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Previews

Hypothalamic Tanycytes: Gatekeepers to Metabolic Control

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How circulating signals of hunger and satiety enter the brain to reach neurons that govern energy balance has long remained a matter of controversy and speculation. Balland et al. (2014) now elucidate molecular mechanisms by which a highly specialized hypothalamic glial cell regulates transport of leptin across the blood-brain barrier.

Like the multiheaded dog Cerberus, protecting the entrance to Hades, and the god of keys, Portunes, distinct components of the blood-brain barrier (BBB) permit or prevent the passage of specific molecules such as leptin into and out of the brain. Understanding the mechanisms of regulated transport through specific "gates" of the BBB represents one of the key challenges of metabolism research. In this issue, Balland and colleagues report that specific glial cells called tanycytes act as "gatekeepers" that regulate leptin's entry into the hypothalamus (Balland et al., 2014).

The regulation of energy homeostasis relies on a highly responsive system in which energy expenditure is exquisitely balanced with nutrient intake to maintain a constant body weight (Schwartz and Porte, 2005). To achieve this, circulating factors of hunger and satiety reflecting nutrient availability must cross the BBB to reach effector neurons. A defect in this process invariably leads to uncontrolled body weight gain (Schwartz and Porte, 2005). One circulating energy indicator is leptin, an adipose-derived hormone that normally enters the brain to promote decreased food intake and increased energy expenditure (Myers et al., 2009). Obesity, however, leads to a state of "leptin resistance," in which a large amount of circulating leptin fails to regulate body weight. The mechanism of leptin resistance may encompass a defect in both leptin entry and action in mediobasal hypothalamus (MBH) target neurons (Banks, 2008; Kalra, 2008). Indeed, in obese animals, leptin delivered centrally through intracerebroventricular injection (ICV) activates hypothalamic neurons but is ineffective when given peripherally.

The median eminence (ME), a BBB structure located at the bottom of the third ventricles, is uniquely positioned to regulate the passage of blood-borne signals to the cerebrospinal fluid (CSF) and MBH neurons (Banks, 2008; Kalra, 2008). Abutting tight junctions in the third ventricle (3rdV), tanycytes are specialized glial cells that extend from the 3rdV to a plexus of permeable fenestrated capillaries, representing the first rampart between blood and CSF (Mullier et al., 2010) (Figure 1). Previously, Prevot and colleagues showed that tanycytes regulate BBB plasticity according to nutrient status by releasing vascular endothelial growth factor A (VEGF-A) to endothelial cells (Langlet et al., 2013). Now the same group shows that tanycytes are the "gatekeepers" that regulate leptin's entry into the hypothalamus.

Balland and colleagues first dissected the kinetics by which peripheral leptin enters the brain. Following the phosphorylation of the transcription factor and leptin effector STAT3, leptin's signaling cascade begins with tanycytes in the ME and then transitions to hypothalamic neurons. This sequence of events was confirmed using Western blot analysis of leptin content in the ME and the MBH, which were microdissected at different time points after peripheral injection. In animals rendered obese with high-fat feeding (DIO), leptin still accumulated in the ME but failed to appear in the MBH, suggesting that DIO disrupted the leptin signaling pathway and the coordinated release of leptin from the ME to the MBH. This phenomenon could be recapitulated in *db/db* mice, lacking the signaling-competent form of the leptin receptor (LeptR), suggesting that the integrity of the leptin signaling cascade is required for proper distribution of leptin from the ME to the MBH. Further, a leptin antagonist that retains LepR binding activity but has no signaling activity failed to accumulate in the ME or MBH. STAT3 activation in MBH neurons following peripheral injection of leptin could be selectively dampened in the arcuate nucleus, ventromedial hypothalamus, and dorsomedial hypothalamus by ICV delivery of leptin-neutralizing antibodies, suggesting that blood-borne leptin has to be routed through the CSF to access MBH neurons.

Next, the authors dissected the molecular pathway engaged in tanycyte regulation of leptin transport. They found that tanycytes express the mRNA encoding all LepR isoforms, respond to leptin treatment with STAT3, Akt and ERK activation, and are able to internalize leptin through clathrin-coated vesicles. Intriguingly, inhibitors of the leptin-signaling cascade failed to prevent leptin transport by tanycytes, suggesting that although tanycyte transport of leptin depends on LepR, it is independent of the classical LepR-signaling cascade. Furthermore, once loaded with exogenous leptin, the tanycytes progressively released leptin into the medium in a process requiring ERK pathway activation and involving colchicine-sensitive intravesicular trafficking. Indeed, ERK pathway activation through epidermal growth factor (EGF)

