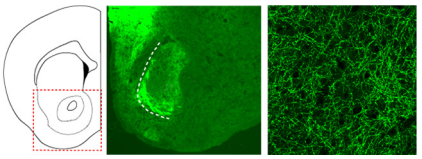
This Week in The Journal

Glutamatergic Potentiation of Cholinergic Synapses

Yan-Gang Sun, Vanessa Rupprecht, Li Zhou, Rajan Dasgupta, Frederik Seibt, et al.

(see pages 7886–7896)

Acetylcholine (ACh) signaling contributes to brain functions as diverse as learning and memory, sensory processing, and the sleep-wake cycle, but much remains unknown about how cholinergic neurons are regulated throughout the brain. This week, Sun et al. identify novel modulation of cholinergic inputs from the basal forebrain (BF) to the thalamic reticular nucleus (TRN) by ambient glutamate acting through metabotropic receptors. Recent work from the same group showed that TRN neurons display biphasic responses to ACh, which evokes excitatory postsynaptic nicotinic (nAChR)-mediated currents and inhibitory muscarinic (mAChR)-dependent responses. The researchers made whole-cell recordings from mouse TRN neurons in thalamo-cortical slices while electrically stimulating local cholinergic inputs. The glutamate transporter inhibitor TBOA, which increased extracellular levels of glutamate, rapidly and reversibly increased the amplitude of excitatory currents through nAChRs, indicating a modulatory effect of glutamate. The increase was completely blocked by antagonists for either metabotropic glutamate receptor 1 (mGluR1) or 5 (mGluR5). The augmentation persisted in the presence of an intracellular calcium chelator or an inhibitor of phospholipase C (PLC). Block of mGluR1 attenuated nAChR but not mAChR currents. To determine the source of glutamate enhancing cholinergic signaling, the researchers used an optogenetic approach. They expressed the excitatory channel rhodopsin ChR2 specifically in glutamatergic cortico-thalamic projection neurons to the TRN. Activation of those neurons resulted in enhanced cholinergic responses, indicating a role for synaptically released glutamate. An mGluR agonist produced lasting enhancement of cholinergic responses, which was mediated through postsynaptic nAChRs and not increased presynaptic ACh release. The mGluR- and nAChR-mediated long-term potentiation (mGluR-nLTP) could not be induced in mice lacking mGluR5, indicating that mGluR1 and mGluR5 work synergistically to boost cholinergic signaling. Antagonists for either receptor subtype reversed mGluR-nLTP, demonstrating that both receptors were also required for maintenance of the potentiation. Like other forms of mGluR-dependent LTP, mGluR-nLTP depended on intracellular calcium and PLC activation. Finally, the authors determined that synaptically released glutamate was only transiently increased, and that mGluR-nLTP depended on constitutive activation of mGluR1 and mGluR5 by ambient glutamate. The authors report this as the first known form of LTP at cholinergic synapses in the mammalian brain.



Fluorescently labeled inputs expressing ChR2 to the NAc from mPFC. Left drawing depicts area shown in center (4 × magnification) and right (60 × magnification). See Liu et al. for details.

Sleep Effects on Reward-Seeking Rooted in Prefrontal Cortex

Zheng Liu, Yao Wang, Li Cai, Yizhi Li, Bo Chen, et al.

(see pages 7897–7910)

Motivation for reward-seeking behavior increases with sleep deprivation, with potentially negative consequences. An imbalance in excitatory and inhibitory signaling to the nucleus accumbens (NAc) adversely affects reward-seeking behaviors, which can lead to overeating or drug abuse, for example. This week, Liu et al. trace the roots of this increase in mice to reduced glutamatergic input from the medial prefrontal cortex (mPFC) to the NAc. Following six hours of sleep deprivation, mice spent more time lever-pressing for sucrose pellets compared to control mice. When given free access to food or sucrose, sleep-deprived mice consumed more sucrose but not food than control mice, suggesting a specific effect on reward-seeking behavior. The researchers then measured excitatory currents through AMPA-type glutamate receptors and inhibitory currents through GABA receptors in medium spiny neurons (MSN) in NAc. The ratio of excitatory to inhibitory inputs fell significantly after sleep deprivation and recovered the following day. The researchers next determined whether the fall was due to a change in excitatory or inhibitory transmission mediated either pre- or postsynaptically. The excitatory (but not inhibitory) paired-pulse ratio increased following sleep deprivation, indicating that the release probability of glutamate was reduced, whereas GABA release was unaffected. Recordings of miniature excitatory and inhibitory postsynaptic potentials were unchanged by sleep deprivation, suggesting that the effect was primarily presynaptic. The frequency of minis was also unchanged, suggesting that glutamate release was decreased from only a subset of inputs. To determine which input neurons were affected—from mPFC, hippocampus, thalamus or basolateral amygdala—the researchers injected each of these areas with a virus carrying channel rhodopsin 2 (ChR2) and then optically activated the neurons to isolate projections from each area to NAc. Sleep deprivation affected glutamate release probability only from inputs from the mPFC but not the other brain areas. Using a mutant version of ChR2 called stabilized step function opsin (SSFO) that passes a persistent depolarizing current following brief light activation, the authors demonstrated that they could normalize reward-seeking behaviors altered by sleep deprivation by strengthening the inputs from mPFC. The work identifies a specific mPFC-NAc pathway that mediates the effect of sleep deprivation on reward seeking behavior.

This Week in The Journal was written by Stephani Sutherland, Ph.D.