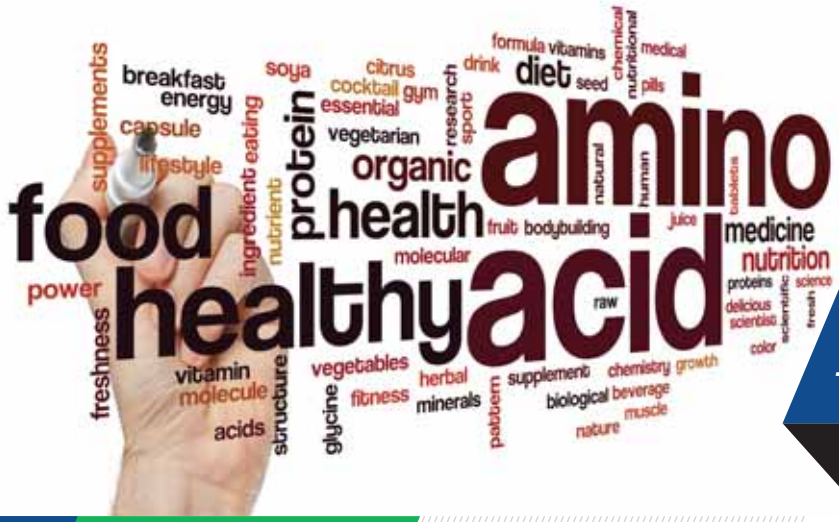


Effect of Dietary Protein on Plasma Insulin-Like Growth Factor-1, Growth, and Body Composition in Healthy Term Infants

Introduction

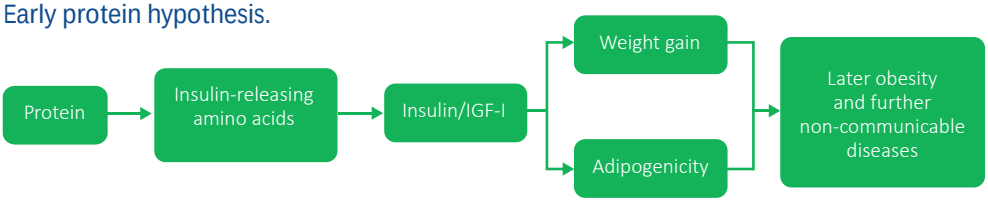
Obesity has reached epidemic proportions, and looking to prevention rather than cure is more effective in targeting this rising phenomenon. Early nutrition and weight gain have been associated with obesity well into adulthood. A high protein intake during infancy has been linked to rapid growth in infants. As growth is mediated by insulin-like growth factor-1 (IGF-1), the study of IGF-1 could hold the key for an early intervention.[1,2]

Obesity is now an epidemic worldwide Early nutrition can have a significant impact on the growth and weight gain in infants leading to being overweight or obese in adulthood. Protein intake during infancy and childhood plays a significant role in influencing obesity in later life. The effect of protein intake on rapid weight gain during infancy is mediated by the insulin-like growth factor (IGF-1), which can be an important target for intervention to tackle obesity early in its course.

The Early Protein Hypothesis

Breast milk is thought to be more protective than cow's milk-protein formulas, as the protein levels in breast milk is much lower compared to cow's milk. This increased protein intake with cow's milk can stimulate insulin-releasing amino acids, such as valine, leucine, isoleucine, and threonine, which in turn stimulate insulin and IGFs. These factors activate the growth-signalling pathway, which leads to growth and adipogenic activity.[3,4]

Early protein hypothesis.



Adapted from: Koletzko, *et al*. *Am J Clin Nutr*. 2016;103:303–304.

Association Between Weight Gain and Protein Intake

Higher energy intake during infancy could be associated with a higher body mass index in childhood.[5] A study has also suggested that high dietary protein intake after the first year of life can increase the risk of obesity and other non-communicable diseases. The study also reported that the risk is greatly increased from consumption of meat and dairy sources for protein rather than from plant sources.[4] This is primarily because milk proteins and not plant proteins are associated with the stimulation of IGF-1 axis. An increase in IGF-1 of 30% has been reported with an increase in milk intake from 200 mL/day to 600 mL/day. Furthermore, animal protein intake in 12-month-old children was associated with an increase in body fat at 7 years of age and this was mostly due to the consumption of dairy products and not meat or cereals.[3] Therefore, dairy products have been deemed to be the primary sources of protein that stimulate IGF-1, which in turn stimulates the growth pathway, thereby activating adipogenesis.[2,6]

"Cow-milk-based infant formulas have been shown to stimulate adipogenesis through the action of insulin and IGF-1, which is known as the early protein hypothesis."

