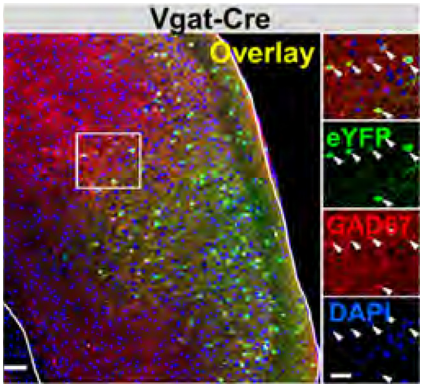
This Week in The Journal

Novel Cholecystokinin Receptor Mediates Inhibitory Potentiation

Ling He, Heng Shi, Ge Zhang, Yujie Peng, Avirup Ghosh, et al.

(see pages 2305–2325)

Cholecystokinin (CCK), the most abundant and widespread neuropeptide found in the brain, has a well established role in long-term potentiation (LTP) of excitatory circuits. But this week, He et al. explore a role for CCK in inhibitory synaptic potentiation, and in the process identify a novel CCK receptor. The researchers used CRISPR technology to create transgenic mice with CCK conditionally knocked out specifically from GABAergic neurons in the auditory cortex (AC). They then delivered an auditory stimulus (AS) while recording from AC neurons. Optogenetic laser stimulation of GABAergic neurons suppressed AC neuronal responses to AS as expected. High-frequency laser stimulation (HFLS) of GABAergic cells, which causes the corelease of GABA and CCK, potentiated this inhibition of the neuronal response to the AS, but only in mice with intact CCK. After genetically labeling either CCK- or parvalbumin (PV)-expressing interneurons, the authors recorded from pyramidal neurons in brain slices of AC and found that HFLS of CCK but not PV neurons led to potentiation of IPSCs in the pyramidal neurons, indicating that the potentiation was specific to CCK neurons. Low-frequency laser stimulation (LFLS) leads to the release of GABA but not CCK; accordingly, inhibitory LTP (iLTP) was induced by LFLS only when exogenous CCK was also applied. Surprisingly, iLTP remained intact in recordings from pyramidal neurons when both known CCK receptors, CCK1R and CCK2R, were knocked out (but not when CCK itself was knocked out), suggesting that a novel CCK receptor mediated the potentiation. The authors then used bioinformatics prediction to search for novel CCK receptors combined with a cell surface-binding assay with CCK to test candidate G-protein-coupled receptors. They identified GPR173, a novel CCK receptor. Histochemical analysis confirmed that GPR173 was found at CCK–GABAergic synapses in the AC. Further experiments confirmed that CCK-induced calcium responses were mediated by GPR173 and that GPR173 recruited β-arrestin in response to activation. GPR173, now named CCK3R, was also required for HFLS-induced iLTP. The findings further expand the role of CCK in multiple types of synaptic potentiation, in this case inhibitory LTP in the AC in mice.



Immunohistochemical labeling of eYFP, GAD67, and DAPI showing CCK interneurons in the AC of Vgat-Cre mice.

Circadian Rhythm Influences Stroke Damage via Autophagy

Haifeng Lu, Yugang Wang, Hua Fan, Yiqing Wang, Shenghao Fan, et al.

(see pages 2381–2397)

The effects of circadian rhythms are far reaching, even influencing the outcome of a stroke. Previous work had shown in rodent models that infarct volume is larger in the inactive phase—during the day for rodents—than in the active phase at night. Likewise, in human patients, the infarct core is smaller in daytime strokes than in those that happen at night. This week, Lu et al. investigate the source of circadian differences using the middle cerebral artery occlusion/reperfusion (MCAO/R) mouse model of stroke. They focused on glutamate receptors, which are a major source of neurotoxic calcium during ischemia. Mice with MCAO/R during the inactive period [zeitgeber time 5 (ZT5) to ZT7] showed a bigger infarct volume than mice operated during the active period (ZT17 to ZT19) at 24 and 72 h postocclusion. Expression of AMPA-type glutamate receptors (AMPARs) has been shown to fluctuate during the time around cerebral ischemia. The authors collected protein from the infarct penumbra and found that the AMPAR subunit GluA1 was present at lower levels in the ZT17 to ZT19 group than the ZT5 to ZT7 mice, whereas the GluA2 subunit was increased in ZT17 to ZT19 mice. The researchers then examined autophagy rates in mice with MCAO/R during active or inactive periods. Measurement of autophagy marker proteins light chain 3 and p62 indicated that autophagic activity was increased after stroke during the active phase, perhaps explaining the decrease in GluA1. The authors were able to manipulate autophagy in either direction using pharmacological tools. Increasing autophagy decreased the infarct volume of active-period stroke, and, conversely, decreased autophagy led to larger infarct volume. GluA1 levels were also lower with increased autophagy, whereas GluA2 levels were unchanged. The results were similar in mice with inactive-period stroke or sham operation. Knockdown of Atg5, an autophagy-related protein also led to decreased autophagy and a subsequent increase in GluA1 expression in both ischemic and nonischemic conditions. Disruption of the association between GluA1 and the autophagy adapter protein p62 led to a larger infarct volume, abolishing the protective effect of autophagy during active-phase stroke. Finally, knockout of the clock gene *Per1* blocked autophagy-dependent degradation of GluA1, thereby aggravating brain injury during active-phase stroke. The work provides new clarity around the mechanisms behind circadian influences on ischemic stroke.

This Week in The Journal was written by Stephani Sutherland

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