COMMENTARY ON: **FUNCTIONAL INTERLEUKIN-6 RECEPTOR-A IS LOCATED TO TANYCYTES AT THE BASE OF THE THIRD VENTRICLE. FREDERIK ANESTEN, CRISTIANO SANTOS, EDWIN GIDESTRAND, ERIK SCHÉLE, VILBORG PÁLSDÓTTIR, TEODOR SWEDUNG-WETTERVIK, BJÖRN MEISTER, KAROLINA PATRYCJA SKIBICKA, AND JOHN-OLOV JANSSON. *J NEUROENDOCRINOL* 2017;DOI: 10.1111/JNE.12546.**

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In the recent issue of Journal of Neuroendocrinology, Anesten and co-authors examined the role of interleukin 6 (IL-6) in the regulation of energy metabolism and body fat mass, and the possible involvement of tanycytes in this process (1). Tanycytes are specialized hypothalamic glia-like cells, with cell bodies forming the ventricular floor of circumventricular organs and processes extending into the brain parenchyma and contacting the fenestrated vasculature of the blood brain barrier-lacking areas, thereby coming into direct contact with the peripheral circulation (2, 3). Recent studies suggested that tanycytes located in the median eminence (ME) and the adjacent arcuate nucleus (ARC) are implicated in the regulation of energy balance and feeding behavior (4, 5). Specifically, tanycytes were shown to be involved in glucosensing (6) and serve as the gatekeepers to control the access of leptin and other metabolic signals into the central nervous system (7, 8). Likewise, changes in tanycyte functions were shown to be associated with diet-induced obesity (7).

Over the last years, accumulating evidence indicates that diet-induced obesity is associated with chronic hypothalamic microinflammation (9). Obesity-induced neuroinflammation in areas related to energy homeostasis and metabolism (e.g. ARC) contributes to central insulin and leptin resistance (10, 11). The inflammatory response, triggered by diet-induced obesity, involves many components of the classical inflammatory response, including the upregulation of pro-inflammatory cytokines in the hypothalamus. IL-6 is one of the major pro-inflammatory cytokines involved in the chronic low-grade inflammation associated with obesity and insulin resistance (12). However, several studies hint to a more complex picture, reporting that mice lacking pro-inflammatory cytokines are not protected from the diet-induced weight gain and display obesity phenotypes (11). Furthermore, previous studies by the group of Jansson demonstrated that IL-6-deficient mice develop mature-onset obesity (13) and display deficient lipid metabolism and energy expenditure, which can be restored by an i.c.v. (intracerebroventricular) administration of IL-6 (14). Additionally, they found that chronic i.c.v administration of IL-6 causes a decrease in body mass and an increase in energy expenditure and thermogenesis in rats fed a high-fat diet (14), suggesting that IL-6 has an anti-obesity effect. Consistent with these pivotal findings in rodents, studies in humans reported that the levels of IL-6 in cerebrospinal fluid (CSF) are inversely correlated with body fat mass (15). In the present study, the authors investigate a fascinating hypothesis that the anti-obesity effect of the centrally-administered IL-6 is mediated by tanycytes.

Using immunohistochemistry, the authors demonstrate that in mice ~ 90% of cells expressing tanycyte markers are immunoreactive for IL-6 receptor alpha (1). The immunoreactive cells are mostly localized to the ventral portion of the third ventricle at the level of the ME and ARC, where β-tanycytes are typically found (2). Moreover, about 50% of these cells displayed a rapid (5 min) increase in STAT3 phosphorylation following i.c.v. administration of IL-6, suggesting that tanycytes have functional

receptors for IL-6, whose activations triggers intracellular signaling events in tanycytes (1). Interestingly, similar effects can be achieved by both systemic and i.c.v. administration of leptin**.** However, systemic administration of IL-6 in doses sufficient to trigger STAT3 activation in other brain areas does not increase STAT3 phosphorylation in tanycytes. Based on these results and on the fact that IL-6 levels are higher in CSF than in serum in many humans (15), the authors speculate that local production of IL-6 in the brain (e.g. by microglia or astrocytes) may play an important role in the regulation of energy metabolism (1). Interestingly, a recent study exploring the anti-obesity effects of central IL-6 has shown that neuronal IL-6 receptors are not required for central IL-6-mediated suppression of food intake or for the maintenance of energy and glucose homeostasis (16). This finding implies that IL-6 might exert its beneficial metabolic effect through a non-neuronal cellular population, consistent with the present study of Anesten and co-authors suggesting that tanycytes might be involved in the mediating anti-obesity effects of central IL-6.

Future studies should explore whether the metabolic effects of IL-6 are mediated via IL-6 receptors located on tanycytes, and provide insights into the potential role of tanycytes in the maintenance of energy and glucose homeostasis.

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