Fetal cardiovascular and breathing responses to an adenosine A2a receptor agonist in sheep

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Koos, Brian J., and Andrew Chau. Fetal cardiovascular and breathing responses to an adenosine A2a receptor agonist in sheep. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R152–R159, 1998.—CGS-21680 (CGS), a highly selective adenosine A2a receptor agonist, may excite the fetal carotid bodies. This study was designed to determine 1) whether CGS stimulates fetal breathing and 2) whether sinoaortic denervation abolishes CGS-induced tachycardia. In eight intact fetuses (>0.8 term), intra-arterial CGS infusion (6 µg·min⁻¹·kg estimated fetal wt⁻¹) increased mean arterial PCO2 by 3–7 Torr, reduced fetal arterial Po2 by 2–5 Torr, and produced a mild metabolic acidemia. Heart rate increased from 154 ± 7 (control) to 249 ± 12 beats/min, but mean arterial pressure was not significantly affected. CGS initially increased the frequency, amplitude, and incidence of fetal breathing, but this hypopnea was followed by prolonged respiratory depression that was not reversed with blockade of adenosine A1 receptors. Denervation of both carotid bodies together with interruption of the vagi abolished the hypopnea without altering the respiratory depression or the maximum rise in heart rate. We conclude that CGS induces 1) tachycardia by a mechanism independent of the peripheral arterial chemoreceptors, 2) hypopnea by stimulating peripheral adenosine A2a receptors, and 3) respiratory depression by activating central A2a receptors.

CGS-21680; chemoreceptors; heart rate; metabolism; respiration

HYPOXIA ELICITS A NUMBER of physiological responses that help the fetus survive acute O2 deprivation. Although cardiac output is unaltered, blood flow increases to vital organs, such as the brain, heart, and adrenal glands, with reduced flow to less important tissues (8). This redistribution of cardiac output is associated with a transient bradycardia in older fetuses (>0.8 term) and a rise in mean arterial pressure (6). Other fetal adaptations to hypoxia include a reduction in O2 consumption (2) caused, in part, by decreased breathing activity (6, 29). This reduction in breathing appears to be part of an O2-conserving mechanism that allows more O2 to be available to essential organs during fetal O2 deprivation.

The carotid chemoreceptors have a critical role in these fetal cardiovascular adaptations to hypoxia. For example, hypoxic stimulation of the carotid bodies triggers the bradycardia through a chemoreflex involving increased vagal tone (12). Hypoxic excitation of the carotid bodies increases arterial pressure primarily through reflex vasoconstriction of the femoral arteries (12), which contributes significantly to the redistribution of cardiac output. Recent evidence suggests that these carotid chemoreflexes crucially depend on the hypoxia-induced rise in fetal systemic adenosine concentrations (18).

Hypoxic inhibition of fetal breathing presumably arises through central effects of O2 deficiency, because it persists in fetuses with denervated carotid bodies and section of the cervical vagi (21). Adenosine also helps mediate hypoxic inhibition (3, 20) by activating brain adenosine A1 receptors, which depress breathing (4, 31, 32). The inhibitory effects of hypoxia and adenosine are abolished by lesions of the pons or midbrain (9, 13, 15, 18). In fetuses with these brain lesions, hypoxia (14, 16) and adenosine (16) increase the rate and amplitude of breathing activity, a stimulation that depends on intact afferents from the peripheral arterial chemoreceptors. Because hypoxia inhibits breathing in intact fetuses, hypoxic excitation of the carotid bodies (5) is normally gated out of the central respiratory drive.

Three types of cell surface receptors have been cloned that mediate the physiological effects of adenosine: A1, A2, and A3, with the A2 receptor subdivided into A2a (high affinity) and A2b (low affinity) subtypes. This heterogeneity of receptors may explain the opposing effects of adenosine on the fetus. For example, intravascular infusion of adenosine A1 agonists in fetal sheep decreases heart rate (31, 32), most likely through direct effects on A1 receptors in the sinoatrial node (10), whereas administration of an agonist highly selective for the adenosine A2a receptor elicits tachycardia (19).

Adenosine A1 receptor agonists inhibit fetal breathing (4, 31, 32), but the effects of selective stimulation of adenosine A3 receptors are unknown.

