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Previews

Transmitter Time: Synaptic Plasticity and Metabolic Memory in the Hypothalamus

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Hunger elicits feeding behavior by activating Agouti-related peptide (AgRP) neurons. Two recent studies show how fasting, or the hunger hormone ghrelin, promote excitatory glutamate release onto AgRP neurons (Yang et al., 2011) and increase postsynaptic glutamate receptor-mediated drive (Liu et al., 2012).

Adipocyte-derived leptin reciprocally inhibits AgRP and activates prooioimelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (ARH), and increases the activity of inhibitory GABAergic synapses onto POMC neurons, to control energy homeostasis in a negative feedback manner. Agouti-related peptide (AgRP) neurons express GABA, and some of them establish inhibitory synapses onto POMC neurons (Cowley et al., 2001; Vong et al., 2011). AgRP neurons also express neuropeptide Y (NPY) and project to the same target sites as POMC neurons, where POMC and AgRP neurons act antagonistically on energy balance. Thus, AgRP neurons inhibit POMC neurons in the ARH and oppose POMC neurons at target sites. Since the initial discovery of leptin, most studies of its mechanism of action have focused on regulation of neuropeptide production. However, it has been recently suggested that fast synaptic transmission plays a crucial role in the central control of energy balance.

Two studies published in *Cell* and *Neuron* report that the excitatory synaptic control of AgRP neurons, but not POMC neurons, is dynamically regulated by fasting and hormones and that increased glutamate action is necessary for a normal response to fasting (Liu et al., 2012; Yang et al., 2011). Yang and colleagues showed that presynaptic glutamate release onto AgRP neurons in mice is enhanced in fasted states, mimicked by ghrelin, and mediated via an AMP-activated protein kinase (AMPK)-dependent feedback loop that can be reversed by opioids released from leptin-activated POMC neurons (Yang et al., 2011). These signaling pathways are proposed to provide the glutamatergic terminals with synaptic plasticity and a metabolic memory of energy status. In the current issue of *Neuron*, Liu and colleagues describe a critical role for postsynaptic NMDA receptors in synaptic plasticity of AgRP neurons (Liu et al., 2012). They showed that inhibition of NMDA receptor function in AgRP neurons by deletion of the NR1 subunit in mice led to reduced synaptogenesis, spinogenesis, and excitatory tone of glutamatergic terminals impinging on these neurons. Furthermore, AgRP neurons lacking functional NMDA receptors failed to respond to fasting, indicating that the integrity of both pre- and postsynaptic glutamatergic sites is required for storage, retrieval, and functional use of metabolic memory by AgRP neurons.

These significant studies describe a further layer of control of AgRP neuronal activity and emphasize the critical importance of glutamatergic control of AgRP neurons. They identify a new site for controlling energy balance and further establish synaptic plasticity as a key factor in determining how energy status signals are integrated and contribute to coordinating appropriate behavioral responses at the level of the hypothalamic circuitry (Figure 1). Interestingly, the lack of effect of fasting on AgRP neuronal activity in AgRP-specific NMDA-R KO mice suggests that none of the energy balance signals, including leptin, ghrelin, glucose, or insulin, have any impact on the activity of AgRP neurons if the neurons do not express functional NMDA receptors. A possible explanation could be that these signals may only work in the face of adequate excitatory tone or require the integrity of an ''intact'' functional circuitry. Alternatively, signaling pathways activated by ghrelin, leptin, glucose, and insulin via specific receptors expressed on AgRP neurons may influence alternative cell functions—for example, protein synthesis to support neurosecretory and synaptic activity.

Work from both groups revealed increased presynaptic release of glutamate onto AgRP neurons in fasted animals leading to increased frequency of AMPA receptor-mediated synaptic events. Additionally, Liu et al. reported increased postsynaptic glutamate receptors, which support observations made by Pinto et al. (2004). Functional NMDA receptors are comprised of NR1 subunits, essential for ion channel pore formation and binding of ligands that modulate NMDA receptor function, and one or more NR2 subunits (NR2A, B, C, and D) which bind glutamate, determine receptor characteristics, and are key sites for modulation of receptor function and synaptic plasticity. Thus removing NR1 effectively knocks out all functional pore-forming NMDA receptors, including those containing NR2 subunits. We need to understand more about the role of the NR2 subunits in AgRP neurons, the relative contribution of non-NMDA and NMDA receptors to normal synaptic transmission and synaptic plasticity, and postsynaptic parameters such as membrane properties and postsynaptic active conductances to interpret the effect of changes in presynaptic activity on AgRP neuron activity.

