This Week in The Journal

Adenosine and Weight-Dependent Synaptic Plasticity

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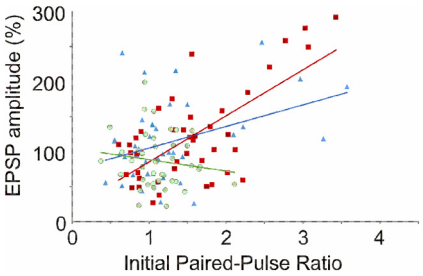
(see pages 1439–1452)

Associative learning is thought to be mediated by Hebbian plasticity: when presynaptic spikes are immediately followed by postsynaptic spikes, the synapse is strengthened, but when postsynaptic spiking occurs independently of presynaptic activity, the synapse weakens. Such positive feedback would ultimately drive all synapses to be maximally potentiated or depressed if Hebbian mechanisms were not countered by various homeostatic mechanisms. Volgushev et al. have argued that one such mechanism is weight-dependent heterosynaptic plasticity, which occurs at inactive synapses onto a spiking cell.

Previous work has shown that although paired presynaptic and postsynaptic spiking tends to produce long-term potentiation (LTP), the effects of such pairing can range from LTP to long-term depression (LTD), depending on the initial probability of neurotransmitter release: strong synapses undergo LTD while weak synapses undergo LTP. Similar weight-dependent plasticity occurs at heterosynaptic sites, and computational models have shown that this weight dependence prevents runaway Hebbian plasticity (reviewed in Chistiakova et al. Neuroscientist 20:483).

Bannon et al. now suggest that adenosine acting on A_1 receptors (A_1Rs) modulates the strength of the relationship between initial release probability and activity-dependent heterosynaptic plasticity. As shown previously, stimulation of inputs to layer 2/3 neurons in mouse visual cortical slices produced changes in EPSP amplitude at both homosynaptic and heterosynaptic sites. Furthermore, the magnitude and direction of the change was correlated with the initial paired pulse ratio (PPR), a measure of release probability. Adenosine strengthened this relationship at both homosynaptic and heterosynaptic sites, whereas an A_1R antagonist abolished the relationship at heterosynaptic sites. A computational model showed that modulating the weight dependence of heterosynaptic plasticity in this way changed the extent to which spike-timing-dependent plasticity protocols drove segregation of synaptic strengths.

These results demonstrate that weight-dependent heterosynaptic plasticity can prevent runaway synaptic dynamics inherent in Hebbian plasticity. They also suggest that by strengthening this weight dependence, adenosine limits the influence of spike timing on synaptic plasticity. This is intriguing because adenosine levels increase during neural activity and over the course of wakefulness, and high adenosine levels trigger the onset of sleep, a state in which homeostatic plasticity mechanisms are thought to be the predominant force shaping synaptic weights.



Adenosine increases the influence of initial release probability on the magnitude of heterosynaptic plasticity. The influence is strongest when adenosine is added (red squares), weaker under control conditions (blue triangles), and weakest in the presence of A_1R antagonist (green circles). See Bannon et al. for details.

Amygdala Serotonin Receptors in Neuropathic Pain

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(see pages 1378–1393)

Activity in the amygdala has a central role in protecting animals from harm: it enables animals to learn warning signs associated with painful events, and it triggers appropriate defensive actions when those signs appear. In addition, when pain is experienced, the amygdala promotes behaviors that reduce risk of further injury. These include behaviors associated with anxiety and depression.

Sensory information enters the amygdala primarily through the basolateral nucleus (BLA), which regulates activity in the central nucleus (CeA) via direct excitatory and feedforward inhibitory projections. CeA neurons, in turn, project to the brainstem and forebrain to initiate appropriate behavioral responses. Noxious stimuli can drive neural plasticity that increases excitation and/or decreases inhibition of CeA neurons, leading to increased and more irregular spiking. Consequently, CeA neurons may continue to drive pain-related behaviors in the absence of noxious stimuli (Neugebauer 2015 Handb Exp Pharmacol 227:261).

Ji et al. report that activation of type 2C serotonin receptors (5-HT_{2C}Rs) in rat BLA increases irregular spiking in CeA and promotes downstream affective and behavioral changes associated with neuropathic pain. After spinal nerve ligation, the proportion of non-GABAergic BLA neurons that expressed 5-HT_{2C}R increased. In addition, nerve ligation increased the amplitude of EPSCs evoked in CeA neurons by BLA stimulation, increased baseline and stimulation-evoked spiking in CeA neurons, and increased the receptive field size of CeA neurons. Furthermore, nerve ligation led to decreases in mechanical threshold for paw withdrawal, increases in stimulation-induced vocalization, stronger avoidance of the open arm of an elevated plus maze (an anxiety-related behavior), and reduced sucrose preference (a depression-related behavior). Remarkably, knocking down 5-HT_{2C}Rs in the BLA reversed all of these electrophysiological and behavioral effects of spinal nerve ligation. In contrast, knocking down 5-HT_{2C}Rs in CeA had no effect.

Thus, upregulation of 5-HT_{2C}Rs in non-GABAergic BLA neurons, and subsequent activation of these receptors by serotonin, appear to play prominent roles in behavioral and affective responses to neuropathic pain. Although the subpopulation of non-GABAergic BLA neurons in which 5-HT_{2C}R expression increases was not identified, neurons that excite CeA neurons are likely candidates. Targeting this pathway might therefore relieve some symptoms of neuropathic pain and other types of chronic pain.

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