Pharmacological studies in cats indicate that adenosine stimulates the carotid body through activation of A2 receptors (26). Because adenosine A2a receptor mRNA is expressed in the rat carotid body (33), this receptor subtype may modulate the transduction mechanism of O2 chemoreception in glomus tissue. Thus activation of these peripheral adenosine A2a receptors in the fetus may increase heart rate and breathing activity. This study was designed to determine 1) whether adenosine A2a receptor stimulation enhances breathing in normal fetuses and 2) whether sinoaortic chemodenervation abolishes the tachycardia induced by adenosine A2a receptor activation.

METHODS

Under halothane anesthesia, 15 pregnant ewes (Rambouillet-Columbia breed) were operated on at ~120 days gestation.
(0.8 term). A polyvinyl catheter was inserted in the right brachial artery of the fetus and advanced 5 cm toward the aortic arch, and another catheter was placed in the right carotid artery. Other catheters were placed in the right external jugular vein, trachea, and amniotic sac (22). Bipolar stainless steel electrodes were implanted on the parietal dura of the fetus to record the electrocorticogram (ECOG) and on a medial and lateral orbital ridge to record eye movements.

In four fetuses, bilateral denervation of the carotid bodies was performed by cutting the carotid sinus nerve and stripping the fascia from the external wall of the carotid artery from 0.5 cm below the occipital branch to the origin of the lingual artery (21). The fascia was stripped from the first 0.5 cm of the occipital artery, and all small vessels near the occipital-carotid artery junction were ligated and cut. Bilateral cervical vagotomy was also performed to denervate the aortic bodies and other peripheral chemoreceptors that might otherwise compensate for the loss of carotid body function (23).

Fetal arterial, tracheal, and amniotic fluid pressures were measured using pressure transducers (Cobe Laboratories, Lakewood, CO); arterial and tracheal pressures were corrected by subtracting amniotic fluid pressure. Fetal heart rate was determined from the arterial pulse pressure using a cardiotachometer. Fetal heart rate, arterial pressure, tracheal pressure, electrooculogram (EOG), and ECoG were recorded on a Grass polygraph (model 7E). Heart rate and arterial and tracheal pressures were sampled at 100 Hz by a microcomputer using data acquisition software that had an algorithm for detecting and analyzing fetal breathing movements from tracheal pressure recordings (16). Minute averages of heart rate, mean arterial pressure, inspiratory time, breath interval, and breath amplitude were recorded on disk. Arterial blood gases and pH were measured on blood gas electrodes (model 1304, Instrumentation Laboratories), with values corrected to 39.5°C.

Adenosine receptors are classified by binding affinities for agonists and antagonists (11). Because agonist potency depends on receptor binding as well as transduction mechanisms, antagonists have been the preferred agents for pharmacological classification. Unfortunately, antagonists for the adenosine A₃ receptor have had neither the preferred degree of selectivity nor the desired aqueous solubility for intravenous administration. However, the agonist CGS-21680 [2-(2-carboxyethyl)phenethylamino-5'-N-ethyl-carbamoyladenosine (CGS)] is highly selective (∼200-fold) for A₂a relative to A₁ receptors, with virtually no affinity for A₂b and A³ receptors. Because of its high selectivity for the A₂a receptor, CGS has been widely used to characterize physiological responses to A₂a receptor activation (30); in these studies it was administered to chronically catheterized fetal sheep to determine cardiorespiratory responses to stimulation of adenosine A₂a receptors.

In separate studies, fetal responses to CGS were determined in conjunction with the administration of the adenosine A₁ receptor antagonist 8-cyclopentyl-1,3 dipropylxanthine (DPCPX). DPCPX was infused intra-arterially at 1.0 mg·min⁻¹·kg⁻¹ for 10 min, then at 0.25 mg·min⁻¹·kg⁻¹ for 50 min. This rate of DPCPX administration blocked the inhibitory effects on fetal breathing of cyclopentyladenosine (1.6 µg·min⁻¹·kg⁻¹, 60-min intravenous infusion), an adenosine analog highly selective for the A₁ receptor, indicating that this DPCPX dose was appropriate. These DPCPX studies were conducted to confirm that fetal responses to CGS were not mediated by activation of adenosine A₁ receptors.

