Influence of adenosine A₁-receptor blockade and vagotomy on the gasping and heart rate response to hypoxia in rats during early postnatal maturation

James E. Fewell, Chunfen Zhang, and Anne M. Gillis

Departments of ¹Physiology and Biophysics and of ²Cardiac Sciences, University of Calgary and Libin Cardiovascular Institute of Alberta, Health Sciences Centre, Calgary, Alberta, Canada

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Influence of adenosine A₁-receptor blockade and vagotomy on the gasping and heart rate response to hypoxia in rats during early postnatal maturation. J Appl Physiol 103: 1234–1241, 2007. First published July 19, 2007; doi:10.1152/japplphysiol.01421.2006.—Failure to autoresuscitate from apnea has been suggested to play a role in sudden infant death. Little is known, however, about factors that influence the gasping and heart rate response to severe hypoxia that are fundamental to success-ful autoresuscitation in the newborn. The present experiments were carried out on 184 rat pups to investigate the influence of the parasympathetic nervous system, as well as adenosine, in mediating the profound bradycardia that occurs with the onset of hypoxic-induced primary apnea and in modulating hypoxic gasping. On days 1 to 2, days 5 to 6, and days 10 to 11 postpartum and following bilateral cervical vagotomy (VAG) or administration of a selective adenosine A₁ receptor antagonist (8-cyclopentyl-1,3-dipropylxanthine; DPCPX), each pup was exposed to a single period of severe hypoxia produced by breathing an anoxic gas mixture (97% N₂-3% CO₂). Exposure to severe hypoxia resulted in an age-dependent decrease in heart rate (P < 0.001), accentuated with increasing postnatal age, that was attenuated in all age groups by DPCPX but not by VAG. Furthermore, DPCPX but not VAG decreased the time to last gasp but increased the total number of gasps in the 1- to 2-day-old and 5- to 6-day-old pups but not in the 10- to 11-day-old pups during exposure to severe hypoxia. Thus our data provide evidence that adenosine acting via adenosine A₁ receptors plays a role in modulating hypoxic gasping and in mediating the profound bradycardia that occurs coincident with hypoxic-induced primary apnea in rats during early postnatal life.

apnea; autoresuscitation; 8-cyclopentyl-1,3-dipropylxanthine; postnatal age; sudden infant death syndrome

IN HUMAN INFANTS, spontaneous recovery from obstructive apnea and positional asphyxia during sleep can occur early with or without cortical and/or behavioral arousal (36, 46, 48) or later as a result of “autoresuscitation” from “asphyxial coma” by hypoxic gasping (25, 46). Because it occurs when early defense mechanisms are absent or fail to restore effective ventilation, autoresuscitation serves as a backup mechanism and is considered to be the last operative mechanism used by mammals to ensure survival during severe hypoxia. The respiratory response of both newborn and adult animals to progressive hypoxia or asphyxia, as may occur during obstructive apnea and positional asphyxia, typically passes through four stages: hyperpnea, primary apnea, gasping, and secondary or terminal apnea (19, 24, 26, 30). A profound bradycardia, the mechanism of which is presently unknown, occurs concurrently with the onset of primary apnea. If oxygen becomes available during gasping following hypoxic-induced primary apnea, recovery is possible. From experiments carried out on infant mice, Gershan et al. (17) have defined three sequential cardiorespiratory stages of a successful autoresuscitation from hypoxic-induced primary apnea. They are stage I, gasping with marked bradycardia; stage II, cardiac resuscitation (with a rapid increase in heart rate to greater than 60% of baseline); and stage III, respiratory resuscitation (with an increase in respiratory rate to greater than 60% of baseline). The following physiological events likely accompany the three stages of autoresuscitation: first, introduction of air into the lungs by gasping; second, transport of oxygen from the lung to the heart; third, response of the heart by increasing heart rate and cardiac output; and fourth, response of the central nervous system to reoxygenation and increased perfusion (17).

