Adenosine depletion alters postictal hypoxic cerebral vasodilation in the newborn pig


Adenosine depletion alters postictal hypoxic cerebral vasodilation in the newborn pig. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H1495–H1501, 1998.—Altered postictal cerebral blood flow dilatory responses may contribute to brain injury following neonatal seizures. We developed an initial series of experiments to characterize the effects of seizure activity on cerebral vascular dilatory responses during the immediate postictal period. Significant attenuation of postictal hypoxic cerebral vasodilation was noted. We hypothesize that this diminished cerebral dilator response to hypoxia involves depletion of adenosine (Ado) activity resulting from seizure ictus. Additional experiments were designed to evaluate whether the altered postictal responses were related to a depletion of Ado stores or a decreased response to Ado in the postictal state. Farm-bred piglets were equipped with closed cranial windows. Responses to hypercapnia (10% CO2), hypoxia (fractional inspired O2 = 0.10), and topical sodium nitroprusside (10⁻⁶ M) were compared before and after bicuculline-induced seizures (1 mg/kg). Hypoxia-induced cerebral vasodilation was significantly attenuated in the first 90 min postictal (control: 56.5 ± 6%, 10 min postictal: 6.3 ± 2%, 60 min postictal: 21.7 ± 6%, and 90 min postictal: 21.6 ± 5%, P < 0.01), whereas the dilator responses to hypercapnia and topical sodium nitroprusside remained intact. In a separate group of piglets, both a dilating (10⁻⁵ M) and a nondilating concentration of Ado (10⁻¹¹ M) were topically administered postictically to measure their effects on pial vessel dilatory response to hypoxia. Dilation to topical Ado (10⁻⁵ M) was not altered postictically compared with control. Ado (10⁻¹¹ M) restored hypoxia-induced vasodilation to preseizure control values in the immediate postictal period (control: 51.0 ± 8%, postictal: 46.7 ± 8%, P > 0.05). Postictal administration of Ado will restore hypoxia-induced cerebral vasodilation in piglets even when a nondilating concentration is employed. This suggests that depletion of Ado with seizure activity is a mechanism for the loss of postictal cerebral vasodilation to hypoxia, and the role of Ado in hypoxic cerebral vasodilation is permissive.

seizures; hypoxia; hypercapnia

CONVULSIONS are the most frequent overt manifestation of neonatal neurological disorders and are a common occurrence in the intensive care nursery (35). Hypoxic-ischemic injury remains the primary cause of seizures in the majority of cases in both premature and full-term newborns. Recognition and treatment of neonatal seizures are crucial for several reasons, including the concern that seizures themselves may be particularly harmful to the developing brain (7, 35). Increased metabolic demand with seizure activity results in a compensatory increase in cerebral blood flow (CBF) to meet tissue oxygen and glucose needs (37). Alterations of cerebral vasodilation impairing substrate delivery both during seizure activity itself and into the postictal period may further extend damage to an already injured brain.

Cerebral blood flow autoregulation is important in maintaining constant brain blood flow despite fluctuating systemic arterial pressure. This relationship has been well characterized in both adult and newborn animals (10, 20, 33). Although the precise limits of the autoregulatory range of systemic blood pressure in the healthy human newborn, including premature infants, are imprecisely defined, autoregulation is felt to be intact, but over a much narrower range (8, 9, 15, 26, 28). Monin and colleagues (7, 10, 18) demonstrated in newborn piglets that a pressure-passive state exists between mean arterial pressure and CBF during seizures and that this impairment persists into the subsequent postictal period. Evidence suggests that a similar loss of cerebral autoregulation occurs with seizures in human newborns as in neonatal animal models (24). Development of a pressure passive state may be an important risk factor for intraventricular hemorrhage or ischemia depending on the gestational age of the infant.

