Is programming of weight regulation ‘immune’ to neonatal inflammation?

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Editorial Focus

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Obesity is emerging as a global problem of epidemic proportion that is predicted for example to affect 41% of adults in the United States by 2015 (36). The dramatic increase in the number of obese individuals has a direct and serious economic impact stemming directly from the multitude of health problems associated with this condition. These are wide ranging and include cardiovascular disease, metabolic disorders and certain forms of cancer (9, 21, 25). While genetic and environmental risk factors and their interaction are known to contribute to the current high prevalence of obesity their respective and specific contribution is subject to a broad number of investigations. Among these factors, adverse environmental effects during early development have been shown to trigger a physiological state or behavioral response that is conserved to adulthood [for review see (18)]. The environmental factors can be divided into pre- and postnatal insults ranging from nutritional status to maternal care, exposure to toxins/allergens or infection and inflammation.

In this issue of the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* the manuscript by Spencer et al. (31) extends a variety of earlier reports from the same group examining the effects of postnatal stress following bacterial immune challenge using Lipopolysaccharide (LPS) in neonates on long-term physiological consequences including neuroimmune responses, pain, cerebral ischaemia, and behavioral changes (6, 7, 10, 11, 26-30). Using their considerable expertise in this area of research these workers addressed whether a similar ‘programming’ effect exists in response to an immune challenge during development, that will have long lasting repercussions on the regulation of body weight at the adult stage.
The results of this study essentially show that in rats, body weight regulation is not susceptible to neonatal programming following LPS-stimulation with neither body weight nor body composition found to be altered in the adult rats. Part of the aim of the study was also to monitor the changes in the levels of immune mediators induced by the inflammatory challenge. Previous reports have implicated long-term changes in the levels of pro-inflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-1β the changes in the concentration of which was associated with alterations of various physiological parameters following LPS treatment of neonates (4, 10, 29). It was however another mediator, leptin, that was investigated in the present study. This hormone is known primarily for its control of food intake but more importantly in the context of the present manuscript, in the development of the hypothalamic circuitry responsible for appetite regulation in young animals (8). This makes it an obvious target for examination in studies assessing long-term changes in the mechanisms regulating appetite. Spencer et al., have also taken into consideration the recently described role of this adipose derived hormone in inflammation, thus making it a prime candidate for regulating and potential programming of body weight resulting from a neonatal inflammatory challenge. A great deal of the evidence linking leptin with LPS induced inflammation are the observations that it is upregulated in the circulation of LPS treated animals (3, 12, 14, 24). This in addition to earlier evidence from our own laboratory (16) showing that as well as suppressing appetite, leptin can also induce fever in rats, suggested strongly that this hormone could in fact be acting as an immune mediator in the same mode as other pro-inflammatory cytokines. In the study of Spencer et al measurements of leptin levels of all the animals in the different treatment, age and
gender groups showed no increase in the levels of this hormone after LPS injection. This the authors found surprising, given the reported changes in the literature but offer the explanation that this may have been due to procedural differences including doses of LPS (100µg/kg) used or the time (2.5h) the samples were collected. These parameters differ significantly from some of the studies reporting an LPS induced increase in the levels of circulating leptin and that may indeed explain the observations, or lack of them, in the Spencer study. As the authors point out however, the dose of LPS used in their study is one that they have used previously and repeatedly to induce long-term alterations in adult physiological, behavioral and endocrine responses (6, 7, 10, 11, 26-30). Thus one would have expected a difference in the levels of this hormone if indeed it was physiologically relevant to the long-term changes reported previously. The largely unchanged levels of circulating leptin (a significant reduction was observed in some of the female cohorts) might however reflect the negative outcome of the study in that no evidence of long term changes in body weight were observed. What is somewhat troubling about the lack of effect of LPS on leptin levels if one were to argue for the involvement of this hormone in mediating at least part of the inflammatory response induced, is the contradictory data in the literature. One of the first criteria that a circulating mediator has to fulfill to be designated a mediator of inflammation is that its circulating levels have to reflect at least part of the physiological or behavioral changes associated with infection. We have recently reported that leptin is involved in mediating LPS induced fever and the anorexia of inflammation induced by a single injection of LPS [100µg/kg; Nb: the same dose used in the Spencer study; (23)]. In these experiments we targeted the contribution of endogenous leptin by the systemic co-administration of a neutralizing antiserum with the
LPS. This provided us with strong and convincing evidence that the appetite suppression and fever induced by the administration of leptin reflect a physiological modulatory role in inflammation. Our subsequent studies (C. Rummel, unpublished) and earlier observations from others (13) however failed to show a change in the levels of the circulating hormone that would significantly correlate with the physiological LPS induced changes such as fever or anorexia. Indeed in a time course study lasting for 24h we only observed a moderate increase 8h following a single injection of LPS at 100µg/kg which did not reflect the changes in body temperature observed. It is important to note here that most of the studies showing an effect of LPS on circulating plasma leptin levels were conducted in food restricted rodents (3, 12, 14, 24). Given these observations and the fact that the antiserum studies clearly indicate that leptin is involved in mediating some aspects of LPS induced inflammation, we are currently pursuing the hypothesis that it may be acting at the level of adipose tissue by modulating the release of other pro-inflammatory, fat derived cytokines (32).

Other than mechanistic considerations it is clear that the complexity and variety of environmental factors involved can significantly influence the outcome of studies of this type. These pertain mostly to very basic issues such as gender, maternal care and housing environment. Maternal behavior for example has been shown to potentially ameliorate social-developmental effects of early illness (15). Other factors such as neonatal handling (5) or social isolation/maternal separation (2, 33), depending on the animal species, will have profound effects on neuro-inflammatory processes in adulthood. These and other variables may partly explain the different outcomes from similar studies including those from the same authors of the current manuscript which reported either, decreased (29, 30,
35) or no change in body weight (31, 34) of adult animals after postnatal LPS-stimulation. Prenatal exposure to LPS, however, has been shown in several studies to consistently lead to increased body weight in adulthood (20, 37). It would seem therefore that pre and post-natal stressors can affect the development of regulatory mechanisms in different ways. The significance of the time of administration of the inflammatory/infectious stimulus was recently elegantly demonstrated by Meyer and colleagues who showed that changes in adult brain pathology depended on the time point of the immune challenge during gestation (19). This further emphasizes the importance of the time window of exposure to pathogens and in choosing to investigate a wide range of developmental time points (P3, P7, and P14) the authors ensured that this issue is well addressed. From a human health prospective this however raises the issue of the different developmental stages between the two species. Rat CNS is developmentally less mature than human, and depending on the criteria used, rat brain from postnatal days 7-13 is estimated to be developmentally equivalent to newborn human brains (1, 22). This would mean that some of the time points chosen in this study might actually be reflecting prenatal stages in humans. This is an important point, which might help narrow down the time window for susceptibility to early life stressors in humans especially since the appetite regulating neuropeptide system circuitry is fully developed prenatally (18) compared to rodents where it develops predominantly after birth (17).

It is clear from the study of Spencer et al therefore that the programming of body weight regulation, as opposed to other LPS induced sickness-type behaviors, is particularly dependent on the time window of exposure. This as the authors suggest is
most likely a reflection of the role of leptin, which might not have been actively regulating energy balance at the time of the brief challenge and therefore not influenced long term. The implications of this study for humans is that a very narrow window and most likely prolonged exposure to infection during development is required to influence body weight regulatory mechanisms.

References


