- Bar code scanning or other automated system for HM fortification calculations to reduce risk of mathematical errors and prevent HM waste.

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XI. Relationship Between Feeding and Early Stress in Premature Infant: The Role of Epigenetic Factors

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BACKGROUND

Children born preterm are at risk of developmental and feeding behavior problems (1). Problems with feeding can persist later in life and can affect other aspects of health, setting long-term risk for eating disorders (2,3). Human and animal studies indicate that early environmental influences affect the developmental establishment of energy balance systems (4). Both under- and over-nutrition during critical periods of fetal and early postnatal life can induce alterations to the physiological and structural phenotype of the offspring, with stable consequences for eating disorders (i.e., obesity).

Stress has been shown to affect food intake, inducing either increases or decreases food intake (5). During the NICU stay, preterm infants are exposed to numerous, acute and chronic stressors, including painful stimuli, disruption of sleep, excessive noise and light levels, and frequent handling associated with medical and nursing procedures (6). The physiological systems that control food intake and stress responses share the same anatomy. In particular, the hypothalamic-pituitary-adrenal axis (HPA) is important for the stress regulation and the regulation of food intake and energy expenditure (7). As part of this system, corticotropin releasing hormone is transported from the hypothalamus to the pituitary gland, stimulating the release of adrenocorticotropic hormone, which in turn leads to peripheral secretion of glucocorticoids (cortisol in humans) from the adrenal glands into the blood stream. Interestingly, belong with other effects, cortisol induces insulin resistance in the liver and in skeletal muscle. Furthermore, cortisol and insulin interact in the up-regulation of leptin concentrations (i.e., leptin resistance with possible tendency to later obesity). Finally, cortisol stimulates the food intake branch (i.e., neuropeptide Y, which has an anxiolytic effect and increase of adiposity). Interestingly, preterm infants fed with HM had lower blood pressure, LDL cholesterol, leptin resistance and insulin resistance (8–10). Thus, both early nutrition and early stress might contribute to explain the lifelong susceptibility to feeding problems in preterm infants.

WELL ESTABLISHED

Epigenetic processes are candidate mechanisms to illuminate developmental programming of nutrition and stress regulation (4,6). Epigenetics is the study of alterations in gene expression that occur without alterations of the DNA sequence. One the most known epigenetic mechanisms is the DNA methylation, which leads to an inhibition of the transcriptional activity (11). Importantly, there is evidence that eating disorders and stress are related to DNA methylation of a specific candidate gene with functional implications for the HPA axis (i.e., *SLC6A4,* that is gene encoding serotonin transporter). For example, in adults it has been documented a significant positive correlations between twin-twin differences in adiposity and DNA methylation at *SLC6A4* in peripheral blood leukocytes (12). Furthermore, a study has documented that pain-related stress in NICU is associated with methylation status at *SLC6A4* (13). These results suggest a new area of research in prematurity, that is exploring developmental and feeding behavior problems of preterm infants via epigenetics mechanisms, namely Preterm Behavioral Epigenetics (PBE) (6). In addition to the direct pathways through which early nutrition might affect risk of eating disorders, it would be interesting analyzing the interplay between early nutrition and stress in determining the epigenetic variations associated with feeding behavior problems.

NOT YET ESTABLISHED

Epigenetic research is starting to provide evidence about how early environmental factors might affect biological mechanisms and might program HPA development, including eating problems and stress regulation (4,6). However, much work is needed to convincingly demonstrate that epigenetic processes play a key role in eating problems associated with prematurity. From a general point of view, preterm epigenetics would guard against the assumption of a linear and deterministic view of adverse experience and early experience effects on human early development (14).

RECOMMENDATIONS

It will be interesting to inquire whether early environmental factors (i.e., nutrition and stress) would affect the epigenetic regulation of candidate genes of HPA axis leading to stable alterations of developmental and feeding behavior problems of preterm infants. In fact, benefits of human breast milk on preterm infants health may be at least partly associated with its nutritional components, also likely by epigenetic mechanisms (15). Although the epigenetic processes involved remain unclear, future research should be conducted to clarify the relationship between human breast milk and gene expression (16). On the other hand, as above mentioned, several studies suggest that preterm birth might increase risk for later eating disorders (1–3), but the possible mechanisms are still not known. Given that emerging research suggests that nutrition during infancy might contribute to later obesity via metabolic imprinting of epigenetic gene regulatory mechanisms (17,18), future epigenetic research might be addressed to inquire the associations between early nutrition in NICUs (e.g., human milk vs. formula) and later eating disorders.

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XII. Human Milk in Feeding Premature Infants: Consensus Statement

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HUMAN MILK AND PREMATURE INFANTS

The Panel members agree on the statements from the American Academy of Pediatrics (1) and the ESPGHAN Committee on Nutrition (2) which state that because of the potential benefits all preterm infants should receive HM. OMM should be the primary diet, and if OMM is not available or not in sufficient quantity, pasteurized donor human milk obtained from a recognized HMB should be used.

The Panel agrees with these statements and strongly supports the recommendation that all preterm infants should receive HM.

WELL ESTABLISHED ADVANTAGES OF HUMAN MILK

The advantages of HM include protection against NEC and sepsis, and its trophic effects on the gastrointestinal tract.

- The protection against NEC was supported by studies of Schanler and coworkers in 1999 (3). More recent studies demonstrated that the feeding of HM protects against NEC in dose-dependent fashion (4,5).