Although the loss of autoregulation secondary to seizure ictus has been well documented, the effects of other dilator responses such as hypercapnia and hypoxia on postictal CBF have not been characterized. Altered postictal CBF under these conditions could contribute to neonatal brain injury. A stepwise series of experiments was therefore designed to characterize, in vivo, alterations in cerebrovascular dilator responses in a postictal newborn animal model. Preliminary studies, using bicuculline to induce seizure activity in piglets, were performed to determine the effect of seizures on postictal cerebral vasodilatory response to both hypoxia and hypercapnia. The results of these initial experiments demonstrate that bicuculline-induced seizures cause significant attenuation of hypoxia-induced cerebral vasodilation in the immediate postictal period.

Several investigators have found that adenosine channels contribute to hypoxia-induced dilation of cerebral arterioles (2, 23, 30, 39). In addition, adenosine levels in brain interstitial fluid significantly increase during the initial minutes of bicuculline-induced seizure activity (22, 40). We therefore developed the hypothesis that newborn seizures may result in a depletion of adenosine in the postictal state, impairing cerebral vascular dilation to a hypoxic stimulus. Further experiments were designed using α-chloralose-anesthetized newborn piglets equipped with closed cranial windows to determine 1) whether cerebral vascular response to adenosine is attenuated in the postictal newborn and 2) whether topical administra-
tion of adenosine would accelerate the return of the hypoxia-induced cerebral vasodilation in the postictal period.

METHODS

The animal protocols used were reviewed and approved by the Animal Care and Use Committee of the University of Texas at San Antonio. All animals were maintained in a facility accredited by the American Association for Accreditation of Laboratory Animal Care. Farm-bred newborn piglets (1–14 days old, weighing 1.5–3.0 kg) were anesthetized initially with ketamine hydrochloride (33 mg/kg im) and acepromazine (3.3 mg/kg im) and were maintained on alpha-chloralose (30–40 mg/kg iv initially, supplemented with 5–7 mg·kg⁻¹·h⁻¹). Catheters were inserted into the femoral vein for maintenance of anesthesia and administration of medications and fluid, and into the femoral artery to record systemic blood pressure and sample arterial blood gases and pH. Animals underwent tracheostomy with insertion of an endotracheal tube (3.5-mm internal diameter) and were mechanically ventilated with room air. Core temperature was monitored with a rectal probe and was maintained between 37.5 and 38.5 °C via a warming blanket.

Cranial Window Placement

For insertion of the closed cranial window, the scalp was surgically removed with a cauterizing scalpel, and an opening was made in the skull over the parietal cortex. Incisions were made in the dura, which was retracted over the cut bone edge. The space under the window was filled with dental acrylic. The window was made in the skull over the parietal cortex. Incisions were surgically removed with a cauterizing scalpel, and an opening was topically applied under the cranial window and maintained for 5 min with the recording of maximum vessel diameter. Sodium nitroprusside (5 M) was then readministered for a 10-min period. The window was again gently flushed with aCSF, and the pial surface was allowed to recover for a 10-min period. Seizure activity was then induced with bicuculline as before, and pial arteriolar vessel response to hypoxia was again evaluated in the immediate postictal period. Topical adenosine (10⁻⁵ M) was then readministered for a 10-min period. The window was again gently flushed with aCSF, and the pial surface was allowed to recover for a 10-min period. The hypoxic stimulus was then repeated within 60 min postictal.

In a separate group (group II) of newborn pigs, the preseizure control response to both hypercapnia and hypoxia (5-min exposure) with recovery to baseline were measured, a dilating dose (as confirmed by the dose-response curve of topical adenosine 10⁻⁵ M) was administered topically to the pial surface for a 10-min period of exposure with recording of vessel diameter at 1, 3, 5, and 10 min. The window was then gently flushed with aCSF, and the pial surface was allowed to recover for a 10-min period. Seizure activity was then induced with bicuculline as before, and pial arteriolar vessel response to hypoxia was again evaluated in the immediate postictal period. Topical adenosine (10⁻⁵ M) was then readministered for a 10-min period. The window was again gently flushed with aCSF, and the pial surface was allowed to recover for a 10-min period. The hypoxic stimulus was then repeated within 60 min postictal.

