

# This Week in The Journal

## Clarin-1 Maintains Stereocilia Organization in Hair Cells

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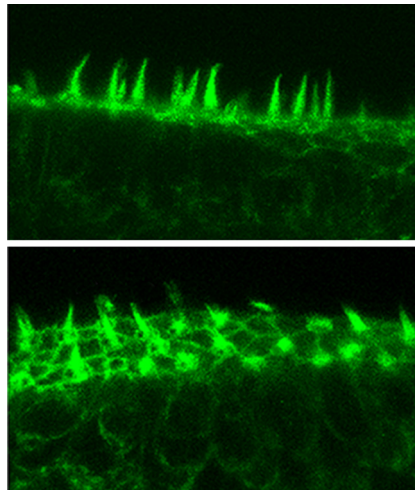
(see pages 10188–10201)

Usher syndrome is a group of genetic disorders that involve loss of hearing and peripheral vision. The least severe of these disorders is type III (USH3), in which vision and hearing are normal at birth but decline beginning in the teens or twenties. USH3 is caused by mutations in *CLRN1*, the gene encoding clarin-1. In mice, clarin-1 is expressed in auditory hair cells, and loss of *CLRN1* causes postnatal hearing loss accompanied by disorganization of stereocilia (“hair”) bundles and degeneration of hair cells. Whereas normal human clarin-1 localizes to hair cell bundles in mice, the USH3-associated form (clarin-1 N48K) does not (Geng et al., 2012, *J Neurosci* 32:9485).

To further elucidate the role of clarin-1 and the effects of its mutation, Gopal et al. manipulated clarin-1 expression in zebrafish. Zebrafish clarin-1 was localized to hair-cell stereocilia bundles, and stereocilia were splayed and disorganized in fish lacking clarin-1. Furthermore, knocking out clarin-1 disrupted hearing and balance, as demonstrated by abnormal startle responses and swimming postures. Clarin-1 knockout also blunted the electrical responses of lateral-line neuromasts elicited by mechanical deflection of the stereocilia. Finally, although normal human clarin-1 was localized predominantly to stereocilia bundles when expressed in zebrafish, clarin-1 N48K was found predominantly in the cell body, with only small amounts appearing in stereocilia.

These results suggest that clarin-1 functions within hair cell stereocilia to maintain the cohesive organization of the stereocilia bundle. They further suggest that the mutation that causes USH3 either disrupts trafficking of clarin-1 to stereocilia or reduces its retention there. The resulting disorganization of stereocilia impairs mechanosensory transduction, causing loss of hearing and balance. Why hearing loss is progressive in people with USH3 and how clarin-3 mu-

tations cause degeneration of rod photoreceptors remains to be determined.



In zebrafish, the stereocilia of inner-ear hair cells are normally organized into neat conical structures (top). Knockout of clarin-1 disrupts this organization, and stereocilia are often splayed (bottom). See Gopal et al. for details.

## Inhibitory and Excitatory Input to Dopaminergic Neurons Decreases during Morphine Withdrawal

Jennifer Kaufling and Gary Aston-Jones

(see pages 10290–10303)

Dopamine neurons in the ventral tegmental area (VTA) encode the reward value of actions and stimuli and thus play an essential role in reward-based learning. Because drugs that directly or indirectly enhance dopaminergic signaling are perceived as rewarding, they are prone to abuse. Repeated use of these drugs induces adaptive changes in reward circuitry, and these changes underlie drug tolerance, dependence, craving, and withdrawal symptoms.

Previous work has shown that when morphine is chronically administered to rats, the baseline firing rate of dopaminergic neurons increases. The firing rate returns to control levels when withdrawal is rapidly induced by injecting opiate antagonists, and it remains at control levels with protracted (14 d) withdrawal. Acute morphine injection after protracted withdrawal does not in-

crease the activity of dopaminergic neurons, indicating morphine tolerance has developed (Georges et al., 2006, *J Neurosci* 26:5720).

Morphine activates dopamine neurons indirectly by reducing inhibitory drive arising in part from GABAergic neurons in the VTA's caudal tail (tVTA). Therefore, Kaufling and Aston-Jones hypothesized that chronic morphine administration and withdrawal would produce changes in the activity of tVTA GABAergic neurons that were the inverse of those in dopamine neurons. As expected, the basal firing rate of tVTA neurons was lower in rats receiving chronic morphine than in morphine-naïve rats, and the rate returned to control levels when withdrawal was induced. Surprisingly, however, the firing rate of tVTA neurons decreased again after protracted withdrawal. Moreover, acute morphine produced similar inhibition in tVTA GABAergic neurons regardless of the previous history of morphine administration, indicating that these neurons did not become tolerant to morphine.

Consistent with previous work, the reduced activity in tVTA neurons after protracted morphine withdrawal was not accompanied by an increase in dopamine neuron activity. Hypothetically, this could occur because tVTA neurons no longer regulate dopamine neuron activity, or because a loss of excitatory inputs to dopamine neurons nullifies the effect of inhibition. Optogenetic stimulation of tVTA neurons produced similar levels of inhibition in dopamine neurons in naïve and cocaine-withdrawn rats, ruling out the first hypothesis. But glutamate receptor antagonists, which reduced firing of dopamine neurons in naïve rats, had no effect in rats after protracted cocaine withdrawal, supporting the second hypothesis.

Together, these results reveal that both inhibitory and excitatory input to VTA dopamine neurons are reduced after protracted withdrawal from chronic morphine treatment. The loss of excitatory inputs to dopaminergic neurons may lead to blunted responses to reward and thus contribute to the anhedonia that accompanies opiate withdrawal.

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