Title: AMINO ACIDS AND RESPIRATION

Authors: C. Weissman, M.D., J. Askanazi, M.D., P. LaSala, M.D., L. Conley, M.D., R. Wurtman, M.D., J. Milic-Emili, M.D., J.M. Kinney, M.D.

Affiliation: Departments of Anesthesiology, Surgery and Medicine, Columbia University, College of Physicians and Surgeons, 630 West 168th Street, New York, New York 10032

Introduction. The effect of nutrients on respiration is of particular interest to those caring for patients with respiratory dysfunction; many of whom require nutritional support. Previous studies have demonstrated that parenteral nutrition, administered as hypertonic glucose plus amino acids results in an increase in $\dot{V}_E$. Although this has been largely ascribed to increases in $CO_2$ production secondary to hypertonic glucose, the contribution of amino acids to the respiratory effects is unclear. This study examines the respiratory effects of intravenous amino acids administered to semistarved normal volunteers. The ventilatory changes are correlated with alterations in metabolic rate and plasma amino acid profile. Since CNS levels of amino acids affect the synthesis of neurotransmitters and tryptophan is a precurser to its competitor's for blood brain transport (valine, leucine, isoleucine, tyrosine, phenylalanine) might be important in the changes observed.

Methods. Eight normal volunteers aged 19 to 31 years were infused with 5% dextrose (100 ml/hr) for seven days, followed by administration of 3.5% amino acid solution (3.5% Aminosyn M) at 125 ml/hr for 24 hours. A canopy-spirometer-computer system (1) was used to study ventilatory patterns, metabolic rate and the response to 2 and 4% $CO_2$. Respiratory studies were performed prior to the period of semistarvation (day 0), after 7 days of 5% dextrose infusion (day 7-$D_5W$) and at 4 (day 7-AA 4) and 24 (day 8-AA 24) hours after the initiation of the amino acid infusion. Minute ventilation ($\dot{V}_E$), tidal volume ($V_T$), frequency (f), mean inspiratory flow ($V_T/T_I$) and oxygen consumption ($\dot{V}O_2$) were measured. Arterial blood samples were obtained from indwelling radial artery catheters and analyzed for $PaO_2$, $PaCO_2$ and pH. The slope ($\Delta\dot{V}_E/\Delta PaCO_2$) and position ($\dot{V}_E$ at $PaCO_2$ = 43 torr) of the $\dot{V}_E$-$PaCO_2$ relationship were measured. Plasma amino acid profiles were obtained in 5 of the subjects and correlated with ventilatory changes. This study was approved by the Institutional Review Board of Columbia University. Written informed consent was obtained.

TABLE 1

Resting Ventilation

| | $\dot{V}_E$ (l/min) | $V_T$ (ml) | f ($min^{-1}$) | $V_T/T_I$ (ml/sec) | $\dot{V}O_2$ (ml/min) |
|---|---|---|---|---|---|
| Day 0 | 5.56 | 388 | 16 | 252 | 234 |
| Day 7-$D_5W$ | 4.13* | 293* | 16 | 189* | 204* |
| Day 7-AA4 | 4.90+ | 343 | 17 | 230+ | 224+ |
| Day 8-AA 24 | 5.48+ | 349 | 16 | 250+ | 231+ |

| | Response to $CO_2$ | | |
|---|---|---|---|
| | $\Delta\dot{V}_E/\Delta PaCO_2$ | $\dot{V}_E$ at $PaCO_2$= 43 torr | val+leu+ile+phe+tyr / trp |
| Day 0 | 3.1 | 5.3 | 7.6 |
| Day 7-$D_5W$ | 2.3 | 8.2 | 7.6 |
| Day 7-AA4 | 3.2 | 9.3 | 10.6+ |
| Day 8-AA24 | 3.4 | 19.1+ | 17.7+ |

Results. Minute ventilation decreased during the period of 5% dextrose infusion in parallel with the fall in $VO_2$ (Table 1). With the infusion of amino acids there is a return of both $\dot{V}O_2$ and $\dot{V}_E$ to near control (Day 0) levels. Alterations in $V_T$ (secondary to changes in inspiratory flow) largely explain the changes in $\dot{V}_E$. The ventilatory response to $CO_2$ does not appear to parallel metabolic rate and is essentially unaffected by the 7 day period of 5% dextrose infusion. With institution of the amino acid infusion there is a marked increase in ventilatory sensitivity, which parallels the ratio of val+leu+ile+phe+tyr/trp.

Discussion. Minute ventilation and metabolic rate ($\dot{V}O_2$) were significantly depressed after seven days of 5% dextrose infusion. No significant changes were seen in the ventilatory response to $CO_2$ or in the (val+leu+ile+phe+tyr)/trp ratio. Ventilation and metabolic rate returned toward normal after 4 hours as well as 24 hours following the start of the amino acid infusion. This effect of amino acids on $\dot{V}_E$ was secondary to an increase in $V_T/T_I$, which in normal subjects is an indicator of central ventilatory drive. Thus, within a 24 hour period isotonic amino acid infusions restored metabolic rate, minute ventilation and ventilatory drive, which are depressed by prolonged 5% dextrose infusions. Administration of amino acids resulted in a leftward shift of the $\dot{V}_E$-$PaCO_2$ relationship that was apparent four hours after the infusion had begun and was significant after 24 hours. This shift exceeded the increment in metabolic rate. The ratio of (val+leu+ile+phe+tyr)/trp observed in the control state and following the administration of 5% dextrose for 7 days, increased significantly after the administration of the amino acids and paralleled the changes in the ventilatory response to $CO_2$. No changes were observed in serum bicarbonate levels. Thus, it appears that resting minute ventilation correlates with metabolic rate ($\dot{V}O_2$) while the position of the $\dot{V}_E$-$PaCO_2$ relationship seems to be more closely associated with plasma amino acid profiles, specifically the ratios of tryptophan to its competitors for transport across the blood brain barrier. Thus, tryptophan, a known precurser to serotonin (a respiratory inhibitor) may play a role in respiratory control.

References.

1. Spencer JL, Zikria BA, Kinney JM, et al: A system for continuous measurement of gas exchange and respiratory function. J Appl Phys 33:428-35, 1972