The neuroscience of metabolism

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Given that the brain can detect and respond to changing levels of body fat and blood sugar, Michael W. Schwartz, MD from the University of Washington Medicine Diabetes Institute, explains how the brain can be targeted to treat obesity and diabetes

Until recently, obesity was perceived even in medical circles as a personal failing characterized by a lack of willpower. However, as more is learned about the biological system known as 'energy homeostasis,' this perception is changing. Controlled primarily by the brain, energy homeostasis works by matching energy intake to energy expenditure over long time intervals. The net effect is that body weight and fat mass are maintained within narrow limits. Should fat mass deviate from this weight, adaptive responses are engaged to return fat stores to their previous, biologically defended level.

Why should body fat mass be subject to biological control?

From a teleological perspective, fat represents the body's primary source of stored fuel, and having either too much or too little can be maladaptive. Because maintaining an optimal amount of stored fat has survival value, systems governing energy homeostasis have evolved in most if not all, mammalian species.

The defended level of body fat mass is not 'set' or fixed, like the temperature on a thermostat. Instead, it can be influenced by a variety of factors. Some of these are lifestyle choices over which we enjoy considerable control (e.g., diet composition and physical activity), while others are not (such as genetics). Yet even as obesity develops, body fat mass will continue to be vigorously defended by the energy homeostasis system. This defense can be illustrated by the response to intentional (diet-induced) weight loss. Once body weight drops by ~5-7%, the energy homeostasis system mounts responses that stimulate appetite while decreasing energy expenditure, effects that persist until lost weight is recovered. As will be familiar to many readers, this tendency to recover lost weight constitutes perhaps the most important single obstacle to effective obesity treatment.

Similarly, blood glucose – the body's primary circulating fuel source – is also tightly regulated through a process known as 'glucose homeostasis.' Just as obesity is characterized by the biological defense of an elevated level of body fat mass, the most common form of diabetes – type 2 diabetes (T2D) – is characterized by the biological defense of a gradually increasing blood glucose level.

Obesity and T2D are linked in several additional ways. First, obesity greatly increases the risk of T2D, such that the two disorders tend to co-occur. In addition, obesity and T2D are both characterized by the biological defense of an elevated level of a crucial physiological

variable – disorders that (with the exception of hypertension) are otherwise uncommon in medicine.

A third area of overlap between obesity and T2D lies in the neurocircuitry involved in energy and glucose homeostasis. Since many of the same circuits are involved, the impairment of one often impacts the other. One such impairment involves the brain's ability to detect the prevailing levels of body fat and blood glucose. Simply put, the brain must sense the level of these variables to regulate them.

How is this sensory information communicated to the brain?

The hormone leptin, which is secreted by fat cells, conveys vital information regarding the level of stored fuel (in the form of adipose tissue). The brain can also detect and respond to changing blood glucose levels. The relevance of these sensory processes to obesity and T2D lies in their potential to explain how the defended levels of body fat and blood glucose come to be elevated in these disorders. If the brain's ability to sense levels of body fat and blood glucose is compromised, the predicted outcome is an increase in the biologically defended level. Consider, for example, that if the brain's ability to detect the circulating glucose level is reduced by 50%, it will mistakenly interpret a value of 200mg/dl (which is elevated into the diabetic range) as a value of 100mg/dl (which is normal). Consequently, the brain will defend the elevated level, as is well-documented in patients with poorly controlled diabetes.

Similarly, if the brain's ability to detect or respond to leptin is compromised, the biologically defended level of body fat stores will increase. This type of link between obesity and 'leptin resistance' is also well established.

Such sensory defects extend beyond the realm of the brain. The hormone insulin, secreted by pancreatic beta cells in response to rising blood glucose levels, plays a crucial role in glucose homeostasis. In T2D, impaired glucose sensing by these cells reduces the amount of insulin secreted for a given blood glucose level. The net effect is, once again, the biologically defended blood glucose level is increased.

Can advances in the neuroscience of metabolism translate into improved therapeutic options?

Since its discovery a century ago, diabetes treatments have focused largely on insulin, but strategies targeting the brain might be more effective. As one example, sustained diabetes remission can be induced in animal models of T2D by administration of a peptide known as fibroblast growth factor 1 (FGF1) directly into the brain. Unexpectedly, this effect is achievable with only a single FGF1 dose and can last for months. Stated differently, FGF1 action in the brain effectively returns the defended blood glucose level to normal.

Even in animals with severe diabetes induced by complete loss of insulin-secreting beta cells, the brain can be targeted (through the administration of leptin) to fully normalize the blood glucose level. Yes, that's right – severe diabetes can be treated by targeting the

brain, even in the absence of insulin. This type of dramatic finding exemplifies how advances in the neuroscience of metabolism can unlock new approaches to therapy.

A particularly notable advance in this field pertains to GLP1 receptor agonist drugs such as Ozempic, Wegovy, and Mounjaro. The efficacy of this class of drugs for the treatment of both obesity and T2D is unprecedented. As they work by activating hormone receptors in the brain and in pancreatic beta cells, they highlight the synergy created by targeting systems governing energy and glucose homeostasis with a single drug.

Yet not all patients can tolerate or afford these drugs, and even among those who can, their benefit is quickly undone should the medication be discontinued. Why? Because the drugs work in part by blocking homeostatic responses to weight loss. Once the drug is discontinued, these responses are ‘re-awakened,’ driving the rapid recovery of lost weight. The pressing need to address these challenges highlights how the future of obesity and diabetes treatment will be shaped by advances in the neuroscience of metabolism.

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