Effect of Amino Acid Infusion on the Ventilatory Response to Hypoxia in Protein-Deprived Neonatal Piglets

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ABSTRACT. Several amino acids (AA) act as neurotransmitters and mediate the ventilatory response to carbon dioxide and hypoxia in adult human beings and animals. To evaluate the influence of AA on the neonatal ventilatory response to hypoxia, 29 newborn piglets less than 5 d old were randomly assigned to a control diet or protein-free diet for 7–10 d. Minute ventilation, arterial blood pressure, oxygen consumption, and arterial blood gases were measured in sedated, spontaneous breathing piglets while they breathed room air and at 1, 5 and 10 min of hypoxia (fraction of inspired oxygen concentration = 0.10) before and after 4 h of AA (Trophamine, 3 g/kg, i.v.) or 10% dextrose infusion. The administration of AA solution in protein-deprived piglets resulted in a significant increase in minute ventilation after 10 min of hypoxia ($26 \pm 19\%$) in comparison with their ventilatory response before AA infusion ($10 \pm 12\%$; $p < 0.02$). Similar increase in the ventilatory response to hypoxia was observed in the control diet group after AA infusion ($23 \pm 17\%$ versus $11 \pm 11\%$; $p < 0.05$). Changes in arterial blood pressure, oxygen consumption, and arterial blood gases during hypoxia were similar before and after AA infusion. The ventilatory response to hypoxia in both protein-free and control diet animals were similar before and after the 10% dextrose infusion. These results stress the importance of nutritional factors in the neonatal control of breathing. (*Pediatr Res* 35: 316–320, 1994)

Abbreviations

AA, amino acids
D₁₀W, 10% dextrose
ABP, arterial blood pressure
BD, base deficit
GABA, γ -aminobutyric acid
V_E, minute ventilation
V_{O₂}, oxygen consumption
V_T, tidal volume

hypercarbia (1). Furthermore, these respiratory changes were reversed by the administration of enteral or parenteral protein (1–3). In preterm infants, the basal V_E and the ventilatory response to hypercarbia were increased after the administration of a standard AA solution (9).

The mechanisms that can explain the ventilatory changes during nutritional intervention are not fully defined. Some of these changes may be mediated by the increase and/or decrease in inhibitory or excitatory neurotransmitters in the CNS (4, 10). One of the latter is glutamate, a central excitatory neurotransmitter that participates in the ventilatory response to hypoxia (5). Other AA that are not neurotransmitters may also influence the central respiratory output. For example, the administration of branched-chain AA to adult human beings resulted in an increase in basal ventilation and the ventilatory response to hypercarbia (6, 7). Branched-chain AA may compete with tryptophan at the blood brain barrier, limiting the entry of tryptophan to the CNS and thereby decreasing the production of serotonin, which may be a respiratory inhibitor (11–16). Branched-chain AA may also compete with glutamate for decarboxylation, resulting in increased glutamate levels and consequently reducing the production of GABA, which is an important respiratory depressant (17–19). Because a late ventilatory depression occurs in neonates during hypoxia (20–23) and because this depression may in part be caused by an increase in inhibitory neurotransmitters, counterbalancing their effect by dietary intervention could reverse the ventilatory depression. To our knowledge, no studies have been conducted to evaluate the influence of AA infusion on the ventilatory response to hypoxia in the neonatal period.

We hypothesized that protein deprivation during the neonatal period will decrease the ventilatory response to sustained hypoxia and that this depression can be reversed by the administration of AA. Therefore, the purpose of this study was to determine whether protein deprivation for 7 to 10 d decreases the ventilatory response to hypoxia in newborn piglets and to evaluate the effect of the administration of a standard AA solution (Trophamine) infusion on the ventilatory response to hypoxia in this animal model.

MATERIALS AND METHODS

Data from adult human beings and experimental animals suggest that several AA play an important role in central respiratory activity (1–8). Studies performed on adult subjects who were in a state of semistarvation demonstrated decreased basal ventilation and depressed ventilatory responses to hypoxia and

Twenty-nine piglets less than 5 d of age were randomly assigned to either protein-free or control diet groups. The control diet consisted of 16.5% solids in solution (protein, 24%; fat, 17%; carbohydrate, 52.35%). The protein-free diet consisted of 16.5% solids in solution (protein, 0%; fat, 21.5%; carbohydrate, 66%). Both diets were prepared by ICN Biochemicals (Cleveland, OH) and were isocaloric (4.6 cal/g). The diets were commenced at 3–5 d of age and maintained for the 7- to 10-d interval until the time of the study.