Experiments were performed at least 4 days after surgery. After a control period of 4 h, CGS (0.08 mg/ml saline) was infused at 6 µg·min⁻¹·kg⁻¹ estimated fetal wt⁻¹ for 40 min in the right brachiocephalic trunk. This dose was based on preliminary studies in which the infusion rate was varied from 1.3 to 12 µg·min⁻¹·kg⁻¹. In this study it was found to stimulate breathing for at least 40 min. Fetal arterial blood was withdrawn for measuring blood gases and pH under control conditions and 10, 30, 60, and 90 min after infusion of CGS had begun.

Because the incidence of fetal breathing can vary throughout the day (7, 25), the incidence of fetal breathing, eye movements, and electrocortical state in each fetus was recorded on a separate day over the same time period as that for the CGS experiment. These measurements provided a control for possible circadian variations in breathing, rapid eye movements, and electrocortical activity. Administration of the vehicle alone was not performed, because, as we have observed (20), slow saline infusions (0.19 ml/min) of limited duration have indistinguishable effects on fetal heart rate, mean arterial pressure, ECoG, EOG, and breathing activity.

The ECoG was analyzed by visual inspection of slow recordings (5 mm/min), which provide clear distinction between episodes of high- (HV) and low-voltage (LV) activity. Because electrode placement and gestational age affect ECoG voltage, voltage criteria for HV, LV, and intermediate-voltage (IV) ECoG states were determined for each fetus from the 4-h control recordings before CGS administration. HV states were defined as voltages >80% of the average value during episodes of HV ECoG activity; LV states were defined by voltages <130% of the average value during episodes of LV ECoG. Voltages between these limits were defined as intermediate states. The voltages for the fetuses as a group were generally 80–345 µV for HV, 40–135 µV for LV, and 70–232 µV for LV. Spectral composition of the ECoG was not evaluated.

Because of the episodic nature of fetal breathing, breathing activity was judged to be present if at least 20 s of each 1-min epoch were filled with breathing movements (20). Respiratory cycle times were calculated from the tracheal pressure measurements (15). Inspiratory time was measured from the start of a breath to the time of the lowest negative pressure recorded during the breath, and breath duration was determined from the onset of one breath to the beginning of the next. The amplitude of breathing was used as a measure of respiratory output.

Mean values were compared using repeated measures of analysis of variance methods. Post hoc comparison of means was carried out using Tukey’s least-significant difference criterion. Single comparisons between control and experimental measurements were performed using Student’s t-test. A logarithmic conversion of the data was carried out when it produced a symmetrical distribution for parametric analysis. Repeated measurements of the incidence of ECoG, EOG, and breathing, which did not vary significantly on drug-free days over the time of study, were compared with the respective control mean. Differences were significant at P < 0.05. Values are means ± SE.

RESULTS

Normal Fetuses

Arterial blood gases and pH. CGS was infused intra-arterially to eight normal fetuses. Compared with the control of 23.5 ± 0.9 Torr, the mean arterial Po₂ (PaO₂) fell by ∼5 Torr during the first 10 min of drug infusion and was also significantly reduced after 30 and 90 min (Fig. 1). CGS significantly increased mean arterial Pco₂ (Paco₂) by >8 Torr compared with the control value of 48.8 ± 1.0 Torr during the first 10 min of infusion, with
subsequent measurements increased by 3–6 Torr. Arterial pH averaged 7.343 ± 0.013 during the control period but fell significantly during the first 10 min of CGS infusion and remained at a reduced level during the next 80 min. Base excess significantly decreased by 5.8 ± 1.1 and 5.9 ± 1.36 meq/l at 30 and 60 min after the onset of drug infusion.

In three fetuses the arterial blood gases and pH were measured 6 h after drug administration. Fetal PaO2 (>18 Torr) and PaCO2 (<55 Torr) were within the normal range; arterial pH (<7.267) remained lower than control.

Cardiovascular effects. Averaging 154 ± 7 beats/min during the control period, mean heart rate significantly rose within 5 min after the CGS infusion was begun. A maximum rate of ~250 beats/min was reached by 1 h after the drug administration was begun (Fig. 2), representing an ~60% increase. Mean arterial pressure, which was 47.5 ± 1.2 mmHg during the control period, was not significantly affected by the adenosine A2a receptor agonist.

