This Week in The Journal

TRPM4-Based Plateau Potentials in Thalamic Reticular Nucleus

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(see pages 4813–4823)

During slow-wave sleep, thalamic and cortical neurons coordinately oscillate between depolarized UP states and hyperpolarized DOWN states. Although this rhythm is shaped by neurons in both areas, similar oscillatory activity can be generated in either area independently. When the thalamus is isolated, for example, tonic activation of metabotropic glutamate receptors (mGluRs) causes neurons in sensory relay nuclei and the thalamic reticular nucleus (TRN) to oscillate in the absence of rhythmic input. These oscillations depend on the closure of potassium leak currents, the opening of T-type low-threshold calcium channels, and the activation of calcium-dependent cation currents (I_{CAN}). O'Malley et al. now describe another type of oscillatory activity that occurs in TRN neurons in thalamic slices in the absence of exogenous stimulation.

Using loose-patch recordings, the authors found that ~36% of TRN neurons exhibited rhythmic activity involving persistent firing. The oscillation frequency was ~0.5 Hz: similar to the frequency of slow oscillations *in vivo*. The oscillations began with brief bursts of AMPAergic EPSPs, which led to the generation of a plateau potential lasting >200 ms. Similar activity could be induced by brief current injection when AMPA receptors were blocked. And blocking small-conductance calcium-activated potassium channels greatly increased the fraction of TRN neurons exhibiting this type of oscillation.

Like previously described thalamic oscillations, oscillations with persistent firing required activation of T-type calcium channels. In contrast, mGluRs were not required. Blocking voltage-gated sodium channels prevented spiking, but it had minimal effects on the underlying plateau potential. Nonetheless, generation of the plateau potential required extracellular sodium. The requirement for both T-channels and extracellular sodium suggested that generation of the plateau potential depends on I_{CAN} . Application

of various TRP channel blockers suggested that TRPM4 underlies this current.

These data suggest that activation of AMPA receptors in TRN neurons leads to activation of T-type calcium channels and downstream activation of TRPM4 channels. This leads to the generation of a long-lasting plateau potential during which persistent firing occurs. Additional experiments indicated that the generation of persistent spiking is regulated biphasically by nicotinic and muscarinic acetylcholine receptors. The conditions under which plateau potentials occur in TRN neurons *in vivo*, how they contribute to thalamocortical oscillations, and whether TRPM4 channels contribute to other forms of thalamic activity remain to be determined.

High-frequency stimulation of MeApv axons (green) in the BNST potentiated synapses and increased the number of attacks mice initiated in subsequent encounters. See Nordman et al. for details.

Amygdala Projections Underlying Escalating Aggression

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(see pages 4858–4880)

Aggression is used throughout the animal kingdom to acquire or defend food, territory, mates, and offspring. The likelihood that an individual will engage in aggression depends partly on experience. In rodents, for example, previous victory during an aggressive encounter increases the likelihood of future aggression—a phenomenon called aggression priming. Traumatic experience can also increase aggression. These

effects are likely mediated in part by plasticity in circuits involving the posterior ventral segment of the medial amygdala (MeApv). This area is activated during aggression, and high-frequency stimulation of the area increases subsequent aggression in mice. Nordman et al. have now uncovered the roles of specific MeApv projections in the escalation of aggression.

Consistent with previous work, high-frequency stimulation of channelrhodopsin-expressing MeApv neurons increased the number and duration of attacks later engaged in by male mice. These effects were replicated by high-frequency stimulation of MeApv axons in the ventromedial nucleus of the hypothalamus (VmH). Stimulation of projections to the bed nucleus of the stria terminalis (BNST) also increased the number of future attacks, but it did not affect attack duration. Notably, selectively inhibiting MeApv–VmH projections while stimulating MeApv prevented increases in the duration of attacks, while inhibiting MeApv–BNST projections prevented increases in the number of attacks. In contrast, activating MeApv projections to two other areas implicated in aggression—the medial preoptic nucleus and the lateral septum—had no effect on subsequent aggression.

At the cellular level, high-frequency stimulation of MeApv potentiated synapses between MeApv axons and neurons in VmH and BNST. Importantly, these synapses were also potentiated after mice engaged in attacks that led to aggression priming and after mice were subjected to footshock-induced traumatic stress. Moreover, low-frequency stimulation of MeApv immediately after an aggressive or traumatic experience prevented both synaptic potentiation and increases in subsequent aggression.

These results suggest that aggressive or traumatic experience increases the number of future attacks by potentiating synapses between MeApv and BNST and increases the duration of future attacks by potentiating synapses between MeApv and VmH. Weakening these synapses might therefore help reduce uncontrollable aggression in people who suffer from that manifestation of post-traumatic stress disorder.

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