Autoresuscitation failure occurs in infant humans and animals following repeated exposure to hypoxia (14, 17, 38, 43). Interestingly, our laboratory has found that the sequence of events leading to autoresuscitation failure in rat pups following repeated exposure to hypoxia is influenced by postnatal age (14). For example, 5- to 6-day-old pups tolerate an average of 15 ± 2 anoxic challenges before autoresuscitation failure, which is most often related to a lack of sustained cardiac resuscitation (i.e., stage II of autoresuscitation), whereas 10- to 11-day-old rats tolerate an average of only 11 ± 3 anoxic challenges before autoresuscitation failure, which is most often related to a lack of sustained gasping (i.e., stage I of autoresuscitation). To the contrary, 1- to 2-day-old pups may tolerate upwards of 125 anoxic challenges without experiencing autoresuscitation failure. Considering this, it is not only important to be knowledgeable of factors that influence gasping but also those factors that influence the heart rate response to severe hypoxia to elucidate the integrated physiology of successful autoresuscitation and the age-dependent pathophysiology of failed autoresuscitation from hypoxic-induced apnea.

In the mature heart of the adult, the sympathetic and parasympathetic divisions of the autonomic nervous system interact to control heart rate. In species that are born relatively immature such as the rat, innervation of the heart is poorly developed at birth, and neural control of heart rate is nonexistent or limited (27, 31, 34). Sympathetic innervation of the rat heart occurs after birth with functional connections occurring at the end of the first week of postnatal life (27, 31). Despite this, various “stressors” (e.g., hypoxia) can elicit secretion of catecholamines from the adrenal medulla via nonneural mecha-
nisms that can have a marked effect on the heart via activation primarily of α-adrenergic receptors (40, 41). Functional parasym pathetic innervation of the rat heart occurs somewhat earlier than functional sympathetic innervation as Marvin et al. (34) have shown that vagal stimulation can elicit a decrease in heart rate as early as day 21 of gestation (i.e., term of gestation). Another factor that may modulate heart rate during the early postnatal period and perhaps temper the heart’s response to catecholamines is the nucleoside adenosine, which is released under conditions of ischemia or increased myocardial energy demand (5, 7). Accordingly, our current experiments have been carried out to determine the role of the parasympathetic nervous system, as well as adenosine, in mediating the profound bradycardia that occurs with the onset of hypoxic-induced primary apnea and in modulating hypoxic gasping in rat pups. Specifically, we have carried out experiments to test the hypothesis that bilateral cervical vagotomy and/or administration of a selective adenosine A1-receptor antagonist would alter hypoxic gasping and abolish the decrease in heart rate that occurs coincident with hypoxic-induced primary apnea in rat pups during early postnatal maturation.

METHODS

One-hundred eighty-four Sprague-Dawley rat pups were studied. Each pup, born by spontaneous vaginal delivery, was housed with its mother and siblings (25 ± 1°C, 20–30% relative humidity in a 12:12-h light-dark cycle) until an experiment. Although 25°C is below the thermoneutral zone of newborn rats (33), each pup had the opportunity to huddle with its siblings and dam in the nest and thus to thermoregulate behaviorally. All experimental procedures described herein were carried out in accordance with the Guide to the Care and Use of Experimental Animals provided by the Canadian Council on Animal Care and with the approval of the Animal Care Committee of the University of Calgary.

Experimental Protocols

Experimental series I: bilateral cervical vagotomy and gasping and heart rate during a single period of unrelenting hypoxia. For an experiment, each 1- to 2-day-old (n = 30), 5- to 6-day-old (n = 30), and 10- to 11-day-old (n = 30) rat pup was removed from its mother and siblings, anesthetized by inhalation of halothane (~1.5% for induction and maintenance) in oxygen, and placed in the supine position. A small medial incision was made on the neck, and both vagus nerves were identified, dissected, and isolated. In the vagotomy group, both vagus nerves were cut, whereas in the sham-operated group, the vagus nerves were identified, dissected, and isolated but left intact. After the aforementioned surgical procedure, which took less than 5 min, was completed, the pups were allowed to recover in a chamber regulated to 37 ± 1°C for 60 min before being instrumented for measurement of cardiovascular and respiratory variables. The pup was then positioned prone, the position normally assumed and maintained, in a metabolic chamber regulated to 37.0 ± 0.1°C into which flowed room air at a rate of 1 l/min for 30 min before control measurements were made; the pups then received a subcutaneous injection of vehicle or 20 mg/kg 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX). After another 30 min, the pup was exposed to a period of unrelenting hypoxia by changing the gas which flowed into the metabolic chamber from room air to 97% N2-3% CO2, and the gasping and heart rate responses were determined on a minute-to-minute basis until the onset of secondary or terminal apnea.