Electrocortical activity. The ECoG was recorded in six fetuses. During the 1st h after the CGS was begun, the mean incidence of LV ECoG decreased to values only ~40% of the control mean of 30 ± 1.3 min/h and remained at a reduced level for the next 4 h (Figs. 3, A and B, and 4). The incidence of LV ECoG averaged ~8 min/h during the control period but was increased two- to threefold with administration of the A2a receptor agonist. The drug did not significantly affect the incidence of HV ECoG.

Eye movements. Eye movements occurred in episodes associated with LV ECoG activity during the control period (Fig. 3A). With administration of CGS, the incidence of eye movements significantly increased by ~37% (Figs. 3B and 5). After 5 h the incidence of ocular activity declined to only 39% of values during the control period but, after 11 h, returned toward normal values.

Breathing movements. The adenosine A2a receptor agonist had a powerful stimulating effect on fetal breathing that began ~2 min after the start of drug infusion (Figs. 3B and 5); it was characterized by a 26% decrease in average inspiratory time, a 28% reduction in mean breath duration, and a nearly fourfold increase in average breath amplitude (Table 1). Breathing movements occurred during LV ECoG and IV ECoG and were also coincident at times with HV ECoG during the first 2 h after the drug infusion had begun.

The incidence of fetal breathing was 45 ± 7 min/h during the 1st h after the onset of CGS administration, which was almost twice the control value of 24 ± 2.1 min/h. After 3 h the breathing incidence declined, with very little respiratory effort during the 5th and 6th h after the drug infusion had begun. As with eye movements, breathing incidence subsequently rose toward control values.

Figure 6 shows the relative change in the number of breaths per 1-h epoch over the time course of the experiment. The number of breaths during the 1-h control period averaged 942 ± 124 but increased nearly threefold during the 1st h after the drug infusion had begun.
begun. As with breathing incidence, the number of breaths in each 1-h epoch fell significantly below the control mean by the 3rd h, with a return toward control values by 6 h.

A delayed stimulating effect of CGS on breathing activity occurred in three fetuses, with continuous large-amplitude breathing occurring 12–18 h after the drug infusion had begun (Fig. 3C). These long periods of respiratory stimulation for individual fetuses lasted 7.8, 12.6, and 18.5 h, respectively, and were associated with normal cycling of the ECoG (Fig. 2C) and normal arterial blood gases and pH (pH > 7.300, PaCO2 < 52 Torr, PaO2 > 20 Torr).

Adenosine A1 receptor blockade. In separate experiments, DPCPX was infused intra-arterially for 1 h in three fetuses with normal arterial blood gases and pH. The DPCPX administration was started 6 h after the CGS infusion was begun. Immediately before DPCPX infusion, fetal arterial pH was 7.252 ± 0.017, PaCO2 was 52.1 ± 2.5 Torr, and PaO2 was 24.3 ± 2.3 Torr. Arterial blood gases and pH were not altered by administration of the adenosine A1 receptor antagonist. The mean incidence of fetal breathing was 26 ± 4 min/h during the control period before CGS administration, 6 ± 3 min/h during the 6th h after the infusion had begun, and 7 ± 5.8 min/h during DPCPX infusion. Eye movements also remained depressed during infusion of DPCPX.

Control experiments. Arterial blood gases and pH were within the normal range for fetuses in which fetal

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**Fig. 3.** Fetal electrocorticogram (ECoG), rapid eye movements [electrooculogram (EOG)], and breathing [negative deflections in tracheal pressure (Ptr)] during control period (A), during CGS-21680 infusion (B), and 22 h after start of drug administration (C).

**Fig. 4.** Effects of CGS-21680 on incidence of low-, high-, and intermediate-voltage electrocortical activity. *P < 0.05 compared with control.
measurements were made without drug administration. The mean incidence of LV, HV, and IV ECoG, rapid eye movements, and breathing activity did not change significantly over the time of observation (Figs. 4 and 5).

Chemodenervated Fetuses

Arterial blood gases and pH. CGS was infused into four sinoaortic-denervated fetuses. Fetal PaO₂, PaCO₂, and pH during the control period were 25 ± 3.2 Torr, 51.5 ± 3.5 Torr, and 7.347 ± 0.025, respectively. PaO₂ declined by ~3 Torr during infusion of CGS. PaCO₂ increased significantly after 30 min of CGS infusion, but the rise in PaCO₂ occurred later during the infusion than in intact fetuses. A progressive decline in arterial pH occurred during the 1st h after the drug administration had begun. Compared with control, the base excess decreased by 2.9 ± 0.6 and 8.1 ± 3.0 meq/l at 30 and 60 min after the onset of infusion.