Role of adenosine in altered responses. A dose-response curve to determine the dilatory effects of topical adenosine was performed with concentrations of adenosine (Sigma) ranging from 10⁻¹² to 10⁻⁶ M as background data to this series of experiments. Pial vessel diameter and MAP were serially recorded during each 10-min exposure of each concentration tested. Between each tested concentration, the pial surface was flushed with aCSF, allowed to return to baseline diameter, and then observed for another 10-min period before another adenosine concentration was administered.

An initial group (group I) of newborn pigs was similarly prepared as described in Characteristics of postictal pial arteriolar responses. After preseizure control responses to both hypercapnia and hypoxia (5-min exposure) with recovery to baseline were measured, a dilating dose (as confirmed by the dose-response curve of topical adenosine 10⁻⁵ M) was administered topically to the pial surface for a 10-min period of exposure with recording of vessel diameter at 1, 3, 5, and 10 min. The window was then gently flushed with aCSF, and the pial surface was allowed to recover for a 10-min period. Seizure activity was then induced with bicuculline as before, and pial arteriolar vessel response to hypoxia was again evaluated in the immediate postictal period. Topical adenosine (10⁻⁵ M) was then readministered for a 10-min period. The window was again gently flushed with aCSF, and the pial surface was allowed to recover for a 10-min period. The hypoxic stimulus was then repeated within 60 min postictal.

Characterization of postictal pial arteriolar responses. All animals underwent an initial observation period of at least 30 min postinseminstration with recording of baseline parameters including pial arteriolar diameter, mean arterial blood pressure (MAP), core temperature, and arterial blood gases and pH. These parameters were recorded for each tested response at 1, 3, and 5 min. Preseizure control responses were then quantified for hypercapnia (ventilation with a 10% CO₂-20% O₂-70% N₂ gas mixture), hypoxia (ventilation with a 10% O₂-90% N₂ gas mixture), and sodium nitroprusside (10⁻⁶ M). Hypercapnia and hypoxia were maintained for 5 min, and maximal vessel diameter was recorded. Sodium nitroprusside was topically applied under the cranial window and maintained for 5 min with the recording of maximum vessel diameter. At the end of each tested response, the area under the cranial window was gently flushed with aCSF to remove the previous stimulus and allow the vessels to return to baseline diameter.

Seizures were induced with intravenous injection of bicuculline (1 mg/kg), a GABA-A receptor blocking agent. Bicuculline (Sigma, St. Louis, MO) was dissolved in 1 N HCl and brought to a pH of 6.0–6.5 with 1 N NaOH to a concentration of 1 mg/ml. The onset and termination of clonic movements defined the duration of the seizures. The cranial window was flushed with aCSF following seizure activity in all piglets before further testing. Maximum pial vessel dilation response to hypoxia, hypercapnia, and sodium nitroprusside was repeated in the immediate postictal period (~10 min). Additional measurements were done at 60, 90, and 120 min in response to both hypoxia and sodium nitroprusside or until vessel dilation with hypoxia returned to preictal baseline.

RESULTS

The arterial blood gases, pH, and MAP measurements recorded at baseline and in response to hypoxia, hypercapnia, and sodium nitroprusside (10⁻⁶ M) before seizure induction are shown in Table 1. Postseizure values are shown in Table 2. The preictal MAP was similar to control except during hypoxia, during which...
systemic pressure decreased (94 ± 3 to 63 ± 7 mmHg). Systemic blood pressure in the postictal period did not vary significantly from control during any of the dilator stimuli including hypoxia (Table 2). MAP did increase in the immediate postictal period versus preseizure control (94 ± 3 to 102 ± 4 mmHg), although the change was not statistically significant (P > 0.05).

