It's all in your gut and mind

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Abstract Obesity has become a global problem affecting adults and children alike. Lifestyle choices both personal and industry driven can be blamed for the rise in obesity. One must distinguish between the possibly reversible overweight condition and the almost intractable actual morbid obesity where predisposing genetic factors may come into play. Both however exhibit consequences to health with a severity that cannot be underestimated. Deleterious changes to metabolism can lead to type II diabetes and atherosclerosis and other organ dysfunctions. It has long been recognized that there are two main types of fatty tissue in the body, white adipose tissue (WAT) serving a storage function and brown adipose tissue (BAT) serving a thermogenic function. The new discovery has been that WAT cells can be induced to undergo conversion (browning) to BAT to yield what is called beige adipose tissue, acquiring the thermogenic function. The clinical dream is to be able to promote browning and to induce, what may be called, burning off the fat. In this B&B article I entice the reader with a recent study that shows how two key hormones insulin and leptin operate cooperatively in the brain to monitor and regulate energy balance and the downstream effect of browning. I present other studies to add additional perspectives to the understanding of the mechanisms in peripheral tissues and other hormones that play additional key roles. Whether obesity can be conquered therapeutically by manipulating the regulatory systems is still an open question.

Keywords White · Brown and beige adipose tissue · Thermogenesis · CNS and peripheral regulatory mechanisms · Factors · Pathways

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It is totally under the radar, it surfaces as a topic for ardent discussion almost weekly, and you cannot help but notice how it affects so many people.

Obesity has become the ‘holy grail’ for science, dietitians, advertisers, food manufacturers, the garment industry, lifestyle coaches, and others. So a recent article in *Cell* caught my eye (Dodd et al. 2015).

Researchers from Monash University in Australia have now shown that insulin and leptin, the two key hormones that

regulate glucose metabolism and satiety and hunger cues, activate satiety neurons in the mouse hypothalamus to promote the conversion of white fat to beige. For those following the field 'beige is the new brown'. White fat for lipid storage and brown fat for energy production (thermogenic tissue). White fat that has been induced to assume a brown phenotype is called beige, being heterogeneous in the adipocyte composition and so in between in anatomical color presentation.

The hypothalamic appetite-suppressing proopiomelanocortin (POMC) neurons relay satiety signals in the bloodstream to other parts of the brain and other tissues to promote energy balance. The new finding is that this signaling stimulates browning of white fat, i.e. to acquire a beige phenotype, as not all white fat is converted. Thus insulin and leptin act in synergy.

The mechanistic basis for this is that specific phosphatases, PTP1B (PTPN1) and TCPTP (PTPN2), in POMC act like dimmer switches controlling sensitivity of leptin and insulin receptors to endogenous ligands. Double knock out mice showed an increase in beige fat and the metabolically active brown fat. When fed a high fat diet the double knockouts did not gain weight suggesting that this leptin/insulin signaling was important for controlling body weight and fat metabolism. Using neural disconnection techniques the investigators showed that the neural connection to the brain from fat pads was absolutely essential. A different set of neurons regulate energy storage during fasting.

Thus we have a yin-yang balance in the storage and utilizations of fats. The thinking is that, if one can switch white fat to thermogenic brown fat storage and burning will be rebalanced and obesity conquered (Cereijo et al. 2014; Giralt and Villaroya 2013). Being able to induce beige adipogenesis in humans (Lee et al. 2014) elicits enthusiasm for the idea. Sounds simple. But like any good field of science if you cannot find a dozen more key regulators to throw into the soup then you have not looked hard enough. On top of that there are a growing list of modulators ranging from cold temperature induction, nitrates, acupuncture, and agonist and antagonists of intermediates (Cereijo et al. 2014; Roberts et al. 2015; Shen et al. 2014; Rachid et al. 2015). Furthermore, as recently elegantly discussed, thermogenesis has to be considered in the context of the thermoneutrality temperature for a given organism (Nedergaard and Cannon 2014). Quoting these authors, "If we require a true browning agent to (1) function through other mechanisms than those affecting heat loss, (2) lead to increased metabolism at thermoneutrality, (3) lead to decreased obesity, and (4) do this without recruiting classical brown adipose tissue, then it would seem that no true browning agent has been fully verified to date. Some of those suggested may eventually achieve this status, but there are presently no unequivocal candidates."

On top of that there are a growing list of modulators ranging from cold temperature induction to agonist and antagonists of intermediates. In many other obesity unrelated mouse

transgenic and knockout models where a browning effect has been noted, the explanation may be simply be heat loss, due to loss of body insulation, and turning up the thermostat via the sympathetic nervous system. Similarly others have looked carefully into this browning issue and the rationale of the approach for treatment of obesity (Cypess et al. 2014).

Nevertheless, it is worthwhile examining the complex biology behind induction of browning. There is the fine level of transcription regulation involving miRNAs since they are there in abundance and usually keep expression under control (Kong et al. 2015; Fu et al. 2014). What appears to be going on at the adipocyte molecular level is the FGF21/SIRT1 dependent deacetylation of PGC-1 α and induction of browning genes Ucp1, Pgc-1 α , and Prdm-16 (Dodd et al. 2015). UCP1 (uncoupling protein 1) is a key decision maker and is regulated by various factors and means (Zheng et al. 2014; Dempersmier et al. 2015).

And if all of the above is too much to take in, then without burning more neurons over this subject, one can be more practical and have a good jog followed up by a cup of black tea and a croissant, which is so much more pleasant (Wu et al. 2014; Yamashita et al. 2014) and simply delegate your intestines to work on the issue (Fang et al. 2015; Mossenbock et al. 2014).

In truth all this focuses the field onto the heaters in the cell, the mitochondria. Let's extend the thinking here. Mitochondria originated a very long time ago from a bacterium entering into a symbiotic relationship with a primitive cell (not energetic) to their mutual benefit. Bacteria, in their myriad of forms, have hit the science scene 'big time' since we now speak of the microbiome in gut that not only aids in digestion but if unbalanced between good and bad bacteria messes up other organ functions. Furthermore, gut and brain get together via the GLP-1/GLP-2 peptides to balance lipoprotein production and act at the CNS level to regulate lipid metabolism affecting the metabolic syndrome and type II diabetes with obesity as the visual readout of a system perturbed (Drucker 2014; Hein et al. 2013; Xiao et al. 2014; Guan 2014).

You really are what you digest and absorb! And stressing over it may just get you heated up.

Finally, as this is JCCS, let's not overlook interesting and relevant studies on CCN2 and WISP1-CCN4 and WISP2, contributing to our understanding of adipogenesis and inflammation in adipose tissue, an immune cell contribution (Tan et al. 2013; Murahovschi et al. 2014; Gruneberg et al. 2014), and the still underappreciated concept of hormetic effects of everyday polyphenols, like resveratrol in red wine, on obesity (Scapagnini et al. 2014).

Perhaps now is a good time, with all this increased understanding, for those in the CCN field to delve deeper into the obesity problem and the roles of CCN proteins in the adipocyte anlage which used to consist only of adipocytes but now involves immune cells and the most topical of subjects, stem

cells (Park et al. 2014). So, if you are a fat cell, do you know who your parents are and what they hold in store for you?

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