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Hypothalamic control of adipose tissue

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A detailed appreciation of the control of adipose tissue whether it be white, brown or brite/beige has never been more important to the development of a framework on which to build therapeutic strategies to combat obesity. This is because 1) the rate of fatty acid release into the circulation from lipolysis in white adipose tissue (WAT) is integrally important to the development of obesity, 2) brown adipose tissue (BAT) has now moved back to center stage with the realization that it is present in adult humans and, in its activated form, is inversely proportional to levels of obesity and 3) the identification and characterization of "brown-like" or brite/beige fat is likely to be one of the most exciting developments in adipose tissue biology in the last decade.

Central to all of these developments is the role of the CNS in the control of different fat cell functions and central to CNS control is the integrative capacity of the hypothalamus. In this chapter we will attempt to detail key issues relevant to the structure and function of hypothalamic and downstream control of WAT and BAT and highlight the importance of developing an understanding of the neural input to brite/beige fat cells as a precursor to its recruitment as therapeutic target.

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Why is understanding innervation of adipose tissue and the nature of central control pathways so important?

The science relating to the hypothalamic control of adipose tissue whether it be white (WAT), brown (BAT) or brite/beige is relatively recent. It is surprising that whether one considers white or brown fat, pivotal observations relating to its innervation, including that derived from the hypothalamus, first occurred in the latter part of the 1990s [1,2]. Before this, there was some ambivalence as to whether in fact white adipocytes received a neural input with the focus on circulating adrenal medullary catecholamines as primary controllers of lipolysis in WAT [3,4]. Noradrenergic fibers directed to fat were thought to innervate blood vessels [5]. It was not until light and electron microscopic observations revealed typically varicose *en passant* adrenergic synapses onto white adipocytes that a neural input to the parenchyma of fat rather then the vasculature was conceded [6]. The subsequent identification of the sympathetic ganglionic source of inputs to white adipocytes [7] was the precursor of studies described below which used retrogradely transported neurotropic viruses to map the distribution and neurochemical characteristics of hypothalamic neurons directed multisynaptically to WAT [1]. The potential to use this information to recruit lipolytic neural pathways particularly to the more metabolically adverse abdominal fat is a potentially attractive therapeutic strategy.

In a similar vein to WAT, the sympathetic innervation of BAT is a relatively new field in metabolism and its background, particularly the innervation of the parenchyma of the tissue, rather than the blood vessels within it, initially drew skepticism as it did for WAT and similarly involved an ultimate proof from electron microscopic observations [for reviews see [8,9]]. As was also the case for WAT, and in fact all sympathetically-innervated tissues and organs, the use of pseudorabies virus to map chains of synaptically-connected neurons projecting from sites in the central nervous system (CNS) to BAT has been pivotal. The sympathetic innervation of BAT is functionally essential as is shown by denervation, which causes not only atrophy but a loss of thermogenic capacity as evidenced by a reduction in levels of uncoupling protein 1 (UCP1) post denervation. Despite the caveat that catecholamines may be secreted by macrophages in BAT [10,11] and may directly activate adrenoceptors under some conditions, BAT requires sympathetic input for its activation [12]. In fact it is an underrated fact that BAT is not innately active, as many researchers would think. Rather there is a tonic inhibition of UCP1 in the resting condition and this ATP – mediated brake needs to be released by a process possibly involving fatty acids, a process which importantly requires noradrenergic stimulation [12]. It is on this background that it is essential that we have a more complete understanding of the extended autonomic innervation of BAT if it is to be recruited in a therapeutic capacity.

The third adipose tissue type, the so-called brite/beige intermediate "brown-like" fat (see below) has captured much recent attention because it is inducible [13,14], it has an impact, when activated, on energy expenditure and body weight [13,15,16], is present in adult humans [17–19] and may be derived directly from specific precursors or importantly trans-differentiated from WAT, particularly in the inguinal depot [see [20,21] and below].

One of the great challenges as we see it is to determine how the innervation of these cells changes after their phenotypic conversion in the latter case. If a single white adipocyte can convert to a brown like adipocyte, how does the complex central neural circuitry dedicated to the coordination of lipolysis in white fat convert to a functional neural circuit committed to the dissipation of energy in a brown-like adipocyte?

It is imperative to understand the detail of the innervation of both classical BAT and the transformed beige state of BAT if these are to be effectively recruited by the activation of central neural pathways and their peripheral extensions. As a platform on which to build such an understanding of the involvement of the nervous system in white to brown fat conversion it is equally important to appreciate the extent to which the hypothalamic control of white fat and its different compartments has been defined.

White, brown and beige fat – similarities and differences

Structural features

WAT is composed of adipocytes, pre-adipocytes, endothelial cells and various immune cells, embedded in a collagen and elastin fiber matrix. Individual white adipocytes characteristically contain