21, 24).

Intravascular administration of CPA, the ADO analog that is highly selective for the A1 receptor, had no significant effect on fetal MAP in the doses used in this study. Another potent A1 receptor agonist (PIA) has been reported to have a dose-dependent depressant effect on AP in chronically catheterized fetal sheep (38). In anesthetized rats, ADO A1 receptors are involved in vasodilation during hypoxia in skeletal muscle (8) but not in cerebral cortex (11) or myocardium (3). On the other hand, activation of ADO A1 receptors induces vasoconstriction in cortical preglomerular arterioles (40), lungs (32), and skin (37). The fall in AP induced by ADO A1 receptor agonists likely results from negative chronotropic effects on HR and from peripheral vasodilation caused by activation of A1 receptors as well as nonselective activation of A2A receptors (3).
Blood Volume

Fetal [Hb] increased by ~12% during hypoxia, which indicates that plasma volume decreased by a proportionate amount (34). ADO mediates part of this hemoconcentration because: 1) intravascular infusion of ADO reduces plasma volume in normoxic fetuses (24, 34), and 2) nonselective antagonism of ADO A1 and A2 receptors in hypoxic fetuses blunts the initial fall in plasma volume (34). The results with ZM-241385 indicate that ADO A2A receptors are involved in this response.

Survival

ADO concentrations in myocardium of adult animals, which rise during hypoxia, increase O2 supply through vasodilation (via A2A receptors) and reduce O2 consumption (via A1 receptors) by depressing contractility (2). In the fetus ADO reduces fetal O2 consumption (19) and evokes autonomic reflexes and hormonal responses that mediate the redistribution of cardiac output. Thus the hypoxia-induced rise in fetal ADO concentrations is involved in increasing O2 availability to the heart, brain, and adrenals. Therefore in the fetus these “retaliatory” effects of ADO appear to involve multiple systemic as well as local vascular responses that participate in a complex negative-feedback mechanism to minimize an imbalance between fetal O2 supply and consumption in critical organs.

Receptor Blockade

Four subtypes of ADO receptors have been identified based on agonist and antagonist binding affinities and molecular cloning (14): A1, A2A, A2B, and A3. DPCPX is a potent ADO A1 receptor antagonist that has a high degree of selectivity (>500-fold) relative to A2A and A3 receptors. DPCPX has moderate selectivity relative to A2B receptors, with an affinity for A1 receptors about 50× that for A2B receptors (14). However, DPCPX has only moderate selectivity for A1 over A2A receptors at human receptors (30), which indicates that selectivity is species dependent. ZM-241385 has high affinity for A2A receptors with very little affinity for A1 receptors and virtually no interaction with A2 receptors (33, 35). ZM-241385 has a 30- to 80-fold greater affinity for A2A compared with A2B receptors (33, 35). Thus ZM-241385 is highly specific for A2A receptors relative to A1 and A3 receptors but less so relative to A2B receptors.

The affinity and selectivity of DPCPX and ZM-241385 for ADO receptor subtypes in sheep has not been reported. The present study provides some information on the relative selectivity of DPCPX for A1 and A2A receptors as determined by fetal HR responses. For example, DPCPX prevented the CPA-mediated bradycardia, which indicates that the dose of DPCPX used in this study blocked the ADO A1 receptors. DPCPX also blunted (by ~32%) the ADO-induced tachycardia, which indicates some antagonism of the A2A receptors. DPCPX may also have interacted with ADO A2B Receptors (30). The abolition of the hypoxia-induced bradycardia and hypertension by ZM-241385 apparently resulted from blockade of A2A receptors; however, these studies cannot exclude the involvement of ADO A2B receptors in these fetal cardiovascular responses.

The doses of ADO receptor antagonists used in this study were based on the amount of drug that inhibited a cardiovascular response induced by an ADO receptor agonist. Administering twice the amount of the receptor antagonists did not alter fetal cardiovascular responses to hypoxia compared with responses observed with the standard dose, which confirmed receptor blockade.

In summary, ZM-241385 abolished the reflex bradycardia and hypertension that normally accompany acute fetal hypoxia. Along with prior work, these results indicates that ADO A2A receptors outside the blood-brain barrier mediate these cardiovascular reflexes. ZM-241385 also blunted the rise in [Hb] that is normally observed during hypoxia, indicating that ADO A2A receptors are involved in the contraction of plasma volume. Thus fetal ADO A2A receptors are critically involved in autonomic, hormonal, and metabolic responses to acute O2 deficiency. Along with direct effects on the myocardium and vasculature, these systemic responses to ADO represent a key component of fetal adaptation to hypoxia.

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