Both pre- and postictal values for arterial blood gases and pH were similar to control values except where predicted during exposure to hypoxic and hypercapnic stimuli. Preseizure PO2 decreased during 5 min of ventilation with fractional inspired O2 of 0.10. Similar findings occurred postictally with PO2 significantly decreasing from control after 10, 60, 90, and 120 min of hypoxia. Both pH and PCO2 did not vary in response to hypoxia throughout the duration of the postictal period; however, pH did decrease predictably during hypercapnia with an increasing PCO2.

Topical sodium nitroprusside, as expected, had no effect on arterial blood gases and systemic pressure both preseizure and throughout the postictal period measured at 60 and 90 min (21.7 ± 6 and 21.6 ± 5%, respectively; P < 0.01). Pial arteriolar response returned to near preseizure control dilation by 120 min (37.0 ± 9%), but the difference did not reach statistical significance (P > 0.05).

Adenosine

Before a dose-response curve to topical adenosine was determined, pial arteriolar dilation consistent with previous responses was noted in response to both hypercapnic and hypoxic stimuli. Figure 3 illustrates a dose-response curve for topically administered adenosine. A topical adenosine concentration of 10⁻⁸ M was the threshold dilator concentration, MAP and blood gas analysis did not change during exposure to adenosine.

Preseizure response in both group I (10⁻⁵ M) and group II (10⁻¹¹ M) adenosine-treated piglets resulted in predicted control vessel dilation to hypercapnic (57.0 ± 3 and 54.4 ± 2%, respectively) and hypoxic stimuli (46.1 ± 7 and 51.0 ± 8%, respectively; Figs. 4 and 5). In addition, significant attenuation of the dilatory response to hypoxia occurred in the immediate postictal period in both groups [5.9 ± 2% (P < 0.001) and 11.7 ± 6% (P < 0.01), respectively; Figs. 4 and 5]. In group I, pre-versus postictal vessel dilatory response to adenosine (10⁻⁵ M) was unaltered by bicuculline-induced seizure activity (18.7 ± 2 and 18.2 ± 3%, respectively; P = 0.32; Fig. 6). Postictal dilatory response to hypoxia in group I was restored to control dilation following

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**Table 1. Physiological parameters preseizure**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypercapnia</th>
<th>Control</th>
<th>Hyperoxia</th>
<th>Control</th>
<th>SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>94 ± 3</td>
<td>83 ± 4</td>
<td>92 ± 5</td>
<td>63 ± 7</td>
<td>103 ± 3</td>
<td>100 ± 3</td>
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<td>pH</td>
<td>7.43 ± 0.01</td>
<td>7.12 ± 0.01*</td>
<td>7.40 ± 0.01</td>
<td>7.36 ± 0.02</td>
<td>7.39 ± 0.01</td>
<td>7.38 ± 0.02</td>
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<tr>
<td>PCO₂, mmHg</td>
<td>31 ± 1</td>
<td>71 ± 2*</td>
<td>33 ± 1</td>
<td>35 ± 1</td>
<td>31 ± 1</td>
<td>33 ± 1</td>
</tr>
<tr>
<td>PO₂, mmHg</td>
<td>92 ± 3</td>
<td>84 ± 4</td>
<td>89 ± 4</td>
<td>26 ± 1*</td>
<td>85 ± 4</td>
<td>82 ± 5</td>
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</tbody>
</table>

Values are means ± SE; n = 10 animals for hypercapnia and hypoxia groups, and n = 8 for sodium nitroprusside (SNP; 10⁻⁶ M) group. MAP, mean arterial blood pressure. *P < 0.001 compared with control values.

