# This Week in The Journal

## NPY Y2 Receptors Reduce GABA Release in Amygdala

James P. Mackay, Maria Bompolaki, M. Regina DeJoseph, Sheldon D. Michaelson, Janice H. Urban, et al.

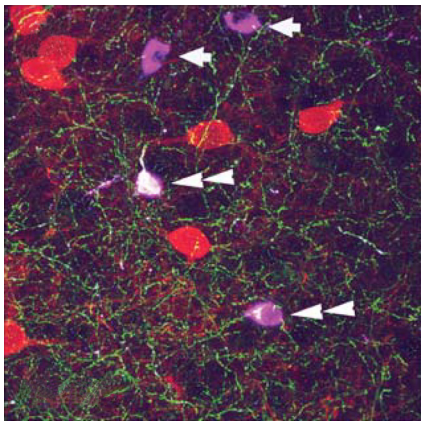
(see pages 4909 – 4930)

Neuropeptide Y (NPY) is an important regulator of stress and anxiety. It is thought to attenuate anxiety and promote resilience to stress. These effects are mediated at least partly by suppression of output from the basolateral amygdala (BLA). In rodents, infusion of NPY into the BLA reduces anxiety-like behaviors by acting on Y1-type receptors ($Y_1$Rs) in principal neurons, suppressing a tonic depolarizing current and thus reducing the neurons' excitability.

In contrast to $Y_1$R activation, selective activation of $Y_2$Rs in the BLA increases anxiety-like behaviors. Because $Y_2$Rs typically suppress neurotransmitter release from presynaptic terminals, Mackay et al. hypothesized that the anxiety-promoting effect stems from reduced GABA release onto BLA principal neurons. Consistent with this, $Y_2$R activation reduced the frequency of miniature IPSCs and the amount of current injection required to elicit action potentials in principal cells. At the same time, input resistance increased, suggesting that ion channels closed. In fact, the $Y_2$R agonist reduced a tonic hyperpolarizing current ($K_{IR}$) mediated by G-protein-coupled inwardly-rectifying $K^+$ channels. In addition, $Y_2$R activation enhanced the spike afterhyperpolarization (AHP) in approximately half of principal neurons. In these cells, $Y_2$R activation increased the interval between spikes elicited by current injection, whereas in cells lacking the AHP enhancement, the interspike interval decreased.

A fluorescent marker expressed under the control of the $Y_2$R promoter indicated the receptor is expressed in somatostatin-expressing GABAergic interneurons, some of which also expressed NPY, as well as in some principal neurons—primarily those in which the AHP was enhanced by $Y_2$R activation. Importantly, however, blocking postsynaptic $GABA_B$ receptors mimicked all the effects of $Y_2$R activation, including enhancement of the AHP.

These data suggest that activation of presynaptic $Y_2$Rs on somatostatin-expressing GABAergic interneurons in the BLA reduces tonic GABA release that activates $GABA_B$ receptors on principal neurons. This leads to a decrease in tonic hyperpolarizing currents in the principal neurons, thus increasing their excitability. Nonetheless, the concurrent enhancement of the AHP resulting from suppression of GABA release reduces the spike rate in some principal neurons, particularly those that express $Y_2$R. The increased spike rate of principal neurons that do not express $Y_2$R may therefore drive the anxiety-like behaviors seen in animals treated with $Y_2$R agonists.



$Y_2$Rs (red) are expressed in somatostatin-expressing neurons (blue) in the BLA. Some of these neurons (double arrowheads) also express NPY (green), but others do not (arrows). See Mackay et al. for details.

## Cc2d1a Regulates Plasticity via Rac1 SUMOylation

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(see pages 4959 – 4975)

Loss-of-function mutations in Cc2d1a, a protein that regulates multiple cellular signaling pathways, cause nonsyndromic intellectual disability. Knock-out of Cc2d1a in mouse forebrain neurons impairs spatial learning, object recognition, and hippocampal long-term potentiation (LTP) and reduces dendritic complexity (Oaks et al., 2017 Cereb Cortex 27:1670), in part by dysregulating activity of the transcription factor NF-kB. Yang et al. now report that the effects of Cc2d1a are also mediated partly by increasing small ubiquitin-like modifiers (SUMOs) on Rac1, a small GTPase that regulates cytoskeletal reorganization and other cellular processes.

Cc2d1a was found in both excitatory and inhibitory neurons in CA1 of mouse hippocampus. Consistent with previous work, knocking out Cc2d1a selectively in excitatory neurons reduced branching of apical and basal dendrites in CA1 pyramidal cells, reduced maintenance of LTP, and impaired performance on an object-location memory task. In addition, Cc2d1a knock-out increased the levels of activated Rac1 and phosphorylation of its downstream effectors PAK1–3 and cofilin in CA1. The increase in activated Rac1 was likely mediated by an increase in its SUMOylation. Indeed, levels of SUMO-specific proteases, which reverse SUMOylation of Rac1 and other proteins, were reduced after Cc2d1a knock-out. Finally, inhibiting Rac1 activity rescued LTP maintenance and object-location memory in Cc2d1a-deficient mice.

These results suggest that Cc2d1a influences neuron growth and plasticity by promoting expression of SUMO-specific proteases that limit the activity of Rac1; the increased Rac1 activity after Cc2d1a knock-out impairs LTP, possibly by altering reorganization of the actin cytoskeleton. Future work should identify other proteins that are dysregulated by reduced expression of SUMO-specific proteases, and how these might contribute to phenotypes resulting from loss of Cc2d1a function. In addition, the effects of Cc2d1a knock-out in inhibitory neurons should be investigated.

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

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