An important question raised by these two studies is the source of the excitatory inputs to AgRP neurons and the source of the inhibitory inputs to POMC neurons,

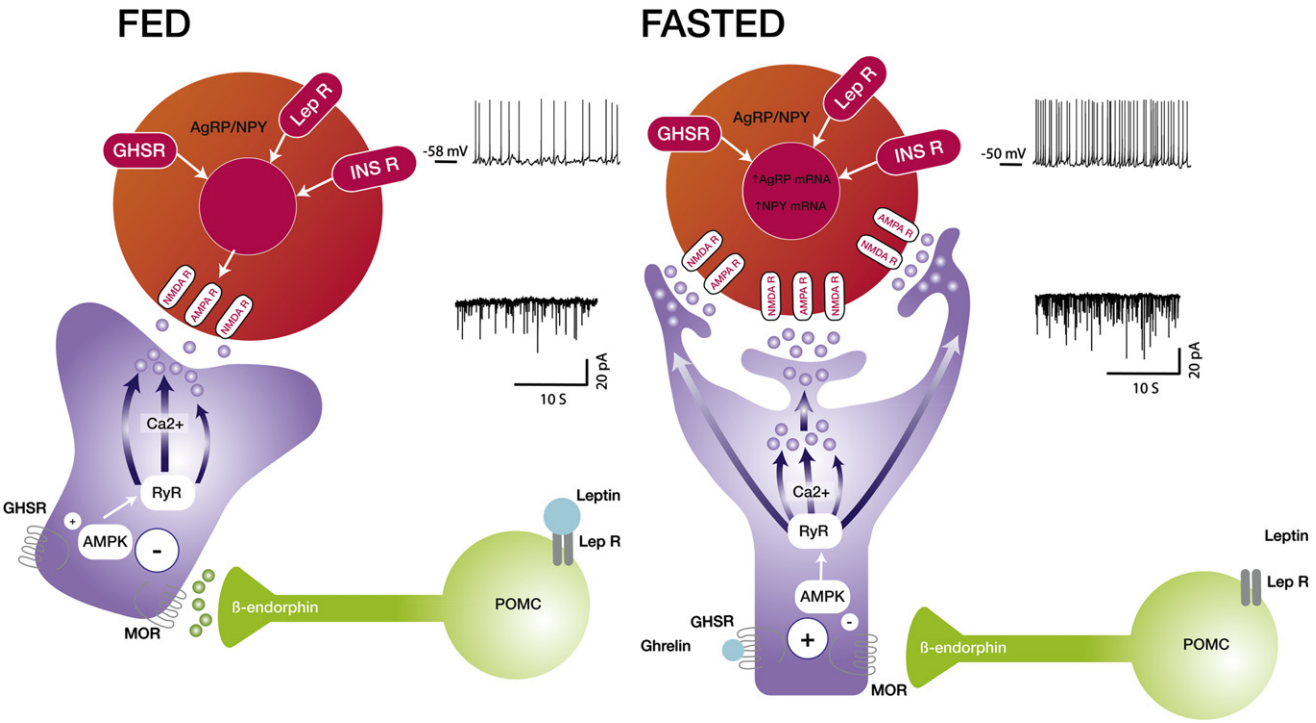

Figure 1. Control of Excitatory Tone onto AgRP Neurons

AgRP neurons receive direct glutamatergic inputs via non-NMDA (AMPA) and NMDA receptors. In the fed state (left panel), high levels of leptin activate POMC neurons promoting opioid release onto these glutamatergic terminals, effectively inhibiting presynaptic glutamate release (lower electrophysiological trace in left panel), via axo-axonic contacts and mu opioid receptors (MOR), leaving the neuron relatively hyperpolarized and firing action potentials at a low frequency (upper electrophysiological trace in left panel). In the fasted state (right panel), high levels of ghrelin enhance growth hormone secretagogue receptor (GHSR)-mediated glutamate release from the presynaptic terminals concomitant with reduced opioid-mediated influence due to low leptin levels. This leads to increased glutamate release onto the AgRP neurons (lower electrophysiological trace on right side of figure), depolarization, and increased frequency of action potential in the AgRP neurons (upper electrophysiological trace, right panel). These changes in presynaptic glutamate release are coordinated via an AMPkinase and ryanodine receptor dependent intracellular calcium-stores (RyR) pathway and associated with increased synapto- and spinogenesis that requires functional postsynaptic NMDA receptors in AgRP neurons. The integrity of this synaptic pathway is required for the storage, retrieval, and functional use of metabolic memory proposed stored in these terminals. Elements of this figure are reprinted with permission of Liu et al. (2012).

which may represent new sites of energy balance regulation. Sternson's earlier work using glutamate uncaging did not identify a major population of excitatory inputs onto AgRP neurons (Sternson et al., 2005), and a recent study from the Lowell lab revealed that only 15% of the GABA input to POMC neurons arises from AgRP neurons (Vong et al., 2011). Presently, the origins of these excitatory inputs to AgRP neurons remain unclear.

A recent series of papers describes that resistance to leptin hypophagic effects is associated with increased glia and astrocytes in the arcuate nucleus, a process termed "gliosis" (Horvath et al., 2010). Increased glia ensheathment has been proposed to impair the ability of AgRP and POMC neurons to receive appropriate synaptic inputs and to isolate them from endocrine signals of energy state. It will be important to determine whether obesity and increased gliosis influence the ability to form new spines and excitatory synapses onto AgRP neurons. It will also be important to determine if leptin resistance changes the effect of leptin on POMC neurons or opioids on presynaptic glutamatergic sites, and prevents "resetting" of the excitatory presynaptic signaling onto AgRP neurons—leading to continued excitatory tone on AgRP neurons.

Although it is unlikely that a single synapse is the site of our body weight "settling point," these significant papers provide new insights into the function of key components of a major circuit controlling energy homeostasis, and further highlight a role for synaptic plasticity in the control of energy balance. Both studies pave the way for future investigation to understand where the presynaptic inputs come from, how the intact circuit and its component parts operate and respond to changes in energy status, and how obesity modifies the activity of these newly identified synapses.

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