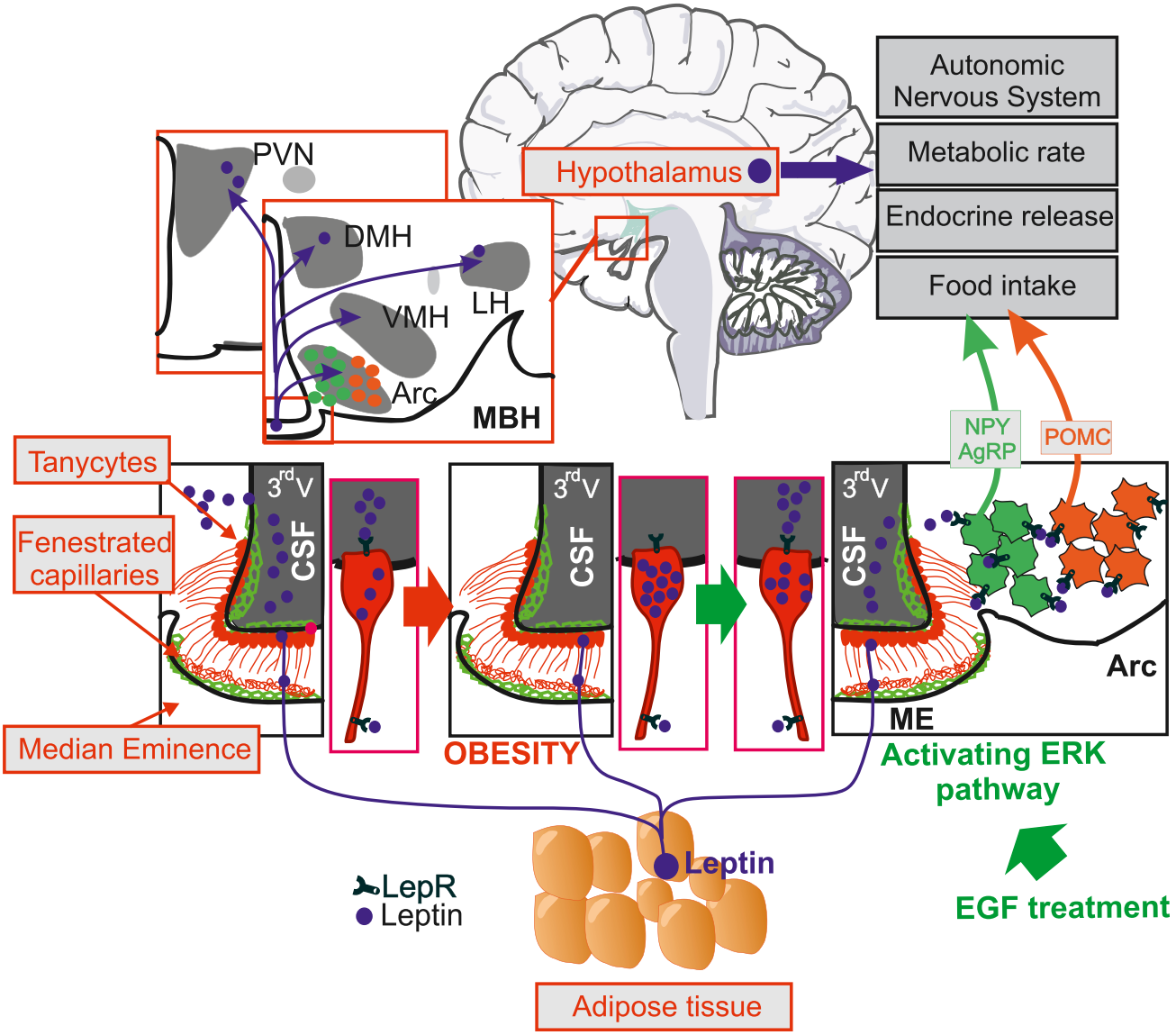

Figure 1. Model Depicting the Control of Brain Leptin Entry by Tanycytes

The median eminence (ME) is a privileged region of the blood brain barrier (BBB) composed of fenestrated capillaries (red) and glial cells highly structured with tight junctions (green) that regulate brain access to blood-borne molecules. Tanycytes (red and shown in inset) are specialized glial cells that extend a "foot" starting from the surface of the third ventricle (3rdV) to the fenestrated capillaries. Tanycytes represent the first rampart between blood and cerebrospinal fluid (CSF).

