

## Invited Commentary

### Hormonal programming in perinatal life: leptin and beyond

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Central nervous system leptin resistance as a possible cause of obesity and associated diseases is a 'hot topic' in nutrition research. Simultaneously, a new field in biomedical sciences has evolved during the past years. 'Perinatal programming' addresses the phenomenon of early (hormonal, nutritional, metabolic etc.) priming of fundamental life functions during critical periods of pre- and neonatal development, potentially causing lasting malfunctions in the case of altered early conditions. The current wide recognition of this field was mainly 'triggered' during recent years by the 'Barker hypothesis' on a 'small-baby syndrome'<sup>(1)</sup>. However, by looking into the literature one has to realize that this concept has scientific roots that go back at least to the 1970s. In fact, more than 30 years ago the German endocrinologist Günter Dörner introduced the term 'perinatal programming' and the concept of hormone-dependent 'functional teratogenesis' of neuro-endocrine networks<sup>(2,3)</sup>. According to Dörner, hormones play a crucial role in the developmental determination of the functional ranges (which actually is a better term for what often is named 'set point') of neuro-endocrine systems regulating key functions of the organism like, e.g., food intake, stress response and reproduction. If hormones occur in non-physiological concentrations during critical periods of development, the functional range of the respective system becomes permanently changed. This malprogramming of regulatory systems may have long-term consequences: permanently changed responses to key signals like those mediating satiety can increase the susceptibility to develop diseases in later life like, for example, obesity, diabetes and accompanying CVD. Other investigators have developed similar concepts named, for example, 'fuel-mediated teratogenesis'<sup>(4)</sup> or 'nutritional programming'<sup>(5)</sup>. However, credit is due to Dörner for having introduced a general cybernetic concept which highlights the key position of hormones with regard to the self-organization of regulatory systems of the organism, like those regulating food intake, body weight and metabolism.

In this issue of the *British Journal of Nutrition*, Passos *et al.* provide an interesting contribution to the ongoing research on hormonal programming<sup>(6)</sup>. They show that exogenous induction of hyperleptinaemia during the first 10 d of life in rats leads to leptin resistance at adult age. Leptin resistance was functionally verified by the absence of a decrease in food

intake in response to leptin injection as well as by a decreased expression of the hypothalamic leptin receptor and an increased expression of SOCS-3, a mediator of leptin resistance, in neonatally leptin-treated rats. This is the second publication from that group indicating that increased levels of leptin during neonatal life may programme leptin resistance, with adverse consequences for the regulation of body weight and metabolism<sup>(6,7)</sup>. More generally, Passos *et al.* extend previous work by our group showing paradigmatically that hormonal programming does not exclusively apply to steroid hormones, but can be extended to proteohormones. In fact, while the impact of altered levels of sex steroids or glucocorticoids, which are, for example, induced by stress exposure during early development, can be considered to be an established mechanism of hormonal programming<sup>(2,3,8,9)</sup>, a comparable role of peptides, proteohormones and cytokines was rarely investigated, nor even considered for a long time. First results pointing in that direction came from experiments which investigated the long-term consequences of increased levels of insulin during perinatal life for later adipogenic and metabolic risk. These early data indicated that perinatal hyperinsulinism, as it typically occurs in the offspring of mothers with diabetes during pregnancy, leads to malprogramming of hypothalamic circuits regulating food intake, body weight and metabolism<sup>(10–12)</sup>. Consequences of exposure to perinatal hyperinsulinism as well as hyperleptinism were investigated, for example in rats which were raised in 'small litters', a well-established model of neonatal overnutrition. Hyperleptinaemia within the first days of life was followed by persisting overweight, hyperphagia, diabetogenic and cardiovascular disturbances throughout later life<sup>(13)</sup>. This was associated with hypothalamic neuronal alterations indicating neonatally acquired leptin resistance, persisting into adult age and leading to a persisting adipogenic and diabetogenic phenotype<sup>(13–16)</sup>. Further data obtained in this model impressively confirmed these findings<sup>(17,18)</sup>, in line with the observations by Passos and co-workers<sup>(6,7)</sup>.

However, at first view all of this seems to contrast observations published by Vickers *et al.*<sup>(19)</sup>. Here, neonatal leptin treatment was shown to protect neonatally growth-restricted offspring of rat dams undernourished during gestation from developing overweight during later life. Similarly, in mice

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carrying a strong genetic predisposition to obesity due to the absence of leptin (*ob/ob*), Bouret *et al.* observed that neonatal leptin injections reduced the development of the typical obese phenotype<sup>(20)</sup>. Interestingly enough, however, only recently Vickers *et al.* observed essentially the opposite of their previous findings when investigating offspring of normally nourished dams<sup>(21)</sup>, in accordance with former observations<sup>(13–18)</sup>.

Moreover, against the background of epidemiological and clinical observations, all of this indicates that both unphysiologically high as well as low levels of leptin during perinatal life may have essentially similar consequences for long-term adipogenic and metabolic risk. This is phenomenologically supported by epidemiological data indicating a u-shaped relation between birth weight and subsequent metabolic risk<sup>(22)</sup>, rather than the widely suggested and recognized inverse relation. It can therefore be postulated that leptin substitution in leptin-deficient states during early development may be beneficial for later outcome while hyperleptinaemia during critical periods seems to have long-term adverse consequences.

Studies like those by Passos and co-workers<sup>(6,7)</sup> are important because they may bridge between apparently contradictory observations and phenomena, helping to integrate empirical, epidemiological and experimental data, and, most of all, uncover concrete pathophysiological factors leading to early malprogramming of the regulation of body weight and metabolism. Understanding the causes of obesity epidemics will critically depend on studies evaluating its developmental origins and, thereby, revealing a basis for primary prevention.

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