This Week in The Journal

Ca²⁺ Channel $\alpha 2\delta$ -2 Subunits Cluster GABA Receptors

Stefanie Geisler, Clemens L. Schöpf, Ruslan Stanika, Marcus Kalb, Marta Campiglio, et al.
(see pages 2581–2605)

Voltage-gated calcium channels have three auxiliary subunits ($\alpha 2\beta$, γ , and δ) in addition to the pore-forming $\alpha 1$ subunit. The auxiliary subunits can regulate channel trafficking and function, but they also appear to have additional functions. For example, recent work has suggested that $\alpha 2\delta$ subunits, which are extracellular, have roles in axon and dendrite growth and synapse formation.

To elucidate synaptic roles of $\alpha 2\delta$ subunits, Geisler et al. overexpressed individual $\alpha 2\delta$ isoforms in cultured neurons. Overexpressing $\alpha 2\delta$ -2 in a subset of cultured hippocampal neurons induced clustering of GABA_A receptors (GABA_ARs), along with the GABA_AR-anchoring protein gephyrin, in untransfected postsynaptic cells. Importantly, the presynaptic varicosities of transfected neurons contained the vesicular glutamate transporter, but not vesicular GABA transporters, indicating that GABA_ARs were inappropriately clustered near glutamatergic presynaptic terminals. Such mismatched synapses were not present in pairs of untransfected neurons in the same cultures or in cultures in which neurons overexpressed $\alpha 2\delta$ -1 or -3.

Like GABA_AR clusters apposed to GABAergic terminals, mismatched clusters were present on dendritic shafts, rather than spines; but the GABA_AR clusters at mismatched synapses were larger than those apposed to GABAergic terminals in the same cells. In contrast, postsynaptic levels of glutamatergic AMPA receptors (AMPA) were lower in mismatched synapses than in spine synapses apposed to untransfected glutamatergic terminals. Consistent with this, EPSCs evoked by stimulation of neurons overexpressing $\alpha 2\delta$ -2 were smaller than those evoked by control neurons.

Knocking out α -neurexins—presynaptic adhesion molecules that interact with postsynaptic ligands to promote synapse formation and clustering of AMPARs and GABA_ARs—also increased mismatching of postsynaptic GABA_AR clusters with presynaptic glutamatergic varicosities. Overexpressing $\alpha 2\delta$ -2 in neurons lacking α -neurexins further increased GABA_AR clustering. Intriguingly, however, overexpressing $\alpha 2\delta$ -3 in neurexin-deficient neurons reduced GABA_AR clustering to control levels.

These results suggest that elevated expression of $\alpha 2\delta$ -2 subunits in presynaptic terminals promotes formation of postsynaptic GABA_AR clusters on dendritic shafts, and this effect is reduced by α -neurexins. Additional work suggested that a particular alpha-helix domain was responsible for this effect: disrupting this helix by the inclusion of an alternatively spliced exon eliminated the GABA_AR-clustering effect. Future work should investigate postsynaptic partners of $\alpha 2\delta$ -2 and determine how the formation of mismatched synapses is normally prevented.

Varicosities (arrowheads) in axons containing normal levels of $\alpha 2\delta$ -2 (green, top) are apposed to AMPARs (red) clustered in dendritic spines, whereas varicosities in axons that overexpress $\alpha 2\delta$ -2 (green, bottom) are apposed to clusters of gephyrin (blue) and GABA_ARs on dendritic shafts. See Geisler et al. for details.

ERK-mGluR-Homer2 Interactions in BNST Affect Alcohol Intake

Rianne R. Campbell, Racquel D. Domingo, Amy R. Williams, Melissa G. Wroten, Hadley A. McGregor, et al.
(see pages 2745–2761)

The bed nucleus of the stria terminalis (BNST) is a collection of nuclei involved

in anxiety- and stress-related behaviors, as well as reward processing. As such, it is thought to have an important role in habitual drug use and addiction. This role might depend partially on plasticity of glutamatergic signaling mediated by NMDA and metabotropic glutamate receptors (mGluRs). Indeed, such plasticity occurs in response to alcohol exposure.

Campbell et al. hypothesized that the effects of alcohol on glutamatergic synapses in BNST might be similar to those in the nucleus accumbens, where alcohol-induced activation of extracellular-signal-regulated kinase (ERK) leads to phosphorylation of mGluR5, thus promoting mGluR5 interactions with the scaffolding protein Homer2. This facilitates mGluR5-dependent potentiation of NMDAR currents. Consistent with this hypothesis, after mice engaged in voluntary alcohol consumption during 2 h binges, ERK activation and Homer2 expression were elevated in BNST. Furthermore, inhibiting ERK activation in BNST, preventing ERK-mediated phosphorylation of mGluR5, or disrupting Homer2b-dependent scaffolds increased alcohol consumption during binges. Finally, injection of alcohol at a dose high enough to induce conditioned place aversion in wild-type mice induced conditioned place preference after ERK activation was inhibited in BNST or when ERK-mediated phosphorylation of mGluR5 was prevented.

These results suggest that binge-like alcohol consumption leads to ERK activation and phosphorylation of mGluR5 in BNST, thus increasing mGluR5 interactions with the Homer2b scaffold, and likely potentiating NMDAR currents. This signaling appears to limit subsequent alcohol consumption by inducing an aversive affective state. Thus, disruption of this signaling might set the stage for excessive alcohol use and dependence. Because the BNST is a complex structure with multiple subnuclei and cell types with different projection patterns, future work should determine which cells and circuits are responsible for the effects observed in this study.

This Week in The Journal was written by Teresa Esch, Ph.D.
<https://doi.org/10.1523/JNEUROSCI.twij.39.14.2019>