Under physiological conditions, peripheral leptin is internalized by tanycytes through a LepR-dependent mechanism. Tanycytes, in turn, release leptin into the CSF allowing leptin to reach energy-sensing target neurons in the mediobasal hypothalamus (MBH) and exert its catabolic/anabolic action. During diet-induced obesity tanycytes "hold on" to leptin, reducing its access to MBH neurons. Activating the ERK pathway through EGF treatment "frees" leptin from tanycytes and restores its access to hypothalamic target neurons.

treatment restored proper ME-to-MBH leptin translocation in *db/db* and DIO mice, and daily injection of EGF in DIO mice increased energy expenditure and locomotor activity, precipitating weight loss.

Altogether, Balland and colleagues present an elegant study establishing tanycytes as the first gatekeepers through which leptin has to pass prior to reaching neurons and exerting its catabolic action. In addition to identifying the BBB doors, the authors provide us with a potential key to unlock tanycytes through the activation of the ERK pathway. Although this work has enormous clinical potential for treating leptin resistance associated with obesity, it needs to be confirmed in humans, as most of the aforementioned studies were performed in rodents. Furthermore, it is unlikely that EGF treatment can be a sustainable strategy for human treatment given its promitotic effects. In addition, manipulating tanycyte permeability may compromise brain protection and lead to "leakage" of potentially dangerous molecules gathered into the BBB from the bloodstream.

The results also raise several questions for future investigations. What is the role

of tanycytes in delivering signals through other circumventricular organs such as the area postrema? Do tanycytes regulate the transport of other signals such as ghrelin or nutrients? What role do tanycytes play in other mechanisms that have been described to promote leptin resistance such as ER stress, inflammation, or nutrient overload (Banks et al., 2004; Milanski et al., 2009; Ozcan et al., 2009)?

Finally, once their function as hypothalamic gatekeepers is established the question remains whether tanycytes are amenable like Portunes, allowing targeted pharmacology to manipulate leptin entry, or more like Cerberus, refusing any negotiation.

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High-Density Lipoproteins Put Out the Fire

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Macrophages in atherosclerotic plaques are activated, inflammatory cells that directly contribute to the disease process. De Nardo et al. (2013), now report that high-density lipoproteins (HDL) can reprogram macrophages to be less inflammatory through an ATF3-dependent pathway, providing another mechanistic basis for the atheroprotective properties of HDL.

Atherosclerosis is commonly referred to as an inflammatory disease. The key player in the early phase of inflammation in plaques is the foot soldier of the innate immune system, the macrophage. These cells become activated in the arterial wall in response to uptake of lipoproteins containing apolipoprotein B, such as low- and very-low-density lipoproteins (LDLs and VLDLs) (Tabas et al., 2007). The cholesterol carried by these lipoproteins causes the macrophages to become engorged "foam cells," which become trapped in the arterial intima, establishing the inflammatory milieu of the plaque. The failure to resolve this inflammation is thought to culminate in "vulnerable" atherosclerotic plaques, which are prone to rupture, leading to heart attacks and strokes. Inflammatory mediators (IL-1β, TNFα, and MCP-1, etc.) secreted by macrophage foam cells following the stimulation of innate immune receptors such as Toll-like receptors (TLR), or via inflammasome pathways, have adverse effects on the other two major cell types in the plaques, endothelial and vascular smooth muscle cells. Furthermore, dying macrophage foam cells contribute to the formation of the necrotic core, which is enriched in cholesterol, inflammatory substances, and thrombogenic Tissue Factor and is a hallmark of vulnerable plaques. Thus, factors that either impede the escalating inflammation process or reverse it may make it possible to derail the march to a clinical event. It is in this context that the studies by Latz and colleagues fall, by showing how HDL may be a fire prevention or extinguishing agent through stimulating an anti-inflammatory pathway in macrophages that is dependent on the transcription factor ATF3 (De Nardo et al., 2013).

De Nardo et al. began by investigating the effects of HDL on the activation of macrophages by TLRs in vitro. First, they confirmed previous studies (e.g., Yvan-Charvet et al., 2008) showing that HDL treatment reduced the inflammatory responsiveness of the macrophages to TLR stimulation. For this purpose, they focused on TLR1, TLR2, and TLR9 (chosen because they had been implicated in previous studies in atherosclerotic mice), using accepted ligands for each. They found that the anti-inflammatory effects of HDL were independent of HDL binding of TLR ligands and did not involve the classical early signaling downstream of the TLRs. They also found in contrast to Yvan-Charvet et al. (2008) that there was no evidence that the impaired TLR responsiveness resulted from HDL-mediated depletion of cholesterol from plasma and endosomal membranes.