This Week in The Journal

NO Mediates Plasticity at Endbulbs of Held

Nicole F. Wong and Matthew A. Xu-Friedman

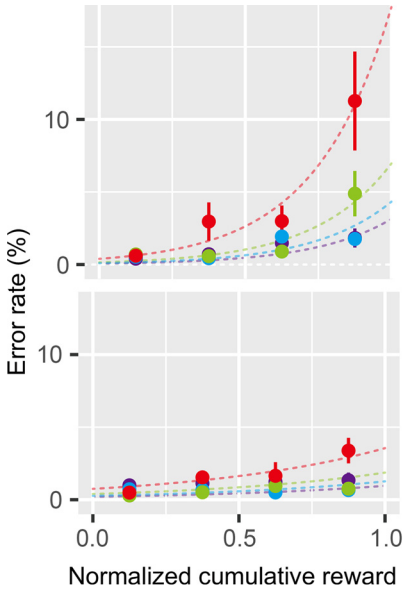
(see pages 6211–6220)

Auditory nerve fibers form large, reliable synapses called endbulbs of Held with bushy cells in the cochlear nucleus. The high release probability, large number of release sites, and large quantal size at these synapses allows them to relay temporal features of sounds with high fidelity. These synaptic properties can be altered by prolonged increases or decreases in auditory stimulation, however. For example, exposure to moderately loud noise for 2 d reduces release probability and increases the number of release sites, whereas blocking the ear canal reduces the number of release sites and increases release probability. To investigate the molecular mechanisms underlying such effects, Wong and Xu-Friedman induced similar plasticity in brain slices and tested the involvement of known mediators of synaptic plasticity.

Brain slices were first treated with high potassium to increase activity. After ≥4 h, the amplitude of evoked EPSCs in bushy cells was reduced and the paired-pulse ratio increased, suggesting the probability of presynaptic vesicle release had decreased. This effect was absent in slices from mice exposed to noise for a week, suggesting it involved similar mechanisms. But the amplitude of spontaneous EPSCs also increased, suggesting potassium also increased quantal content. The effects of high potassium were prevented by blocking the production of nitric oxide (NO) and by inhibiting protein kinase A, and they were replicated by increasing NO. They were not altered by blocking CB1 cannabinoid receptors or ionotropic or metabotropic glutamate or GABA receptors, however.

In additional experiments, a light-gated cation channel was expressed in auditory nerve fibers. Photoactivation of the fibers at 20 Hz for 2 h reduced evoked EPSC amplitude and increased paired-pulse ratio, but did not affect spontaneous EPSCs. Thus, this treatment more closely mimicked the effects of noise exposure. The increases in paired-pulse ratio required NO synthesis and activation of AMPA receptors, with a smaller contribution by NMDA receptors.

These results suggest that prolonged increases in auditory nerve activity induce bushy cells to release NO, which acts on presynaptic terminals to reduce the probability of vesicle release. A similar mechanism may underlie the effects of noise exposure on synaptic transmission at endbulbs of Held *in vivo*.



As untreated monkeys become sated, their error rate increases, especially on trials with small expected rewards (top). This effect is lost when communication between OFC and rmCD is blocked (bottom). Colors indicate reward size: red, small; green, medium; blue, large. See Oyama, Hori, Mimura, Nagai, et al. for details.

Macaque OFC Communicates Subjective Value to Caudate Nucleus

Kei Oyama, Yukiko Hori, Koki Mimura, Yuji Nagai, Mark A. G. Eldridge, et al.

(see pages 6267–6275)

Animals often perform complex actions to obtain rewards. How well they perform such actions is influenced by how much they value the available reward, which depends on both the properties of the reward and the physiological state of the animal. For example, animals perform tasks to obtain food more rapidly and accurately when they are hungry than when they are sated. The computation and updating of reward values as internal and external conditions change occurs in the oribitofrontal cortex (OFC), which is thought to communicate this information to the ventral striatum, which in turn motivates goal-directed actions. Subjective reward value is represented in the striatal rostromedial caudate nucleus (rmCD), and when this area is inactivated, monkeys fail to show the expected improvement in performance as reward size increases. Therefore, communication between the OFC and rmCD may be required for changes in subjective reward value to influence behavioral performance.

To test this hypothesis, Oyama, Hori, Mimura, Nagai, et al. used a modernized version of a classic crossed-lesion disconnection study. Specifically, they expressed the inhibitory designer receptor hM4Di unilaterally in both OFC and the contralateral rmCD of macaques. Because OFC projects to the ipsilateral rmCD, subsequent delivery of designer drugs that activate hM4Di bilaterally inactivated communication between OFC and rmCD while preserving the function of each area in the noninactivated hemisphere. Monkeys then performed a task in which an initial cue informed them how much juice they would receive if they released a bar at an appropriate time. In this simple task, the performance of monkeys is influenced predominantly by expected reward size and how much juice the monkey has already received. Early in a session, monkeys make few errors, but as the session progresses, the error rate increases, particularly for trials in which the expected reward is small.

Previous work showed that unilateral inactivation of the rmCD did not alter performance on this task. Similarly, unilateral inactivation of OFC did not affect error rates in the current study. But inactivating OFC along with the contralateral rmCD significantly reduced the error rate, particularly for small-reward trials occurring late in the session. These results suggest that communication between OFC and rmCD enables satiation to decrease motivation to exert effort to obtain a reward.

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https://doi.org/10.1523/JNEUROSCI.twij.42.32.2022