gut to the brain, as well as the selective vulnerability of dopaminergic neurons, including the involvement of the gut microbiota and the immune system (Figure 1). More research will be necessary to address the triggering event(s) leading to the misfolding of α-synuclein in the gut and how they interact with genetic and other factors that can act as facilitators of the disease (Figure 1) [10]. In inflammatory bowel disease, which is both epidemiologically and genetically linked to elevated PD risk, increased levels of α-synuclein have been found in the gut [8]. In addition, the normal human appendix, that is rich in lymphatic tissue, contains an abundance of α-synuclein, including truncated forms similar to those found in Lewy pathology in PD [8]. Possibly, α-synuclein has a functional role in the gut immune system, and under some pathological conditions this goes awry, leading to pathological forms of α-synuclein escaping the gut and traveling along the vagus nerve to the brain. Other mechanisms might also be at play (Figure 1). Mutations in PINK1 cause rare early-onset PD, and a new study showed that PINK1-deficient mice develop PD-like motor impairment after bacterial infections in the gut [11]. Although this study suggests that systemic inflammation and autoimmunity are involved, with no involvement of α-synuclein in the process, it provides a further link between the gut and PD-like neurodegeneration in the brain. Given a remarkable number of studies linking the gut and PD in different ways, these are exciting times for research into the causes and mechanisms of this elusive disease. We envisage that the continued development of relevant and valid animal models of PD will allow us to identify both triggers and facilitators of the disease process, which should enable the development of novel therapies.

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Spotlight

Hypothalamic Heuristics for Survival

Denis Burdakov[1,*] and Daria Peleg-Raibstein[1]

Hypothalamic neurons implicated in energy homeostasis (Agrp, POMC, orexin, MCH) display fast, nutrient-independent dynamics. They do not simply mirror the slowly changing internal nutrient levels, but adapt rapidly to diverse external cues. Moreover, instead of eating, neonatal Agrp cells stimulate mother-attracting vocalisations, illustrating heuristic energy control beyond nutrient sensing or dietary self-control.

Two decades ago, our conceptual understanding of brain control of energy balance seemed simple. Influential reviews (e.g., [1]) summarised it as a basic feedback scheme, where hypothalamic neurons react to direct internal indicators of body energy status and control eating and energy expenditure according to deviations of these indicators from some set point (Figure 1A). This reactive/feedback model of hypothalamic function was thus conceptually similar to models of peripheral organs (e.g., the pancreas), which are usually

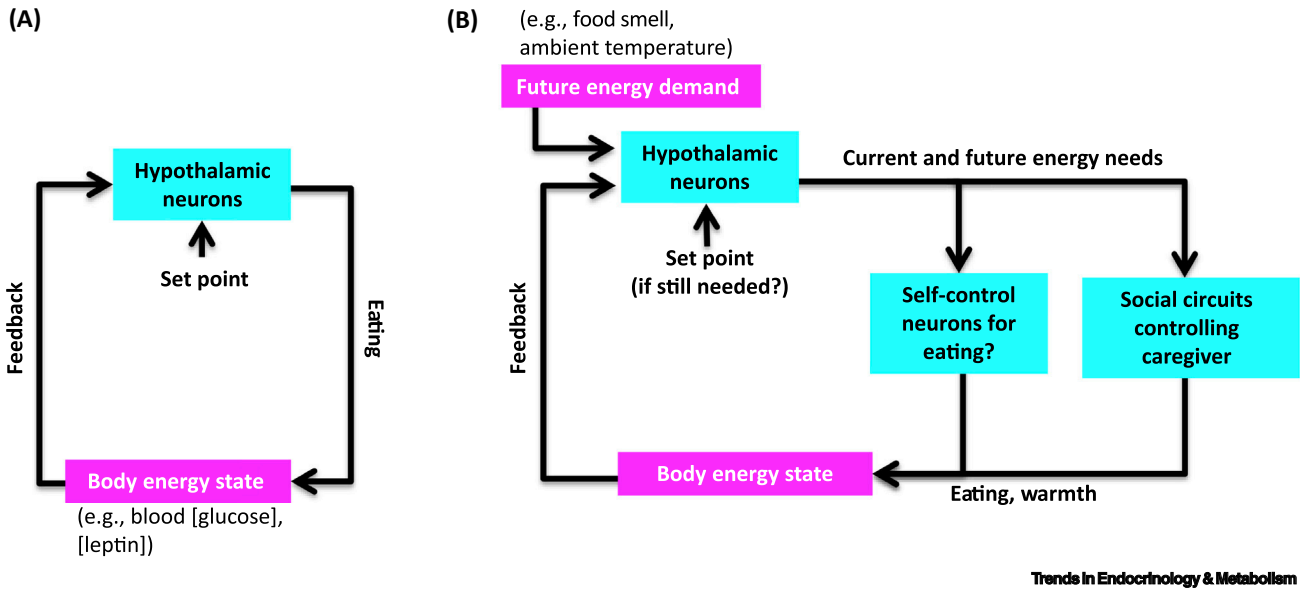

Figure 1. Evolving Models of Our Understanding of the Role of Hypothalamic Neurons in Eating and Energy Balance.
(A) Classic feedback/reactive model. (B) Mixed feedback + feedforward (reactive + predictive) model suggested by recent measurements of real-time hypothalamic neurodynamics.

depicted as feedback controllers of body energy state. However, given that the brain is a talented predictor guiding behaviour according to heuristic estimations of the future from indirect cues [2,3], tasking a major brain area with purely reactive control seemed like a waste of talent, or a suspiciously simple theory.