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At study, the animals were anesthetized with ketamine (20 mg/kg, intramuscularly) and xylazine (2 mg/kg, intramuscularly) for surgical procedures. Lidocaine hydrochloride (0.5%) was used for local anesthesia. The animals were lightly sedated with chloral hydrate, which was administered intraperitoneally at a dose of 100 mg/kg at intervals of 3 to 4 h whenever signs of arousal occurred (opening of eyes, movement of limbs or ears).

Femoral arteries and veins were cannulated and used for ABP measurements, blood gas sampling, and infusion of dextrose or AA solution. Vascular pressures were measured with pressure transducers (model P-23-ID, Gould Instruments, Cleveland, OH) and recorded on a multichannel recorder (Model 3800, Gould Instruments). A tracheostomy was performed, and a 3.5–4.0 mm endotracheal tube was inserted.

The skin temperature was maintained at 38.5°C by means of a servocontrolled radiant warmer. Rectal temperature was continuously monitored with a thermistor probe (Yellow Springs Instrument Co., Yellow Springs, OH). The animals received an infusion of 6 mL/kg/h of 5% dextrose solution through a peripheral vein.

Respiratory flow was measured by a heated Fleisch No. 00 pneumotachograph (OEM Medical, Richmond, VA), a differential pressure transducer (model MP45, Validyne Engineering Co., Northridge, CA), and a pressure amplifier (Gould Instruments). The flow signal was electronically integrated to obtain VT with a Gould integrator amplifier. Calibration of VT was performed before and after each study with a calibrated glass syringe. VE was obtained by summation of the inspiratory volumes measured during 1-min periods of regular respiration.

VO₂ was measured by the open circuit technique (24). The difference between inspiratory and expiratory oxygen concentration was measured continuously by an oxygen analyzer (model 570-A, Servomex, Crowborough, Sussex, UK) throughout the study period. VO₂ was calculated by the formula: $\dot{V}O_2 = \dot{V}_s (F_{iO_2} - F_{eO_2})$, where $\dot{V}_s$ is the flow rate through the system, F_{iO_2} is the fraction of inspired oxygen concentration, and F_{eO_2} is the oxygen concentration in mixed expired gas.

The animals were allowed a 2-h stabilization period after completion of surgery. After this period, the animals were connected to a breathing circuit with a constant bias-flow of 3–4 L/min. After 10 min of basal recording in room air VE, VT, VO₂, ABP, and arterial blood gas measurements were obtained and referred to as room air baseline. The fraction of inspired oxygen concentration was reduced to 0.10 to induce hypoxia, and after 10 min of hypoxia all measurements were repeated. Measurements were performed only when the animals were quiet and showing no signs of distress, as evidenced by stable heart rate and ABP.

After baseline hypoxia measurements were obtained, control and protein-free diet animals received D₁₀W or AA infusion (Trophamine, 3 g/kg, i.v.) for a period of 4 h. Trophamine has the following AA composition (mg/3 g AA): isoleucine, 245; leucine, 420; lysine, 245; methionine, 100; phenylalanine, 145; threonine, 125; tryptophan, 60; valine, 235; cysteine, <10; histidine, 145; tyrosine, 70; alanine, 160; arginine, 365; proline, 205; serine, 115; glycine, 110; aspartic acid, 95; glutamic acid, 150; taurine, 7. The animals were composed of the following four groups: group 1: control diet, D₁₀W (mean ± SD; *n* = 7; age, 12 ± 1 d; weight, 2879 ± 267 g); group 2: control diet, AA (*n* = 8; age, 11 ± 2 d; weight, 2340 ± 300 g); group 3: protein-free diet, D₁₀W (*n* = 7; age, 11 ± 3 d; weight, 1531 ± 386 g); and group 4: protein-free diet, AA (*n* = 7; age, 12 ± 1 d; weight, 1697 ± 396 g). The volume of D₁₀W or AA solution was calculated to provide the same volume and calories. All the measurements were repeated at the end of the infusion period while the animals breathed room air and 10% oxygen.