The rationale for using 20 mg/kg DPCPX in experimental series II was as follows. In preliminary dose-response experiments carried out on 1- to 2-day-old (n = 9), 5- to 6-day-old (n = 9), and 10- to 11-day-old (n = 9) rat pups with testing doses of 0, 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, 5.0, 10.0 mg/kg of the selective adenosine A1-receptor agonist N6-cyclopentyladenosine (CPA), we determined 1 mg/kg to be the smallest dose that elicited a maximal heart rate response (i.e., the EC100) in all age groups (e.g., Fig. 1). Furthermore, at doses of 1 mg/kg and higher, administration of CPA elicited abnormalities in atrioventricular conduction and further changes in sinoatrial automaticity in some pups (e.g., Fig. 2).

In further dose-response experiments, carried out on 1- to 2-day-old (n = 4), 5- to 6-day-old (n = 4), and 10- to 11-day-old (n = 4) rat pups with testing doses of 0, 10, 20, and 30 mg/kg of the selective adenosine A1-receptor antagonist DPCPX, we determined 20 mg/kg to be the smallest dose of DPCPX that abolished the heart rate response to an EC100 dose of CPA. Last, we determined that 20 mg/kg DPCPX was effective in eliminating the heart rate response to an

Fig. 1. Heart rate response to increasing doses of the selective adenosine A1-receptor agonist N6-cyclopentyladenosine (CPA; n = 9; top) and its attenuation by prior administration of the selective adenosine A1-receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX; n = 4) in 5- to 6-day-old rat pups (bottom).
EC\textsubscript{100} dose of CPA for 30, 60, and 90 min in 1- to 2-day-old (\(n = 3\)), 5- to 6-day-old (\(n = 3\)), and 10- to 11-day-old (\(n = 3\)) rat pups. For all dose-response experiments, each pup was used once and only received one dose of one drug.

**CPA and DPCPX**

CPA, DPCPX, and DMSO were obtained from Sigma-Aldrich. Because of the limited solubility of CPA and DPCPX in saline, DMSO was used as a solvent (1\% for CPA and 100\% for DPCPX) and accordingly as vehicle.

**Experimental Apparatus**

The metabolic chamber used in our experiments consisted of a double-walled Plexiglas cylinder (30 cm long; internal diameter 6 cm) into which flowed room air or 97\% \(\text{N}_2\)-3\% \(\text{CO}_2\). Chamber ambient temperature was regulated to 37.0 ± 0.1°C by circulating water from a temperature controlled bath (Neslab-Endocal Refrigerated Circulating Bath RTE-8DD) through the space between the walls. The rationale for studying the various age groups of rats at an ambient temperature of 37.0°C was as follows. Our laboratory has previously determined the selected ambient temperatures of 1- to 2-day-old, 5- to 6-day-old, and 10- to 11-day-old rats, 20–30 min after being placed into a 200-cm thermocline with a linear temperature gradient of 25–40°C to be as follows (14): 1 to 2 day old, 36 ± 1°C; 5 to 6 day old, 37 ± 1°C; 10 to 11 day old, 37 ± 2°C (mean ± 1 SD). Numerous experiments carried out on newborn as well as older animals provide evidence that when given the opportunity, animals select an ambient temperature that is within their thermoneutral zone (13, 20–23, 33).

