This Week in The Journal

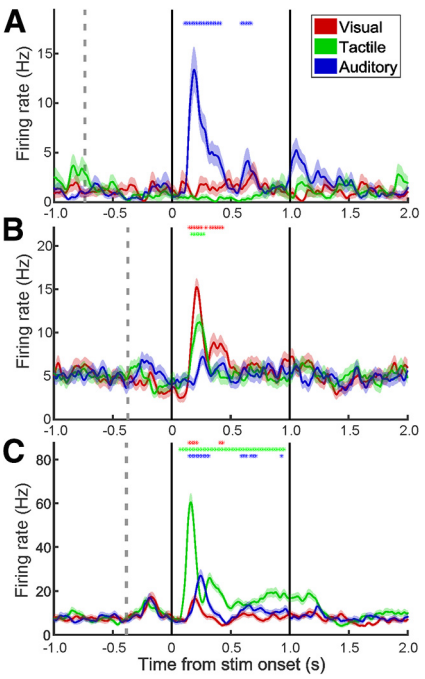
Ambient Glutamate Shapes Inhibitory Interneurons, Circuits

Elizabeth Hanson, Moritz Armbruster, Lauren A. Lau, Mary E. Sommer, Zin-Juan Klaft, et al.

(see pages 3611–3626)

Glutamate is the brain's primary excitatory neurotransmitter, but during development, it acts as a regulatory signal that helps shape inhibitory cortical circuits. That's according to work this week from Hanson et al., who show that ambient glutamate gives rise to a tonic NMDA-mediated current at the end of the first postnatal week in GABAergic interneurons (INs) in mice. In adulthood, extracellular glutamate is tightly regulated by excitatory amino acid transporters that are dynamically expressed by astrocytes in the immature cortex. Fluorescence-based biosensor imaging indicated that extracellular glutamate levels were higher at postnatal day 5 (P5) to P6 than at P9 to P10. Using quantitative electrophysiological measurements of NMDA currents from layer 5 pyramidal neurons (L5Ps) as a proxy for INs, the researchers approximated the extracellular synaptic glutamate concentration at L5Ps was around 100 nM at P3 but fell by about half by P14.

They next used a mouse line in which enhanced green fluorescent protein labels cortical inhibitory neurons, which were detectable in the neonatal cortex as early as P3. Electrophysiological recordings showed that these INs were depolarized at rest by ambient glutamate. Pharmacological block of the IN NMDA-mediated currents with the antagonist DPQ-1105 demonstrated that the receptors contained the GluN2C/GluN2D subunits. GluN2C/D channels have a high affinity for glutamate and a low affinity for magnesium, making them poised to carry a tonic current unimpeded by voltage-dependent magnesium block. Treatment of neurons with DPQ-1105 during P7 to P9, when the GluN2C/D-mediated depolarization of INs was at its peak, resulted in significantly reduced miniature IPSCs (mIPSCs) in the adult INs at P21 to P27 as well as reduced GABAergic synapse density and IN dendritic arbor complexity without affecting IN number. Treating neurons later at P11 to P13 had no effect on adult IN mIPSCs. Adult neurons treated with DPQ-1105 at P7 to P9 also displayed field EPSPs evoked by stimulation that were indicative of cortical hyperexcitability. Together, the findings suggest the NMDA currents elicited by extracellular glutamate during a critical window shape the maturation of INs and of cortical excitability as a whole. The authors hypothesize that disruptions of this developmental signaling at GluN2C/D could have long-ranging, potentially pathological, effects on cortical circuitry.



Representative neural responses to visual (red), tactile (green), and auditory (blue) stimuli. Mean spike density function (solid line) represents responses averaged across eight stimuli. See Morrow et al. for details.

Widespread Amygdala Neurons Respond to Multisensory Stimuli

Jeremiah Morrow, Clayton Mosher, Katalin Gothard

(see pages 3663–3675)

The natural world presents us with a barrage of stimuli that must be integrated and encoded by the brain in order to guide our behaviors. That requires that individual neurons be responsive to input from multiple sensory modalities, a task accomplished by some cortical and hippocampal neurons. Morrow et al. have now identified such "multisensory" neurons throughout the amygdala, a structure known to process socially and emotionally relevant stimuli. The researchers made electrophysiological recordings from amygdala neurons in two macaque monkeys while presenting visual, auditory, and tactile stimuli that were not intrinsically emotionally or socially significant, or familiar. More than two-thirds of amygdala neurons responded to the multisensory stimuli, and neuronal responses were roughly equally split among the three sensory modalities. Among responsive neurons, >60% responded to multiple sensory modalities, challenging the notion that amygdala neurons respond preferentially to visual stimuli. To get a sense of how the neurons encode multisensory stