This Week in The Journal

Role of Estrogen Receptors in Ethanol Consumption

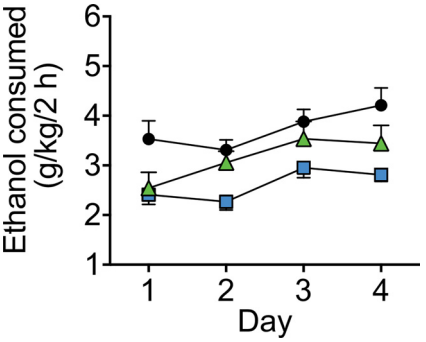
Bertha J. Vandegrift, Elisa R. Hilderbrand, Rosalba Satta, Rex Tai, Donghong He, et al.

(see pages 5196–5207)

Numerous studies have established that sex hormones, particularly 17β-estradiol, influence many CNS functions, including memory, pain processing, and drug use. Although dissociating biological and societal effects on sex differences in humans is difficult, the physiological bases of estradiol's behavioral effects in rodents have been demonstrated repeatedly. Such studies have revealed, for example, that the motivation to seek cocaine or opiates is greater in female rodents than in males, and when given free access to ethanol, female mice consume more than males. These behavioral effects likely stem from modulation of dopamine release by estradiol. Previous work by Vandegrift et al. showed that neurons in the ventral tegmental area (VTA), which contains reward-sensitive dopaminergic neurons, were more strongly activated by ethanol in female mice in diestrus, when estrogen levels are high, than in mice in estrus. Furthermore, treating brain slices from ovariectomized female mice with estradiol increased ethanol-induced excitation of VTA neurons.

Vandegrift et al. now describe the roles of estrogen receptor α (ERα) and ERβ—both of which are expressed in dopaminergic and nondopaminergic neurons in the VTA—in estradiol-dependent modulation of VTA neuron activity and ethanol consumption. Treating brain slices from ovariectomized mice with an ERα agonist significantly increased ethanol-induced excitation of VTA neurons, whereas an ERβ agonist had no effect. Furthermore, knocking down ERα or treating slices with an ERα antagonist reduced ethanol-induced excitation of VTA neurons from gonadally intact diestrus mice. In contrast, antagonizing or knocking down ERβ had no effect. Finally, knocking down ERα—or, to a lesser extent, ERβ—in VTA reduced binge-like alcohol consumption by female mice, whereas knocking down ERα or ERβ did not affect ethanol consumption in males.

These results suggest that estradiol promotes binge drinking in female mice, but not male mice, by acting on both ERα and ERβ in the VTA. The effect of ERα activation is greater, possibly because ERα is more widely expressed in VTA. Activation of ERα makes VTA neurons more sensitive to ethanol, which may make ethanol more rewarding. How ERβ increases alcohol consumption remains to be determined.



Knocking down ERα (blue squares) or ERβ (green triangles) reduces ethanol consumption during 2 h nightly sessions in female mice, relative to controls (black circles). See Vandegrift et al. for details.

Reopening the Critical Period through Cholinergic Signaling

Masato Sadahiro, Michael P. Demars, Poromendro Burman, Priscilla Yevoo, Andreas Zimmer, et al.

(see pages 5214–5227)

During brief time windows after birth, cortical circuits are substantially altered by sensory experience. In primary visual cortex (V1), for example, there is a critical period during which visual experience influences ocular dominance—the ability of inputs from each eye to drive neuronal spiking. If one eye is occluded during this period, V1 neurons become unresponsive to inputs from that eye, and vision remains impaired even after the occlusion is removed. Although closure of the critical period is necessary for sensory stability, restoring critical-period-like plasticity in the mature brain might enhance functional recovery when normal circuitry is disrupted.

Critical-period plasticity depends largely on the activity of somatostatin-expressing (SST) and parvalbumin-expressing (PV) inhibitory interneurons. Both of these inhibit pyramidal cells, but SST neurons also inhibit PV cells and thus can disinhibit pyramidal cells. This disinhibition appears to be required for ocular dominance plasticity. During the critical period, SST neurons are activated by cholinergic inputs, and decline in the sensitivity of SST neurons to acetylcholine coincides with the end of the critical period. Notably, artificially activating SST neurons or inhibiting PV neurons can reinstate critical-period-like plasticity (Hooks and Chen, 2020, Neuron 106:21). Sadahiro et al. now report that restoring the sensitivity of SST neurons to acetylcholine can also reinstate plasticity.

When Lypd6, an endogenous stimulator of nicotinic acetylcholine receptors (nAChRs), was overexpressed selectively in SST neurons in the deep layers of adult V1, subsequent monocular occlusion caused ocular dominance shifts similar to those induced during the critical period. Furthermore, after monocular deprivation, visual stimulation evoked greater activity in SST neurons, less activity in putative PV neurons, and more activity in putative pyramidal cells in Lypd6-overexpressing mice than in controls. Notably, knocking out the nAChR α2 subunit, which in V1 is expressed almost exclusively in layer 5 SST interneurons, prevented ocular dominance plasticity in adult mice overexpressing Lypd6. Finally, when Lypd6 was overexpressed in V1 SST interneurons of mice that had undergone monocular deprivation during the critical period, visual acuity improved.

These results suggest that potentiating nAChR-dependent activation of SST interneurons in adults reinstates critical-period-like ocular dominance plasticity mediated by disinhibition of pyramidal cells. Because the nAChR α2 subunit is largely restricted to SST neurons in cortex, activating these receptors might enhance cortical plasticity with minimal side effects.

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