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**Table 2. Physiological parameters postbicuculline-induced seizures**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hyperoxia, 10 min</th>
<th>Control</th>
<th>Hypercapnia</th>
<th>Control</th>
<th>Hyperoxia, 60 min</th>
<th>Control</th>
<th>Hyperoxia, 90 min</th>
<th>Control</th>
<th>Hyperoxia, 120 min</th>
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<tr>
<td>MAP, mmHg</td>
<td>102 ± 4</td>
<td>106 ± 6</td>
<td>110 ± 4</td>
<td>104 ± 7</td>
<td>103 ± 4</td>
<td>108 ± 5</td>
<td>101 ± 4</td>
<td>106 ± 6</td>
<td>98 ± 5</td>
<td>100 ± 7</td>
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<tr>
<td>pH</td>
<td>7.41 ± 0.02</td>
<td>7.37 ± 0.01</td>
<td>7.40 ± 0.02</td>
<td>7.17 ± 0.04*</td>
<td>7.43 ± 0.01</td>
<td>7.40 ± 0.02</td>
<td>7.45 ± 0.03</td>
<td>7.42 ± 0.02</td>
<td>7.45 ± 0.02</td>
<td>7.43 ± 0.03</td>
</tr>
<tr>
<td>PCO₂, mmHg</td>
<td>30 ± 1</td>
<td>32 ± 1</td>
<td>30 ± 1</td>
<td>71 ± 2*</td>
<td>32 ± 3</td>
<td>33 ± 3</td>
<td>30 ± 2</td>
<td>32 ± 3</td>
<td>29 ± 1</td>
<td>32 ± 1</td>
</tr>
<tr>
<td>PO₂, mmHg</td>
<td>90 ± 5</td>
<td>25 ± 1*</td>
<td>85 ± 5</td>
<td>96 ± 8</td>
<td>95 ± 8</td>
<td>25 ± 1*</td>
<td>94 ± 7</td>
<td>25 ± 1*</td>
<td>93 ± 6</td>
<td>23 ± 1*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10 animals for 10-min hypoxia and hypercapnia groups, and n = 6 for 60-, 90-, and 120-min hypoxia groups. Time in minutes refers to time postseizure. *P < 0.001 compared with control values.
exposure to adenosine ($10^{-5}$ M) in the immediate postictal period (43.3 ± 7%, $P > 0.05$; Fig. 4). Similarly, in group II piglets repleted with a nondilating dose of adenosine ($10^{-11}$ M), pial arteriolar dilation to hypoxia was also restored (46.7 ± 8%, $P > 0.05$; Fig. 5).

**DISCUSSION**

The new findings from the present study in newborn pigs are that 1) pial arteriolar dilatory responses to hypercapnia and nitric oxide (NO) donors are not altered in the postictal period following bicuculline-induced seizure activity; 2) hypoxia-induced cerebral vasodilation is significantly impaired in the postictal period; 3) acute depletion of available adenosine appears to play a role in the impairment of hypoxia-induced cerebral vasodilation in the immediate postictal period; and 4) adenosine has a permissive role in hypoxia-induced cerebral vasodilation.

CBF autoregulation is impaired in the postictal period in both perinatal animal models and human newborns. Pressure autoregulation is lost similarly following perinatal asphyxia. In addition, asphyxia impairs cerebral vasodilation to both hypercapnia and hypoxia depending on the severity of the insult (26, 27, 29). The loss of CBF autoregulation coupled with poor vessel reactivity to hypercapnia, as well as hypoxia, has been correlated with poor neurological outcome in asphyxiated neonates (26, 27). Cerebral vasodilatory reactivity to hypoxia has been shown to be preferentially preserved compared with hypercapnic dilation, although the loss of autoregulation precedes both (26, 36). In contrast to that in asphyxiated infants, we observed in our study that postictal pial arteriolar
reactivity to hypercapnia remains intact, whereas vasodilation to hypoxia is significantly altered.

