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Previews

Does Hypothalamic Inflammation Cause Obesity?

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Obesity-induced inflammation causes cellular resistance to both insulin and leptin. In this issue, Brüning and colleagues (Kleinridders et al., 2009) add to growing evidence that this response occurs in the hypothalamus, as well as in peripheral tissues, which helps to explain how high-fat feeding induces a gradual increase in defended body weight.

Prior to the discovery of the adipocyte hormone leptin, obesity was thought to result more from a lack of will power than from an underlying biological disorder. Now, 15 years after leptin's discovery, a much different picture of how obesity occurs is beginning to emerge. At its heart is evidence that consuming a high-fat (HF) diet induces inflammation in key neuronal systems that govern energy homeostasis, an effect that increases the defended level of body weight. The paper by Brüning and colleagues in the current issue of *Cell Metabolism* (Kleinridders et al., 2009) advances the field by demonstrating that, in mice, the ability of a HF diet to induce obesity and its associated metabolic derangements depends upon neuronal expression of MyD88, a key intracellular mediator of inflammatory signaling.

The link between HF feeding, hypothalamic inflammation, and the control of body weight has its roots in the study of how insulin resistance develops when tissues are exposed to a supply of nutrients that exceeds their energy requirements. In muscle, liver, adipose tissue, and the vasculature, sustained exposure to nutrient excess induces cellular inflammation via multiple, convergent mechanisms (Hotamisligil, 2006; Kim et al., 2007). In addition to the recruitment and activation of immune cells in adipose tissue of obese individuals, nutrient excess can also induce inflammation via cell-autonomous mechanisms (Hotamisligil, 2006). For example, exposure of many cell types (e.g., adipocytes, macrophages, and endothelial cells) to saturated fatty acids such as palmitate increases signaling via toll-like receptor 4 (TLR4), thereby activating the proinflammatory IKKβ-NFκB transcriptional pathway (Kim et al., 2007). Nutrient excess can also trigger cellular inflammation by raising intracellular levels of reactive oxygen species, by causing endoplasmic reticulum stress, and through still other mechanisms. This inflammatory response, in turn, causes insulin resistance via inhibition of the IRS-PI3K signal transduction pathway downstream of the insulin receptor (a key mediator of insulin's metabolic effects) and by induction of suppressor of cytokine-3 signaling (SOCS3), which blocks insulin receptor signaling (Hotamisligil, 2006; Kim et al., 2007). Importantly, these inflammation-induced responses block signaling by leptin as well as by insulin.

Given the diversity of tissues affected by nutrient excess, it is perhaps unsurprising that the hypothalamus is also susceptible (De Souza et al., 2005). Unlike inflammation in peripheral tissues, however, this hypothalamic response has the potential to cause obesity, rather than simply being its consequence. This is because leptin and insulin are crucial signals that convey "adiposity negative feedback" information to the hypothalamus regarding the amount of body fuel stored in the form of fat. When input from these hormones is reduced, therefore, the hypothalamus perceives this as evidence of reduced body fat and triggers an adaptive increase of food intake relative to energy expenditure that favors weight gain. Indeed, the same phenomenon helps to explain why it is so hard to keep off weight lost through calorically restricted diets. Accordingly, when inflammation-induced impairment of insulin and leptin signal transduction occurs in key hypothalamic neurons, this elicits a state of positive energy balance until body fat stores, along with plasma leptin and insulin concentrations, rise sufficiently to overcome the resistance. This picture—increased plasma insulin and leptin levels, combined with the defense of an elevated level of body weight—is characteristic of common obesity.

The concept that common forms of obesity might arise from hypothalamic leptin resistance is not new, having first been reported in rodent models of diet-induced obesity (DIO) nearly a decade ago (El-Haschimi et al., 2000). But broad acceptance of acquired leptin resistance as a cause of common obesity has been hampered both by a lack of insight into how it occurs and by uncertainty about whether it is simply a consequence of obesity and not a cause. By offering an answer to the first question, the emerging role of hypothalamic inflammation is beginning to clarify the second (Wisse et al., 2007).

Last year, Cai and colleagues (Zhang et al., 2008) reported that mice with neuron-specific deletion of IKKβ are resistant to the effect of high-fat (HF) feeding to cause both obesity and central insulin and leptin resistance, whereas interventions that predispose to neuronal inflammation favor excess weight gain. Similarly, Niswender and colleagues (Posey et al., 2008) showed that central administration of an IKKβ inhibitor increases hypothalamic insulin sensitivity while reducing food intake and body weight in rats on a HF diet; in rats fed standard chow (that do not have hypothalamic inflammation), this intervention was without effect. These findings imply a role for leptin and insulin resistance induced by hypothalamic inflammation in the mechanism whereby HF feeding causes obesity.

The paper by Brüning and colleagues (Kleinridders, et al., 2009) extends this work by demonstrating that brain-specific deletion of MyD88, an adaptor protein that couples TLR4 and IL-1 receptor

signaling to IKKβ activation, attenuates the deleterious cascade of events initiated by HF: hypothalamic inflammation, leptin resistance, obesity, and peripheral metabolic dysfunction. Increased leptin sensitivity in mice with brain-specific MyD88 deletion was detected early in the course of HF feeding, prior to any difference in body weight from control animals. By suggesting that diminished hypothalamic inflammation and leptin resistance protects against obesity rather than that protection from obesity reduces hypothalamic inflammation and leptin resistance, this observation addresses what has been a troubling chicken-and-egg problem. Moreover, the authors report that mice with brain-specific MyD88 deletion are protected from hypothalamic inflammation and leptin resistance induced by acute central application of palmitate, as well as from impairment of peripheral glucose metabolism induced by either centrally administered palmitate or by consuming a HF diet. Furthermore, they show that, although HF feeding in normal mice induces hypothalamic inflammation via the JNK as well as the IKKβ-NFκB pathway, only the latter seems to be required for the associated hypothalamic leptin resistance and weight gain (because mice with brain-specific JNK knockout are not protected against these responses).

Many compelling questions remain to be addressed. Which hypothalamic cell type triggers inflammation in response to HF feeding? In addition to neurons, microglia (the resident macrophage of the brain) can also induce inflammation, and macrophages in peripheral tissues clearly contribute to obesity-associated inflammatory responses. Because microglia dynamically survey adjacent neurons for evidence of inflammation and can act rapidly to suppress this response, however, the question of whether they might increase or decrease neuronal inflammation during HF feeding awaits further study (see Figure 1). Do genetic factors that affect obesity susceptibility act by modifying hypothalamic inflammation? Does exercise training blunt the effect of HF feeding to induce inflammation in hypothalamus (and thereby favor defense of a lower body weight), as it does in peripheral tissues? Is diet composition critical, or is an excess of nutrients, per se, sufficient to trigger these responses irrespectively of what is eaten? Lastly, hypothalamic inflammation is also implicated in anorexia and weight loss induced by acute, systemic illness (e.g., bacterial sepsis). How can brain inflammation induce negative energy balance in some conditions while predisposing to obesity in others? Answers to these questions may help to inform new approaches to the prevention and treatment of obesity.

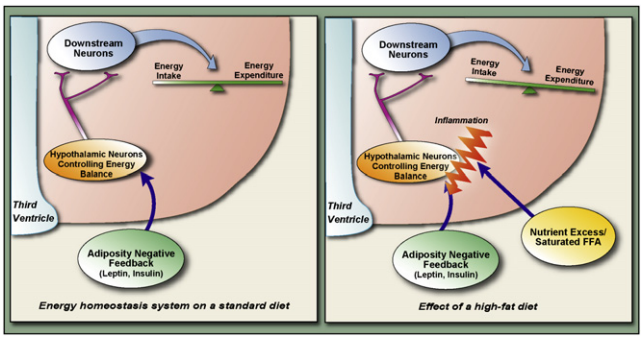

Figure 1. Effect of High-Fat Feeding on the Control of Energy Balance
Energy homeostasis is achieved by hypothalamic sensing and integration of afferent negative feedback from hormones such as insulin and leptin, which circulate at levels proportionate to body fat stores and act in the brain to limit weight gain (left). During high-fat feeding, neuronal inflammation causes resistance to these hormones, thereby favoring weight gain (right).

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