**Experimental Measurements and Calculations**

During an experiment, the ECG, respiratory movements and chamber \(\text{CO}_2\) levels were recorded on a model 7 polygraph (Grass Instrument) at a paper speed of 10 mm/s. Leads I, II, and III of the ECG were recorded from multistranded stainless steel wire electrodes (AS 633, Cooner Wire) sewn on the right shoulder, left shoulder, and the left thigh; the electrodes were connected to model 7HIP5 high-impedance probes coupled to a model 7P5 wide-band EEG AC Preamplifier (Grass Instrument). Respiratory movements were recorded from a mercury-in-silicone rubber strain gauge (model HgPC, D. M. Davis, placed around the chest; the strain gauge was connected to a bridge amplifier (Biomedical Technical Support Center, University of Calgary) that was coupled to a model 7P03 Adapter Panel (Grass Instrument).
Statistical Analysis

Statistical analysis was carried out by ANOVA or ANOVA for repeated measures where appropriate and followed by a Newman-Keuls multiple comparison test. All results are reported as means ± SD, and P < 0.05 was considered to be of statistical significance.

RESULTS

Basal heart rate increased significantly with increasing postnatal age and averaged 323 ± 28 beats/min on postnatal days 1–2, 350 ± 32 beats/min on postnatal days 5–6, and 390 ± 43 beats/min on postnatal days 10–11 (P < 0.001). As previously observed, exposure to a single period of unrelenting hypoxia resulted in a reproducible respiratory and cardiovascular response in all pups (14). The respiratory response consisted of hyperpnea, primary apnea, gasping, and terminal apnea. The cardiovascular response consisted of a profound bradycardia coincident the onset of primary apnea; in all animals, terminal apnea preceded the appearance of arrhythmias (e.g., atrioventricular dissociation) or an isoelectric pattern on the electrocardiogram.

Experimental Series I: Bilateral Cervical Vagotomy and Gasping and Heart Rate During a Single Period of Unrelenting Hypoxia

Basal heart rate was significantly increased by vagotomy but only on postnatal days 5–6 (Fig. 3). Exposure to severe hypoxia resulted in an age-dependent decrease in heart rate (P < 0.001), accentuated with increasing postnatal age, that was not influenced by vagotomy. Bilateral cervical vagotomy did not alter the time to last gasp or the total number of gasps upon exposure to severe hypoxia (Fig. 4).

Fig. 3. Influence of postnatal age and bilateral cervical vagotomy on absolute heart rate and the change in heart rate from control during exposure to a single period of severe hypoxia in rats. Data are means ± 1 SD; n = 15 for sham operated and vagotomy for each age group: 1- to 2-day old, 5- to 6-day old, and 10- to 11-day-old pups. bpm. Beats/min. *P < 0.05 vs. control of respective group; †P < 0.05, sham operated vs. vagotomy at a given time point.

Fig. 4. Influence of postnatal age and lack of effect of bilateral cervical vagotomy on the time to last gasp (top) and total number of gasps (bottom) during exposure to a single period of severe hypoxia. Data are means ± 1 SD; n = 15 for sham operated and vagotomy for each age group.
Experimental Series II: Adenosine A1-Receptor Antagonism and Gasping and Heart Rate During a Single Period of Unrelenting Hypoxia

Basal heart rate did not change following administration of vehicle or DPCPX in any age group (Fig. 5). Exposure to severe hypoxia resulted in an age-dependent decrease in heart rate ($P < 0.001$), accentuated with increasing postnatal age, that was significantly attenuated following administration of DPCPX (Fig. 6). Furthermore, the time to last gasp was decreased but the total number of gasps was increased following DPCPX compared with vehicle in the 1- to 2-day-old and 5- to 6-day-old pups but not in the 10- to 11-day-old pups on exposure to severe hypoxia (Fig. 7).

