This Week in The Journal

Orexin Enhances Afterhyperpolarization in Serotonin Neurons

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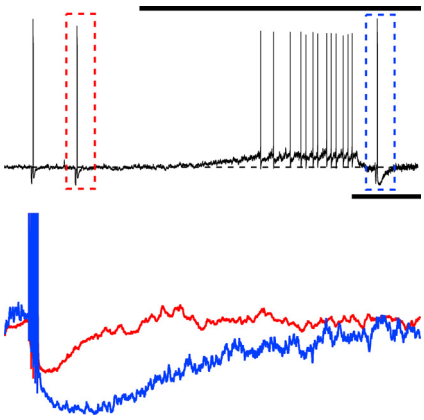
(see pages 10097–10115)

Serotonin and orexins regulate many of the same behaviors, including sleep, feeding, and reward-seeking, and orexins influence serotonin release via projections to the dorsal raphe (DR) nuclei. Like in many other neurons, orexins depolarize and increase tonic firing in DR serotonergic neurons by activating nonselective cation channels. In some neurons, including noradrenergic locus ceruleus neurons and paraventricular thalamic neurons, orexins also shape activity by reducing the spike afterhyperpolarization (AHP) (Leonard and Kukkonen 2014 Br J Pharmacol 171:294). Surprisingly, however, Ishibashi et al. report that orexin-A exerts the opposite effect—enhancing the AHP—in DR serotonergic neurons.

In the absence of orexin, DR serotonergic neurons in mouse brain slices exhibited an AHP of medium duration. Orexin-A increased the amplitude and duration of this AHP by enhancing the medium-duration current (I_{mAHP}) and activating an additional, longer-lasting potassium current (I_{sAHP}). As in other neurons, I_{mAHP} was carried by small-conductance calcium-activated potassium (SK) channels, whereas the channels underlying I_{sAHP} could not be determined. Orexin-dependent regulation of these channels required activation of phospholipase C and influx of calcium, but unlike orexin-induced inhibition of the AHP in other neurons, it did not involve activation of protein kinase A or C. Enhancement of I_{mAHP}, but not induction of I_{sAHP}, also required inhibition of a subthreshold potassium current, activation of ryanodine receptors, and release of calcium from internal stores.

As expected, orexin-induced enhancement of the AHP affected spiking in DR serotonergic neurons. Specifically, it restrained the increase in spike rate and variability resulting from orexin-induced depolarization. Furthermore, AHP enhancement increased spike-frequency adaptation occurring during long current steps. Finally, by enhancing the AHP, orexin-A decreased the fidelity of spiking in response to trains of depolarizing current pulses.

Together, these results demonstrate that orexin-A enhances the AHP in DR serotonergic neurons by enhancing the SK current and activating an I_{sAHP}. These results further expand the long, diverse list of orexin effects. The increase in spike-frequency adaptation and reduced fidelity during repetitive spiking resulting from AHP enhancement is likely to reduce the influence of tonic inputs and thus increase the influence of phasic inputs to serotonergic neurons. Thus, orexin-A may make serotonergic neurons more responsive to transient environmental inputs signaling rewards, including food.



Orexin-A application (black bar above top panel) depolarized serotonergic neurons and increased tonic spiking. It also increased the AHP produced with a 5-spike train (red and blue boxes in top panel, enlarged in bottom panel). Current was injected during black bar below top panel to bring membrane potential to baseline. See Ishibashi et al. for details.

ACC Represents Effort-Discounted Reward Value

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(see pages 10002–10015)

When making choices, people typically consider not only the desirability of the options, but also how much effort will be required to obtain them. When the most desirable option requires considerably more effort than other options, people often choose a less desirable option. Previous work has suggested that brain areas involved in motor planning—including the supplemental motor area (SMA), putamen, and anterior cingulate cortex (ACC)—are active when individuals make decisions that require an assessment of relative effort. Whether and how these structures combine reward desirability and required effort into a single subjective value when evaluating options has been unclear, however.

To address this question, Klein-Flügge used functional magnetic resonance imaging to record brain activity as human subjects chose between two options that differed in both reward magnitude and effort required. They first looked for brain areas that independently encoded differences in the options' reward size and effort requirements. Only two areas encoded the two dimensions independently: the SMA and the caudal portion of the dorsal ACC. The authors then searched for areas that reflected the subjective value of the chosen option based on a previously developed behavioral model of how effort modulates value in each participant. This again identified SMA and the caudal portion of the dorsal ACC, as well as the putamen. Finally, they looked for areas that were most active in participants who most consistently chose the option with the highest model-predicted subjective value. Only the caudal portion of the dorsal ACC was identified in this analysis.

This work suggests that the caudal part of the dorsal ACC not only encodes reward magnitude and effort costs, but also combines these measures into a single subjective value that is used during decision making. Notably, activity in ventromedial prefrontal cortex—an area thought to be involved in making decisions between options that are risky or involve temporal delays—did not reflect the subjective value of options weighted by effort cost. Thus, these results add to increasing evidence that different cortical areas are involved in making decisions that require different types of cost–benefit analysis.

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