PLASTICITY IS a fundamental property of neural systems, enabling animals to change as environmental conditions change. This plasticity is often greatest during perinatal development, making immature animals particularly susceptible to profound, and potentially deleterious, changes in neural function. Despite the critical importance of the respiratory system to oxygen and acid-base homeostasis, the developing respiratory control system is known to be sensitive to a variety of environmental perturbations, including chronic changes in respiratory gases (hypoxia, hyperoxia, hypercapnia), psychological stress (maternal separation), and numerous drugs (e.g., caffeine, nicotine, alcohol) (1). In this issue of the Journal of Applied Physiology, Penatti et al. (10) demonstrate that maternal nutrition should be added to the list.

Serotonergic neurons in the brain stem modulate critical homeostatic functions such as respiration, circulation, and thermoregulation. To determine whether maternal diet impacts the development of these physiological processes, Penatti et al. (10) provided female rats with food containing 45% less of the essential amino acid tryptophan, the precursor for serotonin (5-HT), than typically found in laboratory diets. Consequently, when these rats were bred, their offspring experienced low tryptophan availability throughout gestation and postnatal development. The tryptophan-restricted pups exhibited significantly reduced brain stem levels of 5-HT as expected, but they also expressed a complex, age-specific suite of changes to body temperature, heart rate, eupneic ventilation, and the hypercapnic ventilatory response (HCVR). For example, tryptophan-restricted rats breathed normally at 5 days of age (P5) under resting conditions, whereas they tended to hyperventilate at P15 and hypoventilate at P25. In addition, the acute HCVR was enhanced at P5 but diminished at both P15 and P25 in these pups.

Collectively, these observations confirm that a mother’s nutritional status can influence her offspring’s cardiorespiratory and thermoregulatory control systems, at least during the neonatal period. It will be interesting to learn whether any of these effects linger after the tryptophan deficiency is corrected. On one hand, Penatti et al. (10) report that there were no changes in the numbers of serotonergic cells or the expression of tryptophan hydroxylase, suggesting that brain stem 5-HT, and therefore serotonergic modulation, may normalize if tryptophan is restored to the diet. Alternatively, prolonged reduction in 5-HT may precipitate irreversible developmental cascades leading to long-lasting cardiorespiratory and thermoregulatory dysfunction; these changes could, in turn, predispose individuals to future disease (i.e., the developmental origin of adult disease paradigm).

Regardless of whether the effects of tryptophan deficiency are permanent, this study may have important implications for understanding sudden infant death syndrome (SIDS). There is mounting evidence that SIDS, the leading cause of death in infants aged 1–12 mo, is linked to abnormal development of serotonergic pathways in the brain stem (4, 9). Abnormalities in the serotonergic system (e.g., decreased expression of key synthetic enzymes or 5-HT receptors, changes to the numbers or phenotype of serotonergic neurons) are present in the majority of SIDS cases (4), and brain stem 5-HT levels may be reduced by 26% in SIDS victims (3). Thus defects in the serotonergic system may represent an underlying vulnerability that could lead to unexpected death in the face of an exogenous stressor during a critical period of development (4). Importantly, adverse socioeconomic conditions, and more specifically poverty, are well-established risk factors for SIDS even after controlling for maternal smoking and alcohol use (6, 12).

Penatti et al.’s (10) findings indicate that malnutrition could be the mechanistic link between poverty and increased SIDS risk. While genetic polymorphisms that disrupt development of the brain stem serotonergic system are associated with SIDS (9), maternal diets low in protein, and consequently tryptophan, may produce functionally equivalent phenotypes. Fortunately, from a public health perspective, maternal diet is a modifiable risk factor.

The data presented by Penatti et al. (10) are consistent with homeostatic dysregulation caused by dietary tryptophan deficiency and reduced brain stem 5-HT, but whether the specific abnormalities identified in their study (i.e., changes in body temperature, heart rate, eupneic breathing, and/or HCVR) contribute directly to SIDS remains controversial. Serotonergic neurons in the brain stem appear to function as central CO2 chemoreceptors (11), and the correlation between reduced 5-HT levels and reduced HCVR reported by Penatti et al. (10) for 25- to 26-day-old tryptophan-deficient pups supports this hypothesis. Thus it has been suggested that reduced CO2 sensitivity links abnormal brain stem 5-HT and SIDS in a subset of cases, perhaps by inhibiting arousal responses during asphyxic events (2). However, even while cardiorespiratory dysfunction is widely suspected in SIDS cases, this link is largely based on indirect evidence, and the potential role for chemosensitivity in the etiology of SIDS is not well understood (4, 13). Likewise, it is unclear whether the hypoventilation or hyperventilation observed during resting conditions in tryptophan-restricted rats would be sufficient to destabilize breathing and precipitate respiratory failure. In this respect, future studies should evaluate whether dietary tryptophan deficiency also affects breathing stability and/or apnea frequency in neonatal rats.

The link between brain stem 5-HT, central CO2 sensitivity, and SIDS is intuitively appealing, but it is not the only mechanism by which abnormal serotonergic modulation might increase the risk of SIDS. Another possibility is that 5-HT deficiency interferes with the expression of respiratory long-term facilitation (LTF), a 5-HT-dependent increase in respiratory motor output to the tongue, upper airway, and/or pump muscles after episodic hypoxia. Obstructive sleep apnea (OSA)
has been proposed as a risk factor for SIDS, and it appears as though an obstructive event precedes death in many SIDS cases (13). Although the relevance of LTF to OSA is itself controversial, it has been proposed that LTF reduces the frequency of apneas by helping to maintain upper airway patency during sleep (5, 7). Given that 5-HT signaling is critical to the manifestation of LTF (5) and that neonates express LTF much like adults (see e.g., Ref. 8), dietary tryptophan deficiency might impair respiratory LTF and, by extension, increase vulnerability to SIDS.

The study by Penatti et al. (10) is significant in that it provides a plausible mechanism to explain the observed relationship between poverty and increased risk of SIDS. Clearly many questions remain: Is this the correct mechanism linking poverty and SIDS? Are other aspects of cardiorespiratory control affected (e.g., breathing stability, hypoxic responses, LTF)? Can these influences be reversed? However, by highlighting the link between maternal diet, brain stem neurotransmitters, and homeostatic control, this work opens an important new direction for the study of developmental plasticity.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES