**The brain needs interleukin-6 (IL-6) to maintain a “healthy” energy balance. Focus on “IL-6 ameliorates defective leptin sensitivity in DIO ventromedial hypothalamic nucleus neurons”**

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Larsen and colleagues’ (13) recent paper provides an important piece of evidence that leptin sensitivity is under dynamic control and that interleukin-6 (IL-6) is an important player in this control system. IL-6 may increase leptin sensitivity in the ventromedial hypothalamic nucleus (VMN) at least in part by modifying leptin receptor transport to the cell membrane in VMN neurons. This will help restore normal leptin sensitivity in diet-induced obese (DIO) rats. Leptin receptor trafficking to the cell membrane is facilitated by Bardet-Biedl Syndrome protein 6 [BBS6 (9)], and this effect seems to be enhanced by IL-6. The latter aspect is particularly interesting because mutations of the BBS6 protein are associated with obesity in humans and in pertinent animal models (7). Overall, Larsen and colleagues’ data indicate that leptin resistance in DIO can be reversed by IL-6.

Interleukins such as IL-6 have beneficial metabolic effects, but this contrasts with a large body of literature implicating proinflammatory cytokines in detrimental effects seen in rodents exposed to “unhealthy” high-fat diets (HFD) or being obese (21, 22). Hence, it is important to point out critical differences between these two distinct states. Hypothalamic inflammation in obesity is usually associated with an increased expression or concentration of cytokines, and it is usually thought that this contributes to leptin and insulin resistance in obesity. HFD-induced effects occur rapidly on exposure to the HFD and may therefore be a cause, and not only a consequence, of obesity (21, 22). The HFD-induced neural injury is usually associated with an increase in a number of cytokines, e.g., IL-1β, IL-6, but also many others (22). Markers of gliosis, which include the activation, recruitment, and proliferation of microglia and astrocytes, are increased early in HFD-fed rodents, and obesity in humans and rodents is associated with increased gliosis in the hypothalamic arcuate nucleus (ARC). The activation of astrocytes and microglia was reversible when the HFD was removed, at least in rodents (1).

These reports are only few examples among many others implicating increased hypothalamic cytokine expression in the causes and consequences of obesity. The important point is that in these studies, it is usually a combination of an elevation of many cytokines, i.e., not an effect restricted to one cytokine only. In other words, while the intake of a HFD causes an inflammatory response in association with increased expression of IL-6 in the hypothalamus, this IL-6 rise is accompanied by increases in the expression of several other proinflammatory cytokines. This “cocktail” of cytokines cannot be compared with the selective effect of IL-6 alone, as described and investigated by Larsen and her colleagues (13). IL-6 alone seems to have an antiobesity effect during health.

Larsen and colleagues’ findings complement other work indicating beneficial metabolic effects of IL-6. For example, IL-6 knockout (IL-6−/−) mice have more serious dysregulations of lipid metabolism than wild-type controls after exposure to HFD (27). The most extensive data set has been published by Jansson and colleagues who were the first to show that IL-6−/− mice develop mature-onset obesity that appeared to be due to a decreased responsiveness to leptin. Furthermore, they provided evidence that this effect is due to a central action of IL-6 (10, 24–26). The findings reported in rodents also seem to have translational value because central IL-6 levels are negatively correlated with fat mass in humans (20).

The findings reported by Larsen and colleagues complement prior work by the same group. Le Foll and coauthors (14) recently provided a potential explanation for how IL-6 may be involved in mediating the interaction between leptin and the pancreatic satiating hormone amylin. This interaction and the synergistic effect of leptin and amylin on lowering of body weight and eating had been described before (18, 23), but Le Foll and colleagues added an important perspective to explain the underlying mechanisms. They showed that amylin, acting in the ventromedial hypothalamus (VMH), which includes the ARC and the VMN, to produce a selective increase of IL-6 but not of other cytokines. IL-6 then seems to act on VMH neurons to improve leptin signaling in the rat and mouse hypothalamus; hence, IL-6 sensitized VMH neurons to the action of leptin. The recent data by Larsen and colleagues suggest that this effect may include an increased transport of functional leptin receptors to the cell membrane, as mediated by BBS6 (13).

