Reply to Skoyles: Decline in growth rate, not muscle mass, predicts the human childhood peak in brain metabolism

In his letter addressing our recent paper (1), Skoyles (2) rightfully notes that growth expenditure is a small fraction of what the brain requires at the ages of slowest human body growth during childhood. We are puzzled by the suggestion that this fact challenges the premise of our interpretation, as this is precisely the observation that motivated our study. The point of our analysis was to explore one long-standing hypothesis for why body growth is so slow, and indeed thus metabolically inexpensive, during childhood.

We were also surprised to see our interpretations challenged on the grounds that expenditure on muscle and physical activity should be considered as additional factors that might be reduced to free up resources for the brain. We explicitly noted that, although our analyses support a growth–brain metabolism tradeoff, they also "...lead to the more general prediction that other costly somatic or physiological expenditures will also be reduced at this age to free up energy and substrate to support brain development". We present evidence that physical activity is likely one such attenuated expenditure, concluding that "...activity-related (discretionary) expenditure during human development is also comparatively low at ages of peak brain metabolic demand". These points are ignored by Skoyles.

Skoyles similarly does not acknowledge a fundamental conclusion that we reach: that our research "...points to strong selection on physiologic mechanisms to redirect glucose delivery to the brain" during childhood, and as such we propose that insulin resistance could shunt glucose away from muscle to the brain at this age. This idea is similar in principle to Skoyles' suggestion regarding the role of muscle metabolism as a cause of hypoglycemia, but this again is ignored.

Skoyles proposes that the function of slow childhood growth is to reduce muscle–brain metabolic competition by reducing muscle mass. We assert that changes in muscle mass do not provide a viable alternative explanation for how the body fuels the brain during ages of peak brain metabolism. Whether measured in absolute or relative terms, brain metabolism peaks in childhood (~4–5 y) before declining to adult levels. Because muscle mass increases throughout development (i.e., there is no developmental stage of muscle atrophy), changes in peripheral glucose demand secondary to changes in muscle mass cannot contribute to the childhood peak in brain glucose demand; clearly, muscle mass continues to increase even at ages of maximal brain metabolism. In contrast, we show that body growth declines to its slowest rate at ages of peak brain metabolism, and that there is a tight inverse linear relationship between brain metabolism and body growth rate from infancy until puberty. Although muscle mass does not decline in childhood, muscle growth rate follows a similar trajectory as body growth, being lowest when brain metabolism is highest (3, 4).

In sum, we do not see any substantive challenge to our analyses or interpretations in Skoyles' argument. He repeats several points that are very similar to those we raised and his central hypothesis invoking muscle mass is not a tenable explanation for the observations we report.

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2 Skoyles JR (2014) Skeletal muscle-induced hypoglycemia risk, not life history energy trade-off, links high child brain glucose use to slow body growth. *Proc Natl Acad Sci USA*, 10.1073/pnas.1417468111.
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The authors declare no conflict of interest.

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