DISCUSSION

Our experiments provide new information about factors that influence the newborn's gasping and heart rate response to severe hypoxia as may occur during prolonged obstructive apnea or positional asphyxia. Novel findings in our study carried out on conscious newborn rats were that 1) postnatal age influenced basal heart rate, 2) bilateral cervical vagotomy did not alter the heart rate or gasping response to severe hypoxia, and 3) administration of a selective adenosine A1-receptor antagonist significantly attenuated the heart rate response and altered the pattern of gasping on exposure to severe hypoxia. Thus our data provide evidence that adenosine acting via adenosine A1 receptors plays a role in modulating hypoxic gasping and in mediating the profound bradycardia, which occurs coincident with hypoxic-induced primary apnea in rat pups during the first 10–11 days of postnatal life.

Since the early experiments of Drury and Szent-Gyorgyi (9), adenosine has been recognized to have important effects on the cardiovascular system, including effects on chronotrophy, dromotrophy, inotrophy, and coronary vascular resistance (5). Adenosine functions as a counterregulatory hormone in the heart by increasing oxygen delivery and decreasing work during periods of oxygen supply and demand imbalance, thus protecting the heart against hypoxia/ischemia (5, 11). Under basal conditions, interstitial concentrations of adenosine range from 1 to 50 nM but can increase rapidly to 1,000 nM with ischemia and increased tissue activity (10, 32). Adenosine's diverse physiological effects are mediated by a family of four G protein-coupled receptors designated as $A_1$, $A_2A$, $A_2B$, and $A_3$, which have been identified on the basis of agonist and antagonist binding affinities and molecular cloning experiments (15, 16).

In the relatively immature rat pup that lacks functional cardiac parasympathetic innervation, an adenosine-mediated bradycardia likely plays an important role in tempering the workload placed on the heart during hypoxia and catecholamine stimulation, thus protecting the myocardium against the adverse consequences of oxygen supply and demand imbalance (5, 7, 11, 35). Previous experiments by Rivkees (39), Matherne et al. (35), and Cothan et al. (7) have shown that adenosine A1 receptors are present in the rat fetal heart as early as day 14 of gestation and functionally coupled to their G protein by day 1 of postnatal life. Furthermore, adenosine A1-receptor density peaks in the newborn period with levels twice that found in the 2-wk-old rat pup and adult rat; adenosine A1 receptor affinity, however, is similar in newborn, 2-wk-old, and adult rats. In our experiments, administration of the selective adenosine A1 receptor agonist CPA elicited a profound bradycardia in 1- to 2-day-old, 5- to 6-day-old, and 10- to 11-day-old pups with 1 mg/kg being the smallest dose that produced a maximal decrease in heart rate of $\sim 80\%$ in all age groups (i.e., the EC$_{100}$). In addition, at doses of 1 mg/kg
and higher, CPA elicited abnormalities in atrioventricular conduction and further changes in sinoatrial automaticity in some pups. Our results on heart rate following selective stimulation of adenosine $A_1$ receptors concur with those of Szeto and Umans (45), Smith et al. (42), and Koos and Maeda (29), who showed that intravenous administration of selective adenosine $A_1$-receptor agonists elicits bradycardia in the relatively mature sheep fetus and that high doses result in cardiac standstill. Guntheroth and Kawabori (26) and Lawson and Thach (30) have shown that primary apnea occurs when the arterial $PO_2$ decreases to $\sim8–10$ Torr; this is true during hypercapnic hypoxia produced by airway obstruction (30) and during hypocapnic hypoxia produced by inhalation of a hypoxic gas mixture (26). In our experiments, a profound bradycardia occurred coincident with the onset of primary apnea, which was not altered by bilateral cervical vagotomy but was attenuated by prior administration of DPCPX. Since the chronotropic effects of DPCPX were evident during primary apnea (i.e., during cessation of respiratory activity; see Fig. 6), it likely represents a direct effect of the selective adenosine $A_1$-receptor antagonist on the heart rather than an indirect effect secondary to its effects on the respiratory system. In this respect, our results differ from those of Thomas and Marshall (47), who carried out experiments on anesthetized and acutely operated adult rats and found that the effects of 8-phenyltheophylline, a nonselective adenosine receptor antagonist, on the cardiovascular changes induced by hypoxia during spontaneous ventilation were mainly a consequence of its ability to block adenosine’s centrally mediated effect on the respiratory system (i.e., changes in ventilation). The differences between their results and ours likely result from the magnitude of the hypoxic stress, the use of anesthesia and acute surgical preparation, and the age of the rat at study.