Both amylin and leptin also contribute to the development of brain structures that are critically involved in the control of energy metabolism and in particular in the mediation of leptin action in the hypothalamus. Some of these structures are disrupted in DIO animals and in animals with insufficient leptin action (2, 4). Interestingly, and similar to leptin (3), amylin also seems to participate in the early brain development of hypothalamic pathways from the ARC to the hypothalamic paraventricular nucleus (PVN); amylin enhanced pathway development including Agouti-related protein (AgRP), and α-melanocyte stimulating hormone (α-MSH) positive neurons of the ARC, but only the AgRP pathway was IL-6 dependent (11).

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One important aspect with respect to the role of IL-6 in the control of energy metabolism (or in sensitizing the brain to the effect of the pertinent signals) is that IL-6 may also have a transgenerational effect (12). Adult IL-6−/− mice were heavier and had more adipose tissue than control mice, but the effect was more pronounced when the knockout mice were derived from a IL-6−/− dam rather than a hemizygous IL-6−/+ dam. Hence, lack of maternal IL-6 promotes adiposity also in their offspring during adulthood (12). Based on Larsen and colleagues’ findings (13), one may ask whether the latter could be due to an insufficient maturation of leptin-responsive pathways in these animals. The results from Larsen and colleagues would clearly be consistent with such an idea.

Amylin and leptin are not the only hormones whose action on energy metabolism may be mediated by the action of IL-6. A recent study indicated that hypothalamic IL-6 signaling may also be involved in mediating the eating inhibitory action of glucagon-like peptide-1 (GLP-1) and its analogues, perhaps together with IL-1β (19). Whether these effects also depend on an interaction with leptin has not been formally studied. The interaction between GLP-1 and IL-6 seems to be complex because IL-6 has also been reported to increase insulin secretion indirectly by stimulating the release of peripheral GLP-1 from intestinal L-cells (6).

Overall, the available literature suggests that IL-6 alone may have beneficial metabolic effects, in particular, as a direct mediator of enhanced leptin sensitivity in the ventromedial hypothalamus and as a mediator of the amylin-induced increase in hypothalamic leptin sensitivity. Larsen and colleagues’ recent paper lays the ground for future studies that should, e.g., address the following points:

1) What are the physiological stimuli that increase IL-6 expression and release in the hypothalamus? It is known that physical exercise increases IL-6, and this may contribute to its anti-inflammatory effects (16), but further in-depth studies are warranted. How does exercise interact with other metabolic signals, e.g., with insulin? Is IL-6 the key mediator of improved whole body insulin sensitivity after exercise (12, 17)?

2) Is microglia the main source of IL-6 for its effects on brain energy metabolism? Are there other stimuli that increase IL-6 release from microglia, such as amylin?

3) Do we need to consider sex-specific differences in IL-6 action? It is well documented that premenopausal women are protected from many metabolic consequences of inflammation and obesity-related diseases, and it has also been shown that PGC-1α, which is an important transcription factor in multiple metabolic pathways, plays a role in this respect, in association with estrogen receptor signaling. PGC-1α is under the control of leptin because it is reduced in ob/ob mice or after HFD feeding (15). The study by Larsen and colleagues only used male animals so it is not clear whether PGC-1α would interact in some way with IL-6 in a sex-dependent manner, similar to Morselli’s observations (15).

4) Finally, can Larsen and colleagues’ findings be exploited pharmacologically, i.e., can the manipulation of the IL-6 system be used to improve leptin sensitivity? If so, any approach may require a strong site specificity because reports about antagonistic actions of leptin and IL-6 can be found in the literature. One example is with respect to colonic function (5), where IL-6 seems to have negative effects in irritable bowel disease, which can be partly counteracted by leptin. Furthermore, the role of IL-6 with respect to liver metabolism may be beneficial or negative, depending on the exact conditions, concentrations, and duration of exposure. IL-6 administration to HFD-fed mice, for example, seems to reduce leptin receptor activity in the liver (8). Hence, while IL-6 seems to affect leptin in a beneficial manner in the brain, the opposite may be true in other tissues.

The major contribution and major novelty of Larsen and colleagues’ recent study is that the leptin resistance in DIO rats may effectively be counteracted by IL-6, which restores the animals’ leptin sensitivity, that the effect of IL-6 may be selective for a subset of ARC neurons, and, most intriguingly, that at least part of IL-6’s effect may be due to an upregulation of the expression of BBS6. BBS6 may promote the translocation of functional leptin receptors to the neurons’ cell membrane. Hence, Larsen and colleagues’ paper may also provide one potential explanation for the frequent occurrence of obesity in BBS6 patients.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


