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PERSPECTIVES

Targeting redox balance to deprogramme obesity: are we starting early enough?

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Obesity and its associated diseases may prove to be the greatest crisis to human health all over the world this century. While the problem is recognized, successful interventions to control the rise in obesity have not been established. Early-life exposure to adverse environments can lead to a variety of adult diseases by a process referred to as 'developmental origins of health and disease (DOHaD)' (Silveira *et al.* 2007). Numerous recent studies have emphasized the importance of pre-, peri- and postnatal insults as a critical influence on the development of obesity-related diseases in adult offspring (Dabelea & Harrod 2013; Bouret *et al.* 2015). Studies using animal models showed that early overfeeding and postnatal catch-up growth play a crucial role in programming of offspring obesity. In this issue of *The Journal of Physiology*, Conceição and colleagues (2015) provided some interesting insight into the potential role of early redox imbalance contributing to postnatal overfeeding-induced liver dysfunctions and adipocyte hypertrophy – common features associated with obesity.

The experimental model of postnatal overfeeding was carried out by litter-size reduction. Raising pups in small litters reduces competition for milk during the lactation period and therefore leads to over-nourishment. Rodents raised in small litters are overweight at weaning and maintain their body weight gain throughout life. Unlike the usual models of diet- or genetic-induced obesity, this model could be used to study the consequences of long-term moderate excess weight and underlying mechanisms in the pre-obese stage. A number of earlier studies demonstrated that postnatal overfeeding by litter-size reduction can programme the hypothalamic system, increase central leptin and insulin resistance, induce corticosterone secretion, elicit cardiovascular and renal dysfunction, and induce oxidative stress in adulthood (for review see Habbout *et al.* 2013). However, little attention has been paid to examining each of the above mechanisms in different developmental windows, especially in early life.

Given that dysregulated genes and pathways in response to overfeeding insults identified in later life could be the consequences of developmental programming, analysing mechanisms in earlier developmental windows may aid in identifying primary programmed changes. In the studies performed by Conceição *et al.* (2015), postnatal overfeeding is able to increase fat accumulation, induce oxidative stress in the liver and adipocytes, and reduce adrenergic sensitivity in visceral adipose tissue in 3-week-old male offspring. Conceição *et al.* (2015) have added an important contribution to our understanding of the development of obesity-related diseases by demonstrating that postnatal overfeeding-induced redox imbalance can appear in early childhood. Oxidative stress-mediated programming may act directly through epigenetic regulation of gene expression or indirectly via the effects of certain free radical signals. The timeframe of vulnerability to oxidative stress damage may differ between organs. Therefore, the following questions arise: (1) Does oxidative stress alone lead to programming of obesity and, if it does, when do the changes occur? (2) Which free radical signal triggers a lifelong alteration in the redox state, with which redox-sensitive signalling(s) leading to programming of obesity-related diseases? (3) Are these redox-related changes caused by overfeeding reversible and organ-specific or not? Further studies are needed to establish the particular developmental window (e.g. *in utero* or at the pre-weaning stage) and organ-specific redox-sensitive signalling responsible for these redox changes. In addition, obesity is a multifactorial disorder, which can originate at the fetal stage of life. In addition to postnatal overfeeding, other maternal and perinatal insults may have additive effects on developmental programming of obesity. On the other hand, postnatal overfeeding may either mask or augment the true effects of fetal programming induced by other insults. It remains to be determined whether early redox imbalance is the major cause in the programming of offspring obesity in response to a diverse range of pre-, peri-, and postnatal insults.

The recent study by Conceição *et al.* (2015) and previous studies indicate that excess weight and obesity is associated with an increase in oxidative stress. At face value, it would be logical to consider antioxidant supplementation in potential therapies for obesity-related diseases. Targeting radical signalling and the antioxidant defense system offers several strategies to eliminate reactive oxygen and nitrogen species and maintain redox homeostasis in the management of obesity-related diseases. However, so far, antioxidant therapy is not proving to be a panacea to control the global rise of obesity. At a deeper level, there remains a lack of data on how and when to deprogramme obesity-related diseases. There remains a long road ahead to determine the 'right' antioxidant for the 'right' person at the 'right' time, to prevent the programming of obesity.

Taken together, increasing evidence, including the current study by Conceição *et al.* (2015), demonstrates that early-life redox imbalance may lead to permanent alterations of function and structure in later life in specific organs that are vulnerable to developing obesity phenotypes. A better understanding of the mechanisms underlying the role of redox imbalance in the early life programming of obesity is essential to developing early intervention to halt the globally growing epidemic of obesity-related diseases.

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Additional information

Competing interests

None declared.