Changes in cardiovascular and respiratory measurements during hypoxia were compared between dietary groups and each of the subgroups who received D₁₀W or AA by repeated measure analysis of variance. Paired *t* test was used to compare the changes

in ventilation with hypoxia before and after the D₁₀W or AA infusion.

Analysis of variance was used to compare the changes in arterial blood gases between groups. A *p* < 0.05 was considered statistically significant.

Handling and care of the animals was conducted in accordance with the guidelines of the National Institutes of Health, and this study protocol was approved by the Animal Care Committee of the University of Miami School of Medicine.

RESULTS

Mean age and weights were not different between study groups before the dietary intervention. However, mean weight in protein-free diet (mean ± SD; *n* = 14; weight, 1617 ± 383 g) animals was significantly lower (*p* < 0.001) than those of control diet (*n* = 15; weight, 2590 ± 700 g) animals after 7–10 d of dietary intervention.

Ventilatory response. The ventilatory response to hypoxia was not different between protein-free and control diet groups before the animals received the test infusions (D₁₀W or AA) (Fig. 1). Although protein-free diet animals did not change their ventilatory response to hypoxia after 4 h of D₁₀W administration, a sustained increase in ventilation (*p* < 0.02) was observed after the administration of AA solution (Fig. 2). After AA infusion, a marked increase in VE (26 ± 19%) was observed after 10 min of hypoxia in comparison with the ventilatory response (12 ± 10%) before AA. In the control diet subgroups, the ventilatory response to hypoxia was also unchanged by D₁₀W infusion, whereas after 4 h of AA administration, VE showed a significant increase after 10 min of hypoxia (23 ± 17 versus 11 ± 11%; *p* < 0.05) (Fig. 3). This increase in ventilation during hypoxia observed in the protein-free and control diet groups was the result of increased respiratory rate and VT (Table 1). Furthermore, the percentage increase in ventilation after 10 min of hypoxia was similar in both protein-free and control diet groups after AA infusion.

Cardiovascular response. Mean ABP did not differ between groups while they breathed room air or during hypoxia before drug infusions (Table 1). An increase in the ABP with hypoxia was observed in all groups independent of the type of solution administered.

Oxygen consumption and arterial blood gases. No significant differences were observed in baseline VO₂ or the changes in VO₂ with hypoxia between protein-free and control diet groups (Table 1).

The VO₂ values obtained during room air and hypoxia after AA infusion increased significantly in the protein-free diet group (*p* < 0.03) in comparison with the baseline values before AA administration.

A decrease occurred in the baseline pH and BD in the protein-

Fig. 1. Ventilatory response to hypoxia in control and protein-free diet groups before D₁₀W or AA infusion.

Fig. 2. Percentage change in the ventilatory response to hypoxia in protein-free diet animals before and after $D_{10}W$ or AA infusion.

free diet group as compared with the control diet group. However, the changes in pH and BD with hypoxia were similar in the protein-free and control diet animals. P_{aO_2} and P_{aCO_2} values were similar during normoxia and hypoxia in all groups (Table 2).

DISCUSSION

These results demonstrate that protein deprivation for a period of 7–10 d does not alter the ventilatory response to sustained hypoxia in neonatal piglets. Administration of a standard AA solution resulted in a sustained increase in ventilation during hypoxia in both protein-free and control diet groups.

The increase in ventilation during sustained hypoxia after 4 h of AA infusion was similar to the observation in semistarved adult human beings after protein intake (1–3). Although the exact mechanism for sustained increase in the ventilatory response to hypoxia after AA infusion is not known, it is likely that the AA administration altered the balance between the excitatory and inhibitory AA neurotransmitters in the CNS (4). Preliminary results from our laboratory showed that glutamate is in part responsible for the increase in ventilation during hypoxia in unanesthetized piglets (25), whereas GABA modulates the hypoxic ventilatory depression in sedated newborn piglets (26). Administration of a standard AA solution increases branched-chain AA levels in plasma, which could increase CNS

Fig. 3. Percentage change in the ventilatory response to hypoxia in the control diet animals before and after $D_{10}W$ or AA infusion.