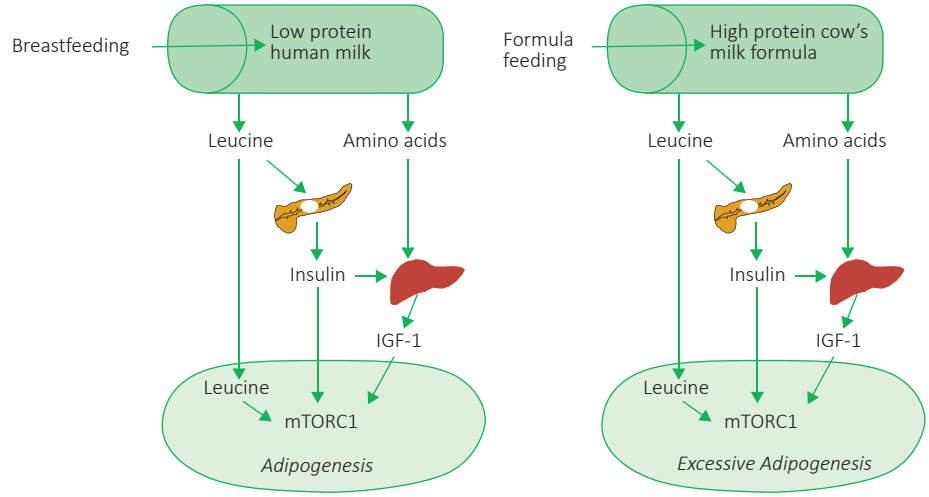
Metabolic Programming and Its Impact

Evidence suggests that rapid weight gain in the first year of life leads to a four-fold increase in risk for being overweight later in life. This is mainly attributed to the imbalance in energy intake and expenditure. Where protein intake is concerned, consuming more than the required protein energy (>15% energy) leads to such an imbalance.[6] Therefore, modulating weight gain in this time is a critical window of opportunity to prevent obesity later on.[3] Modulating such metabolic factors both pre- and postnatally can instigate a lasting effect on the overall health and disease into adulthood, otherwise termed as metabolic programming.[7]

In the early 1900s, researchers suggested that breast milk has innumerable benefits that no other food can offer. More recently, breast milk or mammalian milk has been deemed a natural way of programming against excessive adiposity in adulthood.[8] Evidence shows that infants who are breastfed have a 15% of reduced chance of developing obesity. The protective effect of breast milk is attributed to the presence of hormones and adipokines that contribute to the self-regulation of the infant's appetite. The link between the growth pathways, specifically target of rapamycin (TOR) and the early protein hypothesis, is moderated by the amount of protein intake.[9] When there is high early protein intake, the mTOR pathway is activated, an amino acid, threonine undergoes phosphorylation which in turn leads to the inhibition of Insulin Receptor Substrate (IRS-1). This process, then thereby leads to insulin resistance.[10]

The branched chain amino acid leucine present in cow's milk and cow's milk-based formula is linked to early childhood obesity. This leucine is the main amino acid that activates IGF-1 and, therefore, the growth pathways. Infants on cow's milk-based formula show higher levels of leucine than those in breast milk.[3] Furthermore, weight gain has also been associated with C-peptide excretion and plasma concentration of other branched chain amino acids such as valine, threonine and isoleucine, that are considered to be the main insulin secreting amino acids along with leucine. Amino acids, insulin, and IGF-1 converge at the same pathway to activate mTORC1, which promotes adipogenesis in adipose tissue by activating PPAR-γ. In infants who cannot be breastfed, one way to reduce the effects of these amino acids is to reduce intake of these branched chain amino acids, thereby leading to growth effects similar to breastfed infants.[9]

Metabolic mechanism of human milk mediated mTORC1 signalling and increased adipogenic activity by feeding leucine-rich infant formula.



Adapted from: Luque, *et al*.[3]

Summary

Early dietary high protein intake can increase the risk for obesity in adulthood as a result of high insulinogenic amino acids in the body. Therefore, a reduced intake of these amino acids can lead to the reduced long-term risk of non-communicable diseases such as obesity. In cases where breastfeeding is not possible, the right protein intake can influence risk for adipogenicity via metabolic programming.

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