nerves, muscles, and throat cartilages might even include aspects of verbal and non-verbal communication. Taken together, the CNCC enhancers identified by Prescott et al. represent a comprehensive resource for studies of human evolution and the genetic basis of variations in facial morphology. Their work also introduces the concept of cellular anthropology that, by studying developmentally relevant cell types in vitro, attempts to elucidate mechanisms underlying morphological evolution in primates. Together with the recent advances in molecular paleontology enabling the sequencing of genomes of extinct close human relatives, these novel approaches make this a very exciting time to study human evolution.

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A Sympathetic View on Fat by Leptin

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Zeng et al. reveal that the lipolytic effect of the hormone leptin is mediated by sympathetic nerve fibers that directly "envelope" white adipocytes. Local activation of the sympathetic input to the fat opens new venues to circumvent central leptin resistance in obesity.

In the past 20 years, scientists have uncovered the mechanisms by which the hormone leptin affects different brain areas. Although it is also well known that central administration of leptin results in a myriad of effects at the periphery level (Halaas et al., 1995, 1997), the mechanism of action of these peripheral effects at the various tissue sites has remained elusive (Balthasar et al., 2004; Cowley et al., 2001). In particular, the exact mode of signaling by which leptin triggers changes in white adipose tissue (WAT) function was yet to be identified. In this issue of *Cell*, Zeng et al. (2015) resolve the mystery, showing that the sympathetic nervous system (SNS) is the fine effector of leptin's action on WAT.

The authors begin by visualizing the sympathetic innervation of the inguinal WAT. Then, applying state-of-the stimulating and inhibiting optogenetic approaches at peripheral sites, they reproduce or block, respectively, the effects of leptin on the WAT (Figure 1). Their study goes beyond just the delineation of how leptin triggers lipolysis in WAT. It puts forward an exciting experimental design, which adapts very advanced and powerful techniques to the study of the sympathetic innervation of peripheral tissues, in this case the WAT. First, they use optical projection tomography, or two-photon microscopy, to identify the precise sites of SNS innervation of WAT in vivo, a feat that could not be accomplished before. Then they apply optogenetics to stimulate axonal projections at the post-ganglionic level. To date, optogenetic approaches have been predominantly used to interrogate neuronal function in circuits of the central nervous system. This paper sets the stage for the application of optogenetics to interrogate the functional role of various peripheral neuronal circuits in system physiology.

Many efforts have been put forth during the last decades to identify the type of innervation that is present in the WAT. Some studies erroneously postulated the existence of parasympathetic innervation associated with the vasculature (Giordano et al., 2006). Conversely, other studies investigated the role of the SNS innervation of WAT (Bartness et al., 2014; Diculescu and Stoica, 1970). It has been reported that through the manipulation of sympathetic efferents, it is possible to alter lipid mobilization in different fat depots (Bartness et al., 2014). Other studies have shown SNS innervation of WAT through the use of neuroanatomical methods, using retrograde tracers and immunohistochemical analyses (Bartness et al., 2014; Diculescu and Stoica, 1970). Nonetheless Zeng et al. are the first to

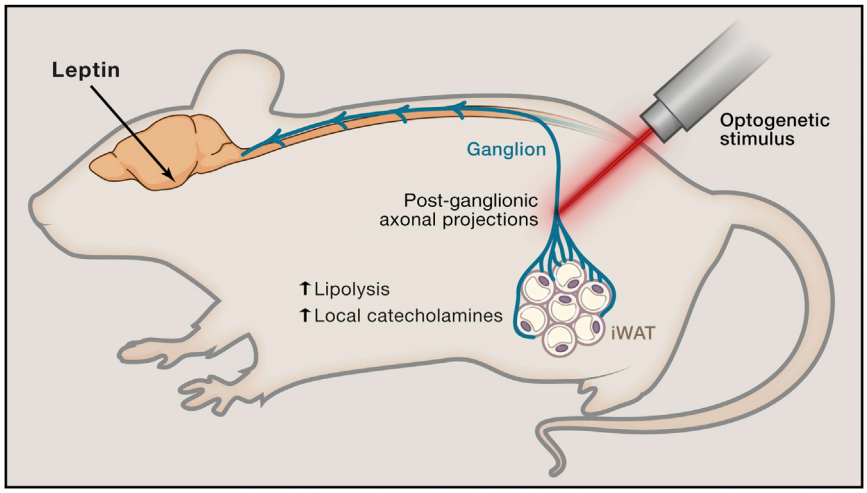

Figure 1. Post-ganglionic Axonal Projections Innervate Fat Depots
Stimuli from the different areas of the brain reach fat depots. Zeng et al. provide evidence that the WAT is innervated by axonal projections from ganglionic neurons. Optogenetic stimulation and genetic, chemical, or physical inhibition of these axons at the post-ganglionic level can mimic or block leptin effects on lipolysis in WAT, respectively.

provide direct evidence for the link between central effects of leptin and lipid mobilization in the different fat depots. The fact that central leptin promotes lipolysis in fat, together with the evidence showing an increase of sympathetic activity after leptin treatment (Pellegrino et al., 2014), led the authors to investigate whether the SNS mediates the lipolytic effects of leptin. They find that the release of sympathetic catecholamines in the fat depots plays a mandatory role in the lypolytic effects of leptin. These data challenge previous hypotheses that the lipolysis in WAT induced by leptin is due to the effects of other circulating hormones. Rather the new data show that signals from different areas of the brain reach the WAT through the SNS. Axonal projections form neural-adipose junctions, where catecholamines (in this case norepinephrine) are released to trigger lipolysis. Because leptin impacts systemic metabolism by action in many other peripheral tissues, it will be intriguing to apply the same approach to other systems as well. In the future, improvement of this technology could allow selective altering of impaired functionality of peripheral tissues, which may vary between patients with metabolic disturbances such as obesity.

Since the discovery of leptin in 1994 (Zhang et al., 1994), thousands of studies have set out to understand the mechanisms of action of leptin at the central level as well in peripheral tissues. Despite all the advances, many questions remain to be answered to fully unravel the mechanism by which leptin controls integrative physiology (Balthasar et al., 2004; Cowley et al., 2001). Investigators continue to utilize elaborate and complicated genetic models to this end. However, fewer studies have been done to dynamically identify the signaling modalities of leptin in control lipid mobilization and other peripheral functions. This paper is an excellent example for this latter approach, looking beyond individual steps of this process and focusing on the whole body. By default, the implications of this study are not limited to leptin and lipolysis but rather offer a new approach and vista for the investigation of the actions of other peripheral hormones in integrative physiology.

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