With regard to the parasympathetic nervous system, our results are similar to those previously reported from experiments carried out during the perinatal period on relatively immature species (e.g., cat, ground squirrel, hamster, rabbit, rat) but somewhat different from those reported from experiments carried out during the perinatal period on relatively mature species (e.g., goat and sheep) (1, 3, 4, 18, 19, 28, 29). For example, Adolph (1) found that administration of atropine (2–4 mg/kg) to infant ground squirrels, rats, or hamsters before anoxic challenge did not modify the latency or magnitude of the heart rate response or survival (i.e., the time to last gasp). Experiments carried on near-term fetal sheep, however, have shown that the bradycardia in response to acute hypoxemia is mediated via adenosine $A_2A$ receptors (29) and can be abolished by elimination of vagal influences on the heart by cholinergic muscarinic blockade or vagotomy (28) or by bilateral denervation of the carotid bodies (3, 18). These differences

![Diagram A: Vehicle - Hypoxia](image)

**A** Vehicle - Hypoxia

Electrocardiogram

Respiration

![Diagram B: DPCPX - Hypoxia](image)

**B** DPCPX - Hypoxia

Electrocardiogram

Respiration

Fig. 6. Segments of 2 polygraph tracings showing the ECG and lack of respiratory efforts during hypoxic-induced primary apnea following sc administration of vehicle (A) or 20 mg/kg DPCPX (B) in two 5-day-old rat pups.

and higher, CPA elicited abnormalities in atrioventricular conduction and further changes in sinoatrial automaticity in some pups. Our results on heart rate following selective stimulation of adenosine $A_1$ receptors concur with those of Szeto and Umans (45), Smith et al. (42), and Koos and Maeda (29), who showed that intravenous administration of selective adenosine $A_1$-receptor agonists elicits bradycardia in the relatively mature sheep fetus and that high doses result in cardiac standstill. Guntheroth and Kawabori (26) and Lawson and Thach (30) have shown that primary apnea occurs when the arterial $PO_2$ decreases to $\sim8–10$ Torr; this is true during hypercapnic hypoxia produced by airway obstruction (30) and during hypocapnic hypoxia produced by inhalation of a hypoxic gas mixture (26). In our experiments, a profound bradycardia occurred coincident with the onset of primary apnea, which was not altered by bilateral cervical vagotomy but was attenuated by prior administration of DPCPX. Since the chronotropic effects of DPCPX were evident during primary apnea (i.e., during cessation of respiratory activity; see Fig. 6), it likely represents a direct effect of the selective adenosine $A_1$-receptor antagonist on the heart rather than an indirect effect secondary to its effects on the respiratory system. In this respect, our results differ from those of Thomas and Marshall (47), who carried out experiments on anesthetized and acutely operated adult rats and found that the effects of 8-phenyltheophylline, a nonselective adenosine receptor antagonist, on the cardiovascular changes induced by hypoxia during spontaneous ventilation were mainly a consequence of its ability to block adenosine’s centrally mediated effect on the respiratory system (i.e., changes in ventilation). The differences between their results and ours likely result from the magnitude of the hypoxic stress, the use of anesthesia and acute surgical preparation, and the age of the rat at study.

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likely result from the magnitude of the hypoxic stress, as well as the relative maturity of the sheep vs. the rat at the time of study and thus the functional state of the developing autonomic nervous system. As postulated by Koos and Maeda (29), it is likely that adenosine A2A receptors in the carotid bodies of the relatively mature sheep fetus triggered the aforementioned reflex bradycardia in response to hypoxemia as it is known that hypoxic stimulation of the carotid chemoreceptors elicits a decrease in fetal heart rate, adenosine excites the carotid chemoreceptors in fetal sheep, and the carotid bodies of postnatal animals express adenosine A2A receptor mRNA (3, 18, 50). It remains to be determined if more severe hypoxia would elicit an adenosine A1 receptor-mediated bradycardia in the early gestation sheep fetus or elicit an adenosine A1 receptor-mediated bradycardia following carotid denervation in the near-term sheep fetus.

