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The Browning of White Adipose Tissue: Some Burning Issues

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Igniting thermogenesis within white adipose tissue (i.e., promoting expression and activity of the uncoupling protein UCP1) has attracted much interest. Numerous "browning agents" have now been described (gene ablations, transgenes, food components, drugs, environments, etc.). The implied action of browning agents is that they increase UCP1, through this heat production, leading to slimming. Here, we particularly point to the possibility that cause and effect may on occasion be the reverse: browning agents may disrupt, for example, the fur, leading to increased heat loss, increased thermogenic demand to counteract this heat loss, and thus, through sympathetic nervous system activation, to enhanced UCP1 expression in white (and brown) adipose tissues.

To harness the thermogenic power of the uncoupling protein UCP1—and thus its ability to nullify the effects of extra energy intake—has attractive perspectives for human health. Not only would it enable us to stay or even to become slim even if an excess of food were eaten, but it would also counteract comorbidities such as type 2 diabetes. Particularly, recent years have seen an intense interest in the ability to "brown" what have traditionally been seen as white adipose tissue depots. The idea is to place the combustion machinery (i.e., UCP1) directly in the excess fat supply.

Until recently (Nedergaard et al., 2007), it was common wisdom that adult humans do not possess active brown adipose tissue. Therefore, the concept that certain white depots could develop brownish characteristics had a great advantage: this way of translating the power of brown fat into human health appeared much more feasible than reintroducing true brown fat into adult men. Additionally, observations that very large increases (100-fold) in the mRNA levels of UCP1 could be induced in rodents in certain white adipose tissue depots had made the browning process very attractive for therapeutic exploration.

In this Perspective, we discuss some of the burning issues concerning the browning process. We pragmatically define browning as any significantly increased UCP1 expression at the mRNA level occurring in what are normally considered as white adipose tissue depots. The resulting cells that express UCP1 may be referred to as beige (Ishibashi and Seale, 2010), brite (Petrovic et al., 2010), convertible (Loncar, 1991), ectopic (Lehr et al., 2009), inducible (Lee et al., 2011), or recruitable (Schulz et al., 2013). (This latter term is unfortunately often misread to indicate that classical brown adipose tissue is not recruitable. However, the opposite is true: classical brown adipose tissue is very recruitable in the sense that it increases its thermogenic capacity some 5-fold from 20°C to 5°C [Nedergaard and Cannon, 2013]). Here, we use a simple "browning" terminology.

Presently, Almost Everything Browns White Adipose Tissue

Some 50–100 different treatments have been demonstrated to induce browning: food components, drug substances, transgenes, gene knockouts, and enhanced or deteriorated living conditions. The list of browning agents is growing rapidly. For simplicity, we refer to any of these compounds or genetic modifications or ways of living as "browning agents." Thus, it should be kept in mind that the expression in this Perspective includes factors of a much broader nature than just drug substances. Several reviews have recently carefully listed these agents (Bonet et al., 2013; Wu et al., 2013), and we will not duplicate these efforts. Rather, we would like to suggest some "unifying hypotheses" for understanding why such a broad variety of agents can all result in browning. Because of the very rapid growth of literature, this Perspective cannot attempt to be comprehensive, and we apologize if we have overlooked contributions with a principal impact on the issues discussed.

Browning as a Sympathetic Event

The first report of the browning phenomenon is that of Young et al. (1984). The authors observed that areas in the parametrial adipose depot developed brown-fat characteristics when mice were acclimated to cold. Given that recruitment in classical brown adipose tissue is due to chronic stimulation by norepinephrine released from the sympathetic nerves innervating the tissue (Cannon and Nedergaard, 2004), the possibility that browning could also be induced by chronic adrenergic stimulation was examined. Indeed, chronic treatment with a β_3-adrenergic agent led to browning (Cousin et al., 1992; Ghorbani et al., 1997; Ghorbani and Himms-Hagen, 1997). In mice without β_3 adrenoceptors, browning was barely induced (Jimenez et al., 2003). Correspondingly, overexpression of β_1 adrenoceptors in white adipocytes was sufficient to induce browning (Soloveva et al., 1997). Thus, adrenergic stimulation of white adipose tissue definitely induces the browning process. Here, we examine to what degree this norepinephrine-induced, and thus centrally mediated, process is sufficient to explain the effect of (some of) the browning agents.

A Hierarchical Activation System

On the basis of the divergent physiological functions we normally ascribe to brown versus white adipose tissue, it would be expected that the innervation of these tissues would be qualitatively very different. Particularly, it would be thought that the

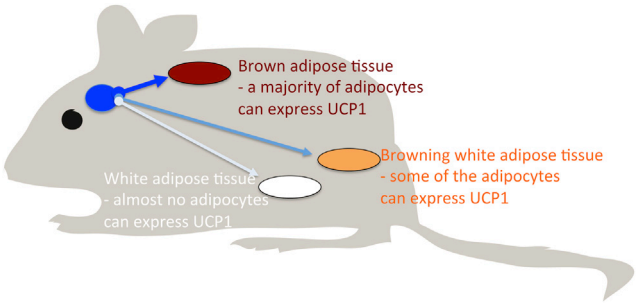

Figure 1. The Hierarchical Organization of the Activation of Brown and White Adipose Tissues

