This Week in The Journal

Leptin Enhances Striatal Dopamine Release via Acetylcholine

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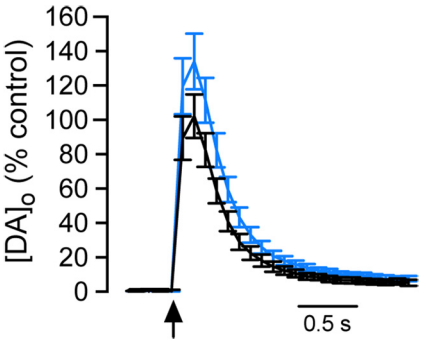
(see pages 6668–6679)

The hormone leptin is released by adipocytes in proportion to the amount of stored fat, and it acts in the brain to regulate food intake and energy expenditure. The rewarding value of food is one motivator of food consumption, and consequently, one target of leptin is the reward circuitry. Leptin receptors are expressed by dopaminergic neurons in the ventral tegmental area (VTA), which signal the presence of reward, and injecting leptin into the VTA reduces the activity of these neurons while reducing food intake. Conversely, knocking down VTA leptin receptors increases food intake. Unexpectedly, however, extracellular levels of dopamine in the striatum, a major target of VTA dopaminergic neurons, are reduced in leptin-deficient mice. Consistent with this, Mancini et al. show that leptin increases evoked dopamine release in mouse striatal brain slices.

Treating slices with leptin increased extracellular dopamine concentrations after electrical stimulation in all three major subdivisions of the striatum: the dorsal striatum, the nucleus accumbens (NAc) core and the NAc shell. This increase occurred despite increased dopamine uptake, indicating that it was mediated by a large increase in dopamine release. Importantly, leptin receptors were found in striatal cholinergic neurons, and leptin-induced dopamine release was prevented by a selective antagonist of $\beta 2$-subunit-containing nicotinic acetylcholine receptors ($\beta 2$*nAChRs), which have previously been shown to regulate dopamine release in the striatum. Furthermore, leptin did not increase dopamine release in mice lacking an enzyme critical for synthesizing acetylcholine. Additional experiments showed that leptin-induced increases in dopamine release in all three striatal areas required activation of phosphoinositide 3-kinase and release of calcium from intracellular stores. But the activation of protein kinase C, Akt, ryanodine receptors, and NMDA receptors was required only in the NAc shell.

These results suggest that leptin enhances acetylcholine release from striatal cholinergic interneurons, leading to activation of $\beta 2$*nAChRs on dopaminergic terminals, which increases dopamine release. Thus, leptin may increase dopamine levels in the striatum despite reducing spiking of VTA dopamine neurons. Dopamine exerts different effects in the striatum depending on whether it is released tonically or phasically. Therefore, leptin actions in VTA and striatum might work together to reduce motivation to eat by enhancing tonic dopamine release and reducing phasic release.



Electrically evoked dopamine release in the dorsal striatum results in greater extracellular dopamine concentration ($[DA]_o$) when leptin is present (blue) than when it is not (black). See Mancini et al. for details.

Timing of Input Regulates Plasticity of Electrical Synapses

Daniel R. Kick and David J. Schulz

(see pages 6751–6760)

Electrical synapses have diverse effects on neural circuit function throughout the brain. For example, by allowing ionic currents to pass between neurons, electrical synapses can reduce input resistance, and thus reduce excitability. But this effect is diminished if electrically coupled neurons receive simultaneous input; in this case, neuronal excitability is increased, which can lead to bursting. The impact of such effects depends on the strength of electrical coupling, which can be altered by neuromodulators. Intriguingly, Kick and Schulz report that coupling strength can also increase or decrease depending on how closely in time the coupled neurons are depolarized.

The authors focused on electrical synapses between motor neurons in the cardiac ganglion of crabs. Electrical coupling helps ensure these neurons fire synchronously to cause proper contraction of the heart. Blocking potassium channels depolarizes the neurons, leading to elevated and desynchronized spiking. Eventually, however, the network becomes resynchronized, in part through long-term potentiation of electrical synapses (eLTP). To determine whether this eLTP requires depolarization, desynchronization, or both, Kick and Schulz mimicked the effects of potassium channel blockers with direct injection of depolarizing current steps. Depolarizing the neurons asynchronously led to a rapid reduction in coupling resistance, indicative of increased coupling strength or eLTP, whereas depolarizing the neurons synchronously did not affect coupling strength. The effect of asynchronous depolarization was blocked in the presence of cadmium, indicating that it required calcium influx. When naturalistic waveforms were used instead of step currents to depolarize cells, asynchronous stimulation again reduced coupling resistance, but only if the cells were stimulated within 0.5 s of each other. When cells were stimulated ~1 s apart, coupling resistance increased, indicative of long-term depression (eLTD). Whether eLTP or eLTD was produced at a given stimulation delay also depended partly on the amplitude of depolarization.

These results indicate that asynchronous depolarization of two coupled neurons can increase or decrease coupling strength, depending on how great the asynchrony is. The authors propose that the induction of eLTP by slightly asynchronous depolarization may help to resynchronize neurons that have drifted apart, whereas induction of eLTD by larger asynchrony may serve to decouple a damaged cell from a circuit, so the abnormal spike pattern doesn't spread to other nuerons..

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