We did not observe arrhythmias on the ECG (e.g., atrioventricular dissociation) before the appearance of secondary or terminal apnea in any age group of pups during exposure to severe hypoxia. This concurs with our previous findings as well as the findings of others but is different from that observed following repetitive exposure to severe hypoxia (6, 8, 12, 14, 44). Of course, the lack of arrhythmias or an isoelectric pattern on the electrocardiogram does not ensure that an adequate blood pressure, which is essential for delivery of metabolic substrate (i.e., glucose) to the brain during oxygen lack, was maintained. Previous experiments by Swann et al. (44) on 4-day-old dogs and experiments by Cassin et al. (6) on 1-day-old dogs, rabbits, and cats, however, have shown that newborns of these species maintain their blood pressure at viable levels long after terminal apnea.

Repetitive exposure to hypoxia leads to autoresuscitation failure in rat pups, the mechanism of which depends on postnatal age; that is, 5- to 6-day-old pups tolerate an average of 15 ± 2 anoxic challenges before autoresuscitation failure, which is most often related to a lack of sustained cardiac resuscitation (i.e., stage II of autoresuscitation), whereas 10- to 11-day-old rat pups tolerate an average of only 11 ± 3 anoxic challenges before autoresuscitation failure, which is most often related to a lack of sustained gasping (i.e., stage I of autoresuscitation). In the majority of 5- to 6-day-old pups, autoresuscitation failure follows atrioventricular dissociation after early cardiac resuscitation, as evidenced by an initial return of heart rate toward control followed by atrioventricular dissociation; the atrioventricular dissociation and ultimate loss of ventricular depolarization precede the cessation of gasping. This would suggest that cardiac output was maintained during hypoxia and that gasping resulted in the transport of oxygen from the lungs to the heart. The subsequent arrhythmia may have resulted from high levels of adenosine following repetitive exposure to hypoxia and a differential latency of reoxygenation of the sinoatrial node vs. the atrioventricular node during gasping. This postulate remains to be investigated.

In addition to its cardiovascular effects, administration of the selective adenosine A1-receptor antagonist DPCPX significantly altered the pattern of gasping in the 1- to 2-day-old and 5- to 6-day-old pups but not in the 10- to 11-day-old pups following hypoxic-induced apnea. In the 1- to 2-day-old and 5- to 6-day-old pups, DPCPX decreased the time to last gasp (often used as an index of survival time) but increased gasping frequency as the total number of gasps was increased. Although our experiments were not designed to investigate mechanisms of this age-dependent response, it may be related to adenosine stimulation of A1 receptors on ATP-sensitive K+ channels or other K+ channels that influence membrane potential and subsequent activity of respiratory-related neuronal tissue (2). Our data would allow one to suggest that inhibition of adenosine A1 receptors mediates the previously observed negative effects of aminophylline on survival in infant rats (37) and mice (49) on exposure to severe hypoxia. As well, Thurston et al. (49) have shown that aminophylline decreases the time to last gasp in the isolated head of 8-day-old rat pups and has postulated that the observed effects are secondary to an aminophylline-stimulated increase in cerebral metabolic rate. With regard to survival, adenosine modulation of hypoxic gasping may confer an advantage by effecting a slow and prolonged pattern of potential autoresuscitation producing gasps until oxygen becomes available.

In summary, our experiments have shown that adenosine acting via adenosine A1-receptors plays a role in modulating hypoxic gasping and in mediating the profound bradycardia that occurs coincident with hypoxic-induced primary apnea in newborn rats during the first 10–11 days of postnatal life. Whether adenosine plays a significant role in mediating autoresuscitation failure following repeated exposure to severe hypoxia is unknown and remains to be investigated.

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GRANTS

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REFERENCES