The nerve pathways stimulating brown and white adipose tissues have similar origins in the brain, but they are differently controlled; thus, with increasing exposure to cold, the nerves to brown fat will initially become active, but, with continued decreasing temperatures, the nerves to white-fat depots may also be successively engaged. The receiving depots contain different fractions of cells able to respond to norepinephrine stimulation with an increase in UCP1 gene expression, as indicated. The browning white adipose tissues are often those referred to as "subcutaneous" adipose tissue depots; the one normally studied is the inguinal depot. The depots least able to respond are those often referred to as "visceral"; the one normally studied is the epididymal depot. Thus, with increasing intensity of sympathetic stimulation, browning of the inguinal depot will be augmented in addition to recruitment of classical brown adipose tissue.

brain centers involved in the control of their activity would be distinct. However, studies where the innervation to brown versus white adipose tissue depots has been delineated tend not to identify distinct brown- versus white-fat-specific control centers in the brain (Bamshad et al., 1998, 1999). Basically, this would mean that an organization exists where similar brain events would evoke qualitatively similar activation of either tissue (Figure 1A). Although this is somewhat unexpected in several respects, it makes it possible to understand that browning of white adipose tissue may not be substantially different from recruitment of classical brown adipose tissue.

The parallel innervation does not mean that the sympathetic activation occurs to the same degree in different depots. Classical brown adipose tissue demonstrates small but significant UCP1 gene expression already at thermoneutrality (≈30°C). This may indicate that sympathetic stimulation can occur in the absence of a thermal signal. White adipose tissue is principally devoid of UCP1 at thermoneutrality, and cold acclimation leads to successive browning, with some UCP1 expression at "normal" animal house temperatures (≈20°C) and much more in the cold (≈5°C) (Waldén et al., 2012). Thus, a hierarchy may be formulated wherein increasing central stimulation successively activates first brown and then white adipose tissue depots. In contrast, experiments with injected adrenergic agents do not show this hierarchical system. Such injections directly induce browning with the bias that injections at normal animal house temperatures appear to have a much greater (relative) effect on white than brown adipose tissues. This is because, under normal experimental conditions, the classical brown adipose tissue is already physiologically adrenergically stimulated and therefore shows only comparatively modest relative effects of additional stimulation—but these effects may be quantitatively large.

This organization of the system is confirmed by classical observations that surgical removal of a given brown adipose tissue depot will result in the activation of other depots (Connolly and Carnie, 1982; Stephens et al., 1981). Also, in accordance with this, a substantial reduction of "classical" brown adipose tissue activity (molecularly introduced by eliminating the bone morphogenetic protein [BMP] receptor 1A from brown adipocyte precursors) results in "compensatory" browning of white depots (Schulz et al., 2013) with a regaining of thermogenic capacity. Thus, the brain will augment the intensity of nerve activity to the relevant adipose tissue depots to the exact extent required to generate the heat needed. If the intensity is sufficiently high, then browning via physiological means will occur.

It may be wondered whether the UCP1 gene in the white adipose tissue can be induced to be expressed without first being "unmasked" by another process. However, Boyer and Kozak (1991) observed that there were DNase hypersensitive sites in the upstream region of the UCP1 gene in both brown and white adipose tissues. These sites were not seen in nonadipose tissues, implying that the UCP1 gene in white adipose tissue is already "open" and merely needs, for example, adrenergic stimulation to become expressed. However, there is the difference that far fewer cells in white than brown adipose tissue have open UCP1 genes (see the in vitro discussion in the Supplement Information available online).

All in all, there is no reason to think that browning of white adipose tissue in the cold is a process that is fundamentally different from the standard recruitment of brown adipose tissue in the cold. Thus, it can be explained by increased sympathetic stimulation of either tissue.

An Efficient, but Very Indirect, Browning Agent: The Feeling of Cold

Given that the most notable physiological factor leading to browning is cold, pertinent but infrequently addressed questions are (1) do (some of) the animals that demonstrate browning feel cold to a greater extent, and (2) can this be the reason that browning occurs?

By this, we do not imply that their nervous system should have been altered by the treatment. Rather, they may experience the normal surroundings as much colder than do mice not exposed to the browning agents.

For a mouse, the temperature of a normal animal house is in itself a cold stress. As seen in Figure 2, at 20°C, a mouse loses so much heat that it needs to increase its heat production (and thus its food consumption as well) by about 50% in comparison to the heat production in the thermoneutral zone. This is the case for a normal wild-type mouse.

If a mouse loses its fur, then much of its insulation will also disappear. Shaved mice increase their metabolic rate at normal animal house temperatures by nearly 50% because of the increased heat loss (Hirata et al., 2011). Similarly, the genetically nude Balb/c mice have a metabolic rate ≈80% higher than normal Balb/c mice (Hirata et al., 2011). We have illustrated the consequence of this in Figure 2. It can be understood from this that shaving a mouse living at 20°C is equivalent to transferring an unshaven mouse from 20°C to 10°C. Also note that, at 20°C, the extra metabolism required to counteract the extra heat loss due to shaving is some 300% of that of the unshaven mouse. This indicates a requirement for 3-fold more thermogenesis in the shaven mouse.