The mechanisms involving altered cerebral autoregulation following seizures, perinatal asphyxia, or other insults remain unclear. It is thought that, in the asphyxiated human newborn, cerebral vasoparalysis may be secondary to a state of maximum vasodilation resulting from elevated perivascular H\(^+\) concentration or release of other factors such as adenosine, prostanoids, and/or free radicals (3, 14, 26, 36). Studies using Doppler ultrasound in asphyxiated neonates have demonstrated cerebral hyperemia secondary to vasodilation coupled with decreased cerebral vascular resistance persisting for as long as several days postinjury (1, 3, 14, 34). Monin et al. (18), however, noted return of CBF to baseline within 30 min following seizure activity, thus suggesting that vasodilation did not contribute to the loss of autoregulation. In our study, pial arteriolar diameter also returned to preseizure control values in the immediate postictal period. Seizure duration was relatively short in our piglets (<15 min). It is possible that a longer duration of seizure activity causing significant metabolic acidosis may have resulted in persistent cerebral vasodilation similar to that observed in the human newborn postasphyxial state. Isolated metabolic acidemia with increased perivascular H\(^+\) concentration in several newborn animal studies has been shown to alter autoregulation (5, 19).

Hypercapnia-induced cerebral vasodilation in newborn animal models occurs via a permissive role of vasoactive prostanoids released by the endothelium in response to increased perivascular H\(^+\) concentration (12, 37). Given the unaltered pial arteriolar dilatory response to hypercapnia in piglets in the present study, it appears that this mechanism of endothelial prostanoid release and subsequent cerebral vasodilation with increased CO\(_2\) remains intact following bicuculline-induced seizures. Cerebral vasodilation to topical sodium nitroprusside remained consistent with the presezile dilatory response throughout the measured postictal period (90 min). Nitrovasodilators such as sodium nitroprusside release NO that stimulates soluble guanylate cyclase in the vascular smooth muscle cell, resulting in relaxation (17). An intact dilator response to sodium nitroprusside demonstrates that vascular smooth muscle response to a NO donor remains unaltered postictally.

The results of the present study demonstrate a marked reduction in cerebral vasodilation with the induction of hypoxia in the immediate postictal period. This altered response persisted 90 min into the postictal period and showed a trend toward incomplete dilatation versus control at 120 min, although the difference was not statistically significant. Whereas pH and P\(_{\text{CO}}\text{2}\) were unchanged during the 5 min of exposure to hypoxia preseizure, MAP was moderately diminished during this period, possibly contributing to the observed vasodilation. However, baseline dilatation was similar to that observed in other studies with stable or minimally changed blood pressure during hypoxia in newborn pigs (2, 13). Furthermore, the moderate decrease in systemic blood pressure that we observed is within the expected range of autoregulation and should not have altered CBF in otherwise healthy piglets (11).

The mechanisms that produce cerebral vasodilation in response to hypoxia remain incompletely understood. Multiple mediators and dilator systems have been proposed to be involved in this process, including adenosine. Adenosine is considered to be an important mediator in both the adult and newborn cerebral circulation, and brain adenosine levels are known to increase during ischemia and hypoxia in several animal models (4, 16, 21, 30, 37, 38, 39). Additional studies have suggested that adenosine has a role in the mediation of dilator responses to hypotension and insulin-induced hypoglycemia as well in newborn pigs (11, 31).

Cerebral blood flow is known to increase significantly during seizure activity in newborn animal models (6, 7, 10, 18, 25), and evidence suggests that a similar elevation in CBF occurs in neonates (24). Coupled with
this increased CBF with seizure activity, Winn et al. (40) showed increased brain adenosine levels during the initial minutes of seizure activity in an adult rat model. Specifically, Park et al. (22) found a significant increase in brain interstitial fluid adenosine levels in association with increased CBF during bicuculline-induced seizures in newborn pigs.

