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Preview

Oscillating from Neurosecretion to Multitasking Dopamine Neurons

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In this issue of *Cell Reports*, Stagkourakis et al. (2016) report that oscillating hypothalamic TIDA neurons, previously thought to be simple neurosecretory neurons controlling pituitary prolactin secretion, control dopamine output via autoregulatory mechanisms and thus could potentially regulate other physiologically important hypothalamic neuronal circuits.

The brain contains multiple dopaminergic systems involved in the regulation of critical processes including pleasure and reward, movement, memory and learning, and neuroendocrine control of hormone secretion. Unbalanced dopamine output contributes to many neurological disorders and impairs fertility, and research on regulatory mechanisms controlling dopamine output is essential for understanding these pathophysiological conditions. In particular, it is important to understand both the similarities and differences between different dopaminergic projections in order to fully appreciate the impact of pharmacological manipulation of dopamine systems in the treatment of these disorders. In this issue of *Cell Reports*, Stagkourakis et al. (2016) provide novel insight into a specific dopamine population, the tuberoinfundibular dopamine (TIDA) neurons of the hypothalamus.

This group has previously demonstrated that TIDA cells have a unique oscillating pattern of activity that is synchronized within the population (Lyons et al., 2010). Functionally, they are well characterized as neurosecretory neurons involved in the control of prolactin secretion from the pituitary gland and, as such, have been thought to have properties quite different from most of the other dopamine systems. In particular, given that dopamine was thought to be removed from the site of secretion by the pituitary portal blood, they were thought to lack the dopamine reuptake and autoregulatory feedback system (Demarest and Moore, 1979) that is characteristic of other dopamine neurons. Instead, they were thought to be controlled by a short feedback loop based on pituitary prolactin secretion (Advis et al., 1977) (Figure 1A). The data presented by Stagkourakis et al. (2016) demonstrate that this perception was not completely accurate, and, in doing so, they open up significant new insights into the regulation and potential function of this physiologically relevant and intriguing dopamine population.

TIDA neurons are unique among hypothalamic hormone-producing neurons. They produce a catecholamine neurotransmitter, dopamine, instead of a peptide hormone-releasing or inhibitory factor, such as growth hormone-releasing hormone (GHRH) or thyrotropin-releasing hormone (TRH). Nonetheless, they are considered an archetypal hypothalamic neurosecretory neuron that releases a hormone into the pituitary portal blood—a classical example of the neuroendocrine systems first envisioned by Geoffrey Harris over 60 years ago (Grattan, 2015). However, in recent years, the notion of the "simple" neurosecretory neuron is gradually giving way to the idea that these cells have much broader complexity than first imagined. Thus, oxytocin and vasopressin neurons, the heart of the neurosecretory machinery of the posterior pituitary gland, were discovered to also secrete hormones within the brain from their dendrites in a manner that is independent of the action potential-driven secretion of oxytocin from their nerve terminals into the blood (Ludwig et al., 2002). Moreover, gonadotropin-releasing hormone neurons were found to lack classical axons, with the signal transmission function controlling release of this hormone in the median eminence being subsumed into an integrated dendrite and axon, termed a dendron (Herde et al., 2013). Stagkourakis et al. (2016) now provide convincing evidence for autoregulatory control mechanisms in TIDA neurons that further the perception that these dopamine neurons are also more complex than original descriptions suggest. Such autoregulation would not be required for a simple neuroendocrine function involving secretion to regulate the pituitary gland. Indeed, evidence is emerging that these uniquely oscillating dopamine neurons also project locally within the arcuate nucleus (Zhang and van den Pol, 2015) as well as to the median eminence and could be a part of integrated hypothalamic circuits. Hence, in addition to their established role in the control of prolactin secretion, these hypothalamic dopamine neurons might in fact be "multitasking neurons" that are involved in regulating a number of functions (Figure 1B).