Eye movements. The incidence of rapid eye movements averaged 27 ± 2.0 min/h during the control period. Within 2 h of the beginning of CGS administration, the incidence fell significantly to 37% of control during the 1st h after the drug infusion had begun, with the reduction in eye activity lasting for another 8 h. Because the ECoG was recorded in only two fetuses, the effects of CGS on ECoG were not analyzed.

Breathing movements. Breathing incidence was 21 ± 3.4 min/h during the control period. Within 2 h of the beginning of CGS administration, the incidence fell significantly to 26% of the control average and remained reduced for another 8 h (Fig. 7).

During the 1 h before drug infusion, the number of breaths per hour relative to control significantly declined after the 1st h after the start of CGS infusion and decreased throughout the remainder of recorded measurements (Fig. 6). This breath ratio in sinoaortic-denervated fetuses was significantly less than the value for normal fetuses during the first 2 h of the experimental period.

Table 1. Effects of CGS-21680 on fetal breathing

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<tr>
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<th>Control</th>
<th>CGS-21680</th>
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<td>Normal fetuses (n = 8)</td>
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<tr>
<td>T₁, s</td>
<td>0.53 ± 0.03</td>
<td>0.39 ± 0.05*</td>
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<tr>
<td>Tₑ, s</td>
<td>1.44 ± 0.10</td>
<td>1.04 ± 0.12*</td>
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<tr>
<td>Amplitude, mmHg</td>
<td>2.6 ± 0.2</td>
<td>9.9 ± 1.3*</td>
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<td>Denervated fetuses (n = 4)</td>
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<tr>
<td>T₁, s</td>
<td>0.62 ± 0.03</td>
<td>0.71 ± 0.04</td>
</tr>
<tr>
<td>Tₑ, s</td>
<td>1.86 ± 0.46</td>
<td>2.92 ± 0.22*</td>
</tr>
<tr>
<td>Amplitude, mmHg</td>
<td>2.8 ± 0.31</td>
<td>7.8 ± 4.5</td>
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Values are means ± SE. T₁, inspiratory time; Tₑ, breath interval. *P < 0.05.
Control experiments. On the day on which measurements were made without drug administration, the fetal arterial blood gases and pH were within the normal range. The incidence of rapid eye movements and breathing activity did not vary significantly over the period of observation (Fig. 7).

DISCUSSION

Cardiovascular Responses

CGS produced a tachycardia of similar magnitude in intact fetuses and in fetuses with bilateral carotid denervation and vagal section. The more rapid response in sinoaortic-denervated fetuses probably resulted from the absence of vagal tone. These results indicate that the rise in heart rate was not mediated by afferents from the heart, great vessels, lungs, baroreceptors, or peripheral arterial chemoreceptors. Our previous work showed that ~25% of the positive chronotropic effects of CGS in fetal sheep may be caused by activation of myocardial A2a receptors, whereas ~75% of rise in heart rate is related to stimulation of the autonomic nervous system by adenosine A2a activation (19). The present work suggests that the autonomic contribution to the elevated heart rate arises from stimulation of adenosine A2a receptors in other afferents, efferents, and/or the brain.

CGS affects vascular tone by direct and indirect mechanisms. It dilates most vascular beds through a direct action on A2a receptors in vascular smooth muscle (10), and it elevates vascular tone indirectly by increasing sympathetic neural activity and circulating levels of catecholamines (19). The net result during prolonged infusions is an increase in systolic blood pressure, with little change in diastolic and mean arterial pressures (19), which explains CGS’s lack of effect on mean arterial pressure in normal and chemodenervated fetuses. The latter suggests that the sympathetic response that maintains mean arterial pressure is triggered by a mechanism independent of the peripheral arterial chemoreceptors, baroreceptors, or other receptors in the lungs, heart, and great vessels.