glutamate concentration and decrease GABA levels by competitive action with glutamate decarboxylase (17). It has also been suggested that the increased branched-chain plasma AA levels (11, 12) may limit the entrance of tryptophan, a precursor of serotonin that may be a respiratory depressant, (13–16) into the CNS. However, several *in vivo* animal studies have provided conflicting results, some showing an excitatory effect of serotonin on the central respiratory system and others demonstrating an inhibitory effect (15, 16, 27–29). The AA solution used in this study contained proportionally more excitatory AA such as glutamate and aspartate than inhibitory AA such as glycine, which may also have an influence on the ventilatory response to hypoxia (5, 30, 31). Furthermore, the fact that this AA solution does not contain GABA, an important inhibitory neurotransmitter, may facilitate the effects of excitatory AA on the central respiratory system. Further studies are needed to explain the mechanisms involved in the increased ventilatory response to hypoxia induced by the administration of AA solution.

The fact that the changes in ventilation at 1 min of hypoxia were not different after AA infusion as compared with before AA infusion in both groups suggests that the sustained increase in $\dot{V}_E$ after AA is mediated centrally and not through a change in the activity of the carotid bodies.

Although the data support the hypothesis that AA play an important role in central respiratory output, we cannot exclude the possibility that these changes are in part related to an im-

Table 1. Changes in $\dot{V}_E$, V_T , respiratory rate, $\dot{V}O_2$, and mean ABP in control and protein-free diet groups*

	D ₁₀ W				AA			
	Pre		Post		Pre		Post	
	RA	10% O ₂	RA	10% O ₂	RA	10% O ₂	RA	10% O ₂
Control diet								
$\dot{V}_E$ (mL/min/kg)	446 ± 74	507 ± 75	406 ± 104	490 ± 98	490 ± 42	540 ± 29	469 ± 70	572 ± 86
V_T (mL/kg)	7.0 ± 0.8	7.6 ± 0.7	8.2 ± 1.8	8.5 ± 1.6	7.6 ± 1.5	8.0 ± 1.4	8.7 ± 2.0	9.5 ± 1.8
RR (breaths/min)	64 ± 10	67 ± 10	53 ± 21	60 ± 19	68 ± 19	70 ± 16	56 ± 15	62 ± 16
$\dot{V}O_2$ (mL/min/kg)	9.7 ± 1.0	9.3 ± 0.8	10.0 ± 0.8	9.4 ± 1.3	10.3 ± 1.1	10.1 ± 0.9	11.6 ± 0.4	11.0 ± 1.0†
Mean ABP (mm Hg)	55 ± 8	62 ± 13	48 ± 6	53 ± 7	55 ± 8	60 ± 10	45 ± 8	47 ± 12
Protein-free diet								
$\dot{V}_E$ (mL/min/kg)	467 ± 110	513 ± 105	444 ± 104	475 ± 118	429 ± 67	473 ± 94	445 ± 82	559 ± 132
V_T (mL/kg)	5.9 ± 0.8	5.9 ± 1.0	6.7 ± 1.3	7.0 ± 1.3	7.0 ± 1.2	7.1 ± 1.3	8.0 ± 1.2	8.7 ± 1.2
RR (breaths/min)	77 ± 11	86 ± 14	66 ± 12	68 ± 15	64 ± 13	68 ± 13	56 ± 7	62 ± 11
$\dot{V}O_2$ (mL/min/kg)	6.7 ± 0.4	6.4 ± 0.5	6.5 ± 0.8	6.5 ± 0.6	7.3 ± 0.9	7.3 ± 0.9	8.6 ± 0.8‡	8.4 ± 0.7‡
Mean ABP (mm Hg)	52 ± 8	54 ± 9	39 ± 8	40 ± 11	57 ± 17	58 ± 14	38 ± 8	46 ± 6

* RA, room air; RR, respiratory rate.

† $p < 0.05$ (control diet, Pre-AA vs Post-AA).‡ $p < 0.03$ (protein-free diet, Pre-AA vs Post-AA).