These suspicions turned out to be true when, in the past 5 years or so, it became experimentally tractable to measure the real-time activity of hypothalamic neurons implicated in body energy control. Putative appetite-promoting (Agrp, orexin, MCH) or -suppressing (POMC) hypothalamic neurons were hypothesised, based on the feedback model, to be inhibited and activated, respectively, by ingested nutrients at the timescale of nutrient digestion (i.e., slowly over minutes after nutrient ingestion). However, it was found that Agrp and POMC neurons were inhibited and activated, respectively, within seconds after food discovery and considerably before food ingestion [4–6]. The activity of these hypothalamic neurons thus appeared to be controlled by the probability of future nutrient ingestion rather simply by nutrient levels in the body. Rapid modulation of activity that did not mirror changes in body chemical composition was also reported for other hypothalamic neurons implicated in energy [7,8] and fluid [9] balance. Such findings triggered a fundamental conceptual shift in our understanding of hypothalamic neurons controlling eating and drinking. It became clear that these neurons were driven not only by internal levels of controlled variables (nutrients, osmolytes) but also by estimations of likely future changes in these variables. In other words, hypothalamic processing turned out to be more predictive than hitherto appreciated.

While the above studies showed that neural inputs regulating hypothalamic Agrp 'hunger' neurons communicate rapid predictive cues, the outputs of these cells were still thought to mediate self-control of eating. A new study [10] now indicates that, at least in the neonatal brain, both inputs and outputs of Agrp can be dissociated from the individual's nutrient status and appetite. When 10-day-old mouse pups were removed from the nest containing their lactating mother, the activity of Agrp neurons profoundly increased within seconds of the removal and fell back to baseline within seconds of return to the nest. A series of elegant control experiments revealed that this modulation of Agrp neurons was unlikely to be driven by changes in body nutrient levels or by anticipation of milk deprivation, but was largely driven by a reduction in ambient temperature. Thus, at least in neonates, the inputs controlling Agrp neurons appear to be even less directly linked to nutrient intake than previously thought. Instead, Agrp neurons sense external cues, such as temperature, that may be indicative of current and/or future metabolic challenges, in this case represented by

distance from the warm nest. Surprisingly, the Agrp cell activation caused by removal from the nest did not significantly increase the food intake of the pups. Instead, it caused the pups to emit ultrasonic vocalisations that attracted the mother. This output of Agrp neurons was reproduced by direct chemogenetic activation of neonatal Agrp cells. Similar to the nest removal-induced Agrp cell activation, the chemogenetic activation of neonatal Agrp neurons did not significantly increase milk ingestion. This is in striking contrast to older (15-day-old or adult) mice, where Agrp cell activation robustly increased ingestion. Therefore, in neonatal mice, Agrp cell output seems not directly linked to eating or appetite but instead stimulates offspring-to-mother communication that maximises the opportunities for energy control [10].

These recent studies [4–7,10] shift our understanding of energy-related hypothalamic neurons from body energy sensors controlling eating around a set point (Figure 1A), to signallers of a mixed current and future energy need that do not necessarily control eating (Figure 1B). Instead, as suggested by the findings of Zimmer *et al.* [10], Agrp cells may flexibly couple to self-control or social-control outputs, to increase the chances of optimal energy control. That Agrp neurons may not directly induce eating is also suggested by the earlier observations that their activity falls sharply on food discovery and before food ingestion [4–6]. This raises fundamental questions about brain control of energy balance. First, how do hypothalamic neurons predict the future? In other words, what circuits couple hypothalamic signals to cues associated with energy balance and how flexible is this coupling? The coupling between temperature and neonatal Agrp cell activity is likely to be innately hardwired [10]. Can Agrp neurons 'unlearn' this coupling? Interestingly, in adult mice the fall in Agrp cell activity caused by chocolate presentation accelerates with subsequent presentations [4], suggesting capability for learning and unlearning. Second, what neural signals drive eating? If Agrp cell activity does not directly stimulate ingestion, as suggested for adults [4] and shown in neonates [10], which neurons are responsible for ingestion? More fundamentally, what neurons/signals communicate set-point information (Figure 1A), and is a separate set point even necessary in control schemes that integrate predictive and reactive signals (Figure 1B)? The answers will require more studies involving real-time monitoring and control of activity in genetically defined neurons prior to, during, and after the act of eating. The recent refinements in genetically targetable rapid sensors and actuators of brain circuit dynamics will help to answer these fundamental questions.

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