Breathing Responses

Stimulation. CGS increased the rate and amplitude of breathing in normal fetuses, indicating that activation of adenosine A2a receptors stimulates fetal breathing. This hyperpnea developed within ~2 min of the beginning of drug administration, a slight delay expected from the time required for drug distribution, A2a receptor stimulation, and second messenger activation. Although CGS increased fetal PaCO2 by 3–8 Torr, the increase in breathing amplitude was greatly disproportionate to the mild rise in PCO2. For example, an 8-Torr rise in fetal PaCO2 elevates the mean amplitude of fetal breathing by only ~33% (6), which is considerably less than the fourfold increase observed with CGS. Thus the enhancement of breathing by CGS primarily results from activation of adenosine A2a receptors that modulate respiratory drive.

The stimulating effects of CGS on fetal breathing were virtually eliminated by carotid sinus denervation and bilateral section of the cervical vagosympathetic trunks. These results indicate that the peripheral adenosine A2a receptors mediate the hyperpnea. This conclusion is further strengthened by previous studies with N6-(R-phenylisopropyl)-adenosine, an adenosine agonist highly selective for the A1 receptor. Intravenous administration of N6-(R-phenylisopropyl)-adenosine to fetal sheep (>0.8 term) only inhibited breathing activity (31, 32).

Because the carotid bodies in adult animals are excited by adenosine (26, 28), these chemoreceptors are a logical site of action for CGS in the fetus. Glomus or type 1 cells may detect low PO2 through mechanisms involving an increase in cytosolic Ca2+ concentrations; this rise in intracellular Ca2+ promotes transmitter release, which triggers the firing of afferent fibers (1). Thus CGS may stimulate breathing by modulating this transduction mechanism or by interacting with A2a receptors that modulate neurotransmitter release on peripheral nerve terminals.

Besides increasing the amplitude and rate of breathing, CGS induced prolonged periods of breathing that were coincident with LV, HV, and IV ECoG. This pattern is unusual, because breathing in fetal sheep...
Depression. The prolonged depression of breathing and eye movements that developed after the initial hyperpnea was, surprisingly, the predominant respiratory effect. This inhibition also occurred in sinoaortic-denervated fetuses, indicating that the depression was unrelated to respiratory stimulation and was likely mediated through activation of central adenosine receptors. Because the adenosine A₁ antagonist DPCPX failed to reverse the inhibition, the reduction in breathing by CGS would not appear to be caused by activation of adenosine A₁ receptors. CGS can depress glutamate-evoked firing of neurons (27), and this may be the mechanism by which CGS inhibits breathing. These provocative findings raise the possibility that central adenosine A₂a receptors may be involved in hypoxic inhibition of fetal breathing.

Although a circadian variation in the incidence of fetal breathing has been described (7, 25), no significant change in incidence was observed over the 16 h of measurements during control observations. This finding, which is consistent with our previous work (24), indicates that significant circadian changes occur only under special conditions in which lighting and feeding schedules are tightly regulated. Thus the effects of CGS on breathing incidence cannot be explained by physiological changes related to time of day.

Arterial blood gases and pH. CGS administration in normal fetuses increased fetal PaCO₂ and transiently reduced PaO₂. These changes in blood gases could be accounted for by reduced placental blood flow, increased uneven distribution of placental blood flow, and/or a rise in fetal metabolism. The maintenance of mean arterial pressure and the metabolic acidemia in association with small changes in PaCO₂ would favor the latter. Hypoxia also produces a metabolic acidemia in the fetus that is attenuated by adenosine receptor blockade (17). These results with CGS suggest that activation of fetal adenosine A₂a receptors contributes to hypoxia-induced metabolic acidemia, probably through adrenergic stimulation and/or direct effects on glucose metabolism (17).

The time course of the rise in PaCO₂ was dependent on the integrity of the peripheral arterial chemoreceptors, with the increase in PaCO₂ delayed by sinoaortic chemodenervation. These results suggest that stimulation of adenosine A₂a receptors in peripheral chemoreceptors mediates the initial changes in respiratory gases.

In summary, CGS increased the incidence, amplitude, and frequency of fetal breathing. This stimulation was followed by prolonged respiratory depression that was not attenuated by adenosine A₁ receptor blockade. Sinoaortic denervation abolished the CGS-induced hyperpnea but not the respiratory inhibition or tachycardia. These results indicate that this adenosine A₂a receptor agonist 1) increases fetal heart rate by a mechanism independent of the peripheral arterial chemoreceptors, 2) stimulates breathing by activating peripheral receptors, and 3) depresses respiration by interacting with central receptors.

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