Recent studies have produced mixed evidence concerning adenosine in its role as a potential mediator of cerebral vasodilation to hypoxia. Pelligrino et al. (23) demonstrated in adult rats that severe hypoxia is dependent on neuronal activation promoting the additive release of both NO and adenosine, with NO having increasing significance going from moderate to severe hypoxia. In his paper regarding newborn pigs, Armstead (2) presented data suggesting a more complex role of adenosine in hypoxia-induced cerebral vasodilation also involving NO, cGMP, cAMP, and activation of ATP-sensitive K\textsuperscript{+} (K\textsubscript{ATP}) channels. Taguchi et al. (32), using adult rabbits, showed that hypoxic-induced cerebral vasodilation appears to involve activation of K\textsubscript{ATP} channels. Adenosine-induced dilation of cerebral arterioles was not mediated by this process in their study, suggesting that adenosine may not contribute to activation of K\textsubscript{ATP} channels during hypoxia (32). In the hypoxia model used by Leffler et al. (13), the authors were unable to demonstrate a role for adenosine in hypoxic cerebral vasodilation, but they did find evidence suggesting a mechanism involving endothelium-derived cytochrome P-450 epoxygenase metabolites of arachidonic acid.

In our study, we speculated that alterations of adenosine activity with seizure ictus may be involved with the loss of pial arteriolar vasodilation to hypoxia acutely in the postictal period. We therefore needed to determine whether this altered adenosine activity was due to a diminished response to adenosine or an acute depletion of available adenosine. Piglets that were repleted with a diluting topical dose of adenosine (10^{-5} M) in the period immediately following bicuculline-induced seizures had return of baseline preseizure pial arteriolar dilation to hypoxia within 60 min postictal. Cerebral vessel responsivity to adenosine (10^{-5} M) was not altered by seizure activity. In addition, similar results were obtained using a nondiluting concentration of adenosine (10^{-11} M), with return of cerebral vasodilation to baseline again by 60 min postictal. From these results, we can make several conclusions about the role of adenosine: 1) the altered postictal response to hypoxia is not due to a decreased sensitivity to adenosine but, rather, to a depletion of available adenosine; and 2) adenosine appears to have a permissive role in hypoxic cerebral vasodilation, and therefore concentration is not the determinant factor of the dilatory response.

Other potential mechanisms that may be involved in hypoxia-induced cerebral vasodilation in piglets postictally cannot be ruled out by the present study because they were not examined. Future studies to further define the role of adenosine and other possible mechanisms involved in this response may be important to help prevent resulting secondary brain injury following seizures in newborn infants.

**Perspectives**

We speculate that the loss of vasodilation to hypoxia in the postictal period may result in inadequate oxygen and substrate delivery to those margins of ischemic tissue in asphyxiated neonates. Furthermore, cardiovascular compromise with decreased cardiac output secondary to hypoxia may further exacerbate injury in high-risk infants. It is possible that preserved cerebrovascular dilation to hypercapnia may be protective of brain injury in those infants that are poorly ventilated, at least in the immediate postictal period, until normocapnia is established. However, depending on the gestational age of the infant, increased CBF during this period may in fact promote injury in those areas such as the vulnerable germinal matrix of premature infants.

In conclusion, the present study suggests that, after seizure activity in newborn pigs, cerebrovascular dilation to hypoxia and sodium nitroprusside is preserved, whereas hypoxia-induced cerebral vasodilation is significantly impaired in the immediate postictal period. Adenosine depletion with seizure activity is a potential mechanism involved in the loss of postictal pial arteriolar dilation to hypoxia, and adenosine appears to have a permissive role in hypoxia-induced cerebral vasodilation.

The authors especially thank Shane Sprague and Tina Vielma for their assistance in the laboratory.

These experiments were funded directly by the Department of Pediatrics, University of Texas Health Science Center at San Antonio, San Antonio, TX 78284.

The opinions and assertions contained herein are the private views of the authors and are not construed as official or as reflecting the views of the Department of Defense (and/or the Department of the Air Force).

Address for reprint requests: R. J. DiGeronimo, Dept. of Neonatology, Wilford Hall USAF Medical Center, 59th MDW/MNP, 2200 Berquist Dr., Ste. 1, Lackland AFB, TX 78236.

Received 22 September 1997; accepted in final form 16 January 1998.

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