EBioMedicine 8 (2016) 28–29

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Low Circulating Amino Acids and Protein Quality: An Interesting Piece in the Puzzle of Early Childhood Stunting

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ARTICLE INFO

Article history:
Received 10 May 2016
Received in revised form 19 May 2016
Accepted 20 May 2016
Available online 21 May 2016

Keywords:
Protein quality
Amino acids
Stunting
Children

We commend Semba et al. (2016) for examining child stunting in the context of protein and amino acids, which, beyond supplying essential nitrogen for protein synthesis, are involved in regulation of linear growth, an issue that has not been addressed sufficiently. The authors reported significant associations between low levels of serum amino acids and stunting in a cross-sectional study of young children in rural Malawi. As the authors note, studies of micronutrient and lipid supplements have failed to demonstrate improved linear growth in malnourished children. Furthermore, the ten most effective interventions recommended for scale up at the global level are likely to reduce stunting by only ~20% even at a coverage level of 90% (Bhutta et al., 2013). Thus, we are writing to comment on the findings of Semba et al., highlight relevant past and current research and advocate for further collaborative effort forward in the area of protein quality and childhood stunting.

The results of Semba et al. raise a number of questions, including the interpretation of circulating amino acids. Plasma concentrations are static, representing the net effect of changes in production and utilization of an amino acid, unlike the dynamic flux. For example, plasma citrulline flux, which indicates enterocyte mass and function, is not reflected in its plasma concentration (Kao et al., 2016). Thus, among stunted children, are low circulating amino acids a biomarker of recent protein intake, the body's amino acid pool, acute protein deficiency, or simply a reflection of short-term physiological processes such as digestion and absorption (Cetin et al., 2015)? Or do the levels of circulating amino acids represent a response to entirely different biological processes such as presence of infection (Laurichesse et al., 1998) or a metabolic adjustment to preserve nutrients critical for maintaining lean body mass during periods of low intake of quality protein? What is clear from the novel approach used by Semba et al. is that physiological outcomes such as stunting and nutritional factors such as protein and amino acids and their metabolism and turnover are complex phenomena, and additional research will be required to answer these questions.

While the emphasis from protein shifted to energy and micronutrients in the late 1970's, as noted by Semba et al., it was by no means an end to the work on protein quality; we would be remiss not to mention the decades of seminal work conducted since then through the leadership of the late Drs. Nevin Scrimshaw and Vernon Young. This included elucidating the relationship of protein and energy interactions, redefining protein and amino acid requirements within the context of high and low energy availabilities, and investigating the health impacts from improving protein quality via increased intake of essential amino acids (EAAs)—especially lysine, the most limiting EAA in cereal based diets. Dr. Scrimshaw's seminal protein work has continued through the Nevin Scrimshaw International Nutrition Foundation, which co-organized a workshop on the topic of protein quality and growth in 2012 (Suri et al., 2013).

One reason that protein and amino acids are often overlooked in relation to stunting may be that while children in low-resource, developing country contexts appear to have adequate protein intake; however, there are two issues that may, in fact, put them at risk of inadequacy. First, failure to adjust for protein quality—a composite of the EAA profile as compared to the requirement pattern, and the "digestibility", or absorption and utilization of the amino acids in foods, both of which can decrease the effective protein available to the body—results in overestimates of dietary protein adequacy. Second, the needs of children in these contexts are systematically underestimated; current protein and amino acid requirements do not account for conditions of energy deficit, and persistent or subclinical infections, which could be compounded by sub-optimal digestive and absorptive intestinal function; emerging

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.02.030.
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http://dx.doi.org/10.1016/j.ebiom.2016.05.026

research also suggests a connection with the microbiome (Kao et al., 2016).

The link to dietary protein quality is of particular interest from a public health lens; as the authors note, "dietary intake of essential amino acids may be insufficient in children with stunting". Previous research supports this hypothesis: An analysis of dietary and anthropometric data collected on Ghanaian children aged 2–13 years, found an association between dietary protein inadequacy (adjusting for quality) and risk of being stunted (Ghosh et al., 2010). A meta-analysis of consumption of conventional versus quality protein maize (higher in lysine and tryptophan) showed significantly higher rates of weight and height gain among young children with mild to moderate undernutrition from populations in which maize is the major staple food (Gunaratna et al., 2010). Additionally, an analysis of national food balance sheet data from developing countries found an inverse association between rates of stunting and the per capita availability of "utilizable" protein (adjusted for quality) but not total protein (Ghosh et al., 2012).

Finally, the authors conclude, "randomized controlled trials would ultimately be required to determine whether essential amino acids… play a causal role in the pathogenesis of child stunting". We wholeheartedly agree with this statement and point to some interesting findings emerging from an RCT recently completed in Ghana (Ghosh et al., 2014). This trial examined the effect of adding a protein quality and micronutrient-improved complementary food supplement to the diets of Ghanaian infants from age 6 to 18 months. Results show a dose response effect of receiving the supplement on HAZ scores at 18 months of age (unpublished). Biomarkers of inflammation, micronutrient status, and plasma amino acids were collected as well. We look forward to presenting the findings of this longitudinal analyses in comparison with the cross sectional association of stunting and amino acids as observed by Semba et al.

Overall, the findings reported by Semba et al. add to evidence for the link between inadequate protein and amino acid intake and stunting in children. We expect that this important discussion on protein quality continue, in conjunction with newer research on the potential effects of the microbiome, enteric infections and chronic inflammation, in collaborative efforts to combat child stunting.

Conflicts of interest

The authors have no conflicts of interest.

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