The studies published in the present issue provide additional insights into the regulatory mechanism controlling the dopamine outputs from cells. Building on earlier work from this group (Lyons et al., 2010), they have now demonstrated that locally released dopamine regulates the pattern of oscillations in these dopamine neurons. This observation electrophysiologically confirms the capability of autoregulatory feedback. Importantly, however, such non-synaptic release of dopamine within the arcuate nucleus

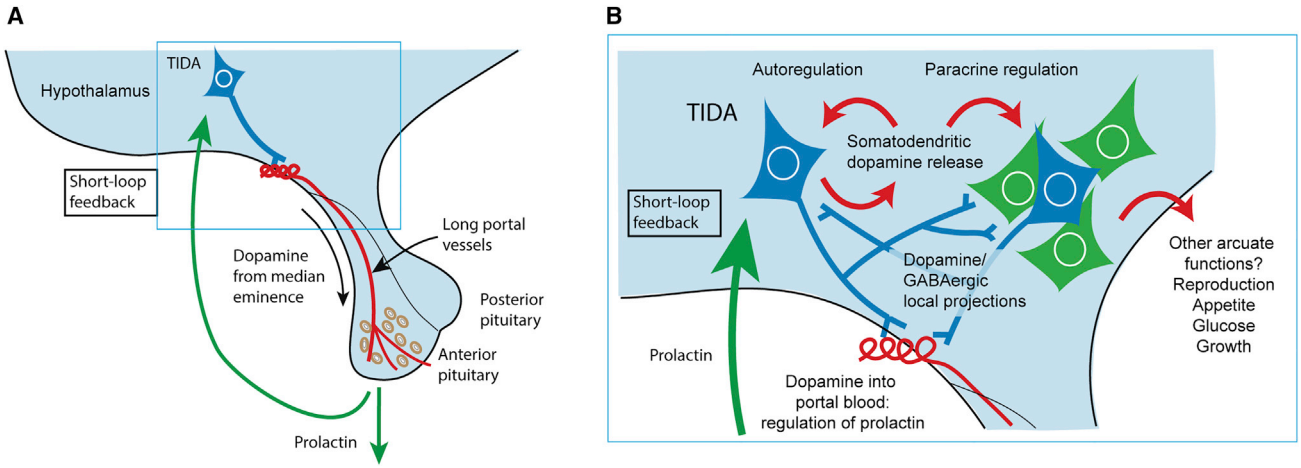

Figure 1. Hypothalamic Neuronal Circuitries with TIDA Neurons

The diagram shows our evolving understanding of the regulation and functions of the tuberoinfundibular dopamine (TIDA) neurons.

(A) Then: "neurosecretory" neurons. Classically, these neurons had a well-defined endocrine neurosecretory role involved in the control of prolactin secretion and were controlled by prolactin levels in the blood through a short feedback loop.

(B) Now: "multitasking" neuronal networks. New insights suggest a multitasking neuronal network, with local somatodentritic release of dopamine having an autoregulatory feedback on the cells producing it and also influencing adjacent neurons. In addition, axonal branching allows synaptic release of GABA (and potentially dopamine) to regulate both the dopamine neurons themselves and other non-dopamine neurons in the arcuate nucleus.

would not be limited to affecting the cells themselves but could also act on neighboring cells. Stagkourakis et al. (2016) beautifully described this as dopamine neurons being able to "tune network behavior to echoes of their own activity reflected in ambient somatodendritic dopamine." If we add these observations to recent evidence that optogenetic activation of TIDA neurons resulted in synaptic release of GABA onto both dopamine and non-dopamine neurons in the arcuate nucleus (Zhang and van den Pol, 2015), then a picture emerges of a complex multitasking neuron capable of regulating multiple systems, potentially including appetite, growth, and reproduction neuronal circuitries, located within the arcuate nucleus (Figure 1B). What are the possible future directions for research on regulation of dopamine output from TIDA neurons and generally in other neuronal circuits? The effect of prolactin to stimulate the synthesis and release of dopamine from TIDA neurons is well established (Grattan, 2015). It implies that prolactin could contribute to autoreceptor-mediated regulation of dopamine output and, as a consequence, regulation of adjacent neuronal circuits. This is a worthy research direction given that mechanisms controlling activation of TIDA neurons by prolactin (Lyons et al., 2012) and that crosstalk between prolactin and oxytocin (Briffaud et al., 2015) are not fully understood.

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