This Week in The Journal

Glucose Activates Sleep-Inducing Neurons

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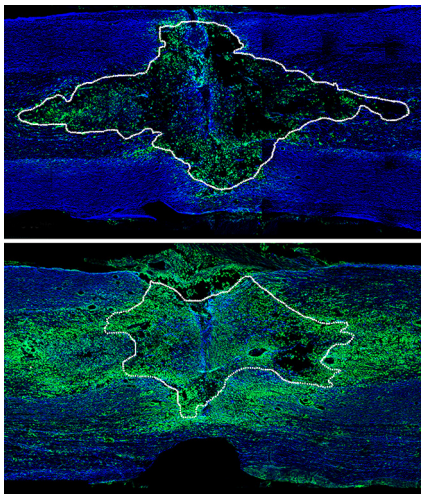
(see pages 9900–9911)

Sleep and arousal are controlled by reciprocally inhibitory populations of sleep-active and wake-active neurons that are located in multiple brain regions. Just before the onset of slow-wave sleep (SWS), GABAergic neurons in the ventrolateral preoptic nucleus (VLPO) become active, and their firing rate is correlated with the depth and duration of SWS. These neurons inhibit wake-active neurons in other areas, including cholinergic neurons in the mesopontine region, orexinergic neurons in the hypothalamus, and noradrenergic neurons in the locus ceruleus. When neurons in these regions become active, they cause arousal, and the cholinergic and noradrenergic neurons inhibit VLPO neurons. Which of these populations are active or inhibited at a given time is determined largely by circadian cues and metabolic indicators. For example, ATP metabolism leads to the gradual accumulation of adenosine, which activates sleep-active VLPO neurons and inhibits various wake-active neurons. Glucose similarly regulates transitions between sleep and wakefulness by inhibiting orexinergic neurons and—as now reported by Varin et al.—activating VLPO neurons.

When injected into mouse VLPO, glucose caused neuronal activation, reduced the latency to SWS, and increased SWS duration. Increasing glucose levels in brain slices depolarized the resting membrane potential and increased the firing rate of putative sleep-active VLPO neurons. These effects required glucose to be metabolized by neurons, and they appeared to result from regulation of potassium channels. Indeed, blocking ATP-sensitive potassium (K_{ATP}) channels reduced holding currents at −65 mV when extracellular glucose levels were low, but not when glucose levels were high. Furthermore, an exogenous activator of K_{ATP} channels induced a larger outward current when glucose levels were high than when they were low.

All together, the data suggest that glucose is taken up and metabolized to generate ATP in VLPO neurons. The increase in ATP leads to closure of K_{ATP} channels, depolarization of the resting membrane potential, and increased spiking. These effects, together with glucose-dependent inhibition of orexinergic neurons, likely contribute to the urge to sleep after eating a large meal. Perhaps more importantly, when glucose levels drop, K_{ATP} channels open, causing VLPO neurons to stop firing. At the same time, orexinergic neurons become active and induce arousal, so the animal gets up to search for food.



When a TLR2 agonist was injected into the spinal cord 2 d after spinal crush injury (bottom), macrophages (green) became activated and the lesion area (indicated by white line) was smaller than in controls (top). Blue labels glial fibrillary acidic protein. See Gensel et al. for details.

Zymosan Helps and Hurts Neurons via Different Receptors

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(see pages 9966–9976)

Damaged cells release molecules that activate macrophages via various pattern-recognition receptors (PRRs). Depending on which PRRs are activated, macrophages can acquire different functional phenotypes that either enhance repair or exacerbate damage. After spinal cord injury, for example, some macrophages facilitate recovery by clearing cellular debris and releasing growth factors, while others inhibit recovery by inducing axonal retraction and secreting molecules that inhibit axon growth. Gensel et al. (2009 J Neurosci 29:3956) previously showed that when spinal cord macrophages were activated by zymosan, a component of yeast cell walls, they promoted growth of distant axons—possibly by inducing astrocytes to secrete neurotrophic factors—but also killed nearby neurons, possibly by secreting neurotoxic factors. Now Gensel et al. present evidence that zymosan exerts opposing effects by binding to different macrophage PRRs: specifically, toll-like receptor 2 (TLR2) and the C-type lectin receptor dectin-1.

Injecting a selective dectin-1 agonist into intact rat spinal cord led to macrophage activation accompanied by extensive loss of axons and myelin. In contrast, injecting a selective TLR2 agonist induced macrophage activation with minimal axonal loss. When the two agonists were injected together, the TLR2 agonist mitigated the damaging effects of the dectin-1 agonist. In addition, medium conditioned by macrophages that had been activated via TLR2 increased the survival rate of cultured dorsal root ganglion neurons, suggesting that when macrophages are activated by TLR2 they secrete pro-survival molecules.

The opposing effects of dectin-1-mediated and TLR2-mediated macrophage activation were further demonstrated after spinal crush injury in mice. Axonal dieback after injury was significantly reduced in dectin-1-deficient mice compared to controls. A TLR2-specific agonist reduced axonal dieback in wild-type mice when it was injected into the spinal cord 2 days after injury. These data support the hypothesis that macrophage activation can be experimentally manipulated to enhance recovery and minimize damage. Such manipulations may eventually become part of combination therapies to improve functional recovery after spinal cord injury. Elaborating the signaling pathways activated downstream of dectin-1 and TLR2 may uncover additional targets that allow researchers to steer macrophages toward beneficial phenotypes.

This Week in The Journal is written by Teresa Esch, Ph.D.