Table 2. Changes in arterial blood gases and acid-base balance in control and protein-free diet groups*

	D ₁₀ W				AA			
	Pre		Post		Pre		Post	
	RA	10% O ₂	RA	10% O ₂	RA	10% O ₂	RA	10% O ₂
Control diet								
pH	7.41 ± 0.04	7.41 ± 0.10	7.40 ± 0.06	7.40 ± 0.06	7.39 ± 0.07	7.40 ± 0.06	7.34 ± 0.06	7.35 ± 0.09
PaO ₂ (kPa)	12.2 ± 1.6	4.1 ± 0.4	12.2 ± 1.6	4.2 ± 0.3	12.9 ± 1.8	4.2 ± 0.4	12.3 ± 1.0	4.5 ± 0.5
PaCO ₂ (kPa)	4.6 ± 0.4	4.3 ± 0.4	4.5 ± 0.3	4.2 ± 0.3	4.4 ± 0.4	4.2 ± 0.6	4.2 ± 0.5	3.8 ± 0.5
BD (mEq/L)	-0.8 ± 3.2	-1.1 ± 2.8	-2.1 ± 3.6	-3.2 ± 3.9	-2.8 ± 4.3	-4.3 ± 4.5	-6.5 ± 3.2	-7.7 ± 4.8
Protein-free diet								
pH	7.35 ± 0.06	7.36 ± 0.04	7.33 ± 0.06	7.32 ± 0.06	7.36 ± 0.09	7.37 ± 0.06	7.29 ± 0.07	7.31 ± 0.09
PaO ₂ (kPa)	13.1 ± 1.0	4.6 ± 0.8	13.9 ± 1.3	4.5 ± 0.9	14.1 ± 1.0	5.0 ± 0.5	13.6 ± 1.4	4.7 ± 0.4
PaCO ₂ (kPa)	4.3 ± 0.5	4.3 ± 0.6	3.8 ± 0.9	3.7 ± 0.8	4.1 ± 0.2	3.8 ± 0.4	3.8 ± 0.5	3.4 ± 0.6
BD (mEq/L)	-5.7 ± 4.4	-5.4 ± 4.2	-8.7 ± 4.0	-9.2 ± 4.3	-6.3 ± 2.9	-6.4 ± 4.6	-11.1 ± 2.6	-11.3 ± 3.5

* RA, room air.

provement in respiratory muscle function after the administration of AA.

A close relationship has been observed between the metabolic rate and ventilation (32). In addition, it has been shown that in adult human beings a significant increase in metabolic rate and ventilation occurs after AA infusion (2), but this increase in ventilation exceeds the increase in metabolic rate. This finding suggests that AA infusion stimulates ventilation not only by increasing metabolic rate but also by specifically increasing ventilatory drive (8). In the present study, the metabolic rate decreased during hypoxia by 2% in the protein-free diet group and by 5% in the control diet animals, whereas $\dot{V}_E$ increased by 26% and 23% after AA infusion in the protein-free and control diet animals, respectively. Therefore, the increase in ventilation during hypoxia was independent of changes in the metabolic rate.

Changes in ABP with hypoxia among the different groups of animals were similar after the infusion of the respective solutions. Therefore, the sustained ventilatory response to hypoxia observed after AA administration cannot be explained by cardiovascular changes.

Protein-deprived animals showed a decrease in the baseline pH and BD. Although we do not have a clear explanation for the metabolic acidosis, this condition could result from diarrhea observed in malnourished newborn piglets. Malnutrition in newborn animals can alter gastrointestinal function (33, 34), and this alteration could lead to diarrhea and metabolic acidosis. After the administration of the test solutions, the BD was more pronounced in the animals that received AA, which could have influenced the ventilatory response to hypoxia (35). However,

this is unlikely because the changes in pH and BD during hypoxia were similar in both protein-free diet groups after D₁₀W or AA infusion.

In summary, this study has shown that protein deprivation for a period of 7–10 d does not alter significantly the ventilatory response to sustained hypoxia in newborn piglets. Furthermore, the administration of a standard AA solution to newborn piglets, independent of dietary intervention, resulted in sustained increase in the ventilatory response to hypoxia, and this effect cannot be explained by changes in cardiovascular function, acid-base balance, or metabolic rate. This study also suggests that the effect of AA infusion on the respiratory control is centrally mediated.

The clinical implication of these results is that AA infusion to preterm infants may influence their respiratory center output. Future studies need to address the influence of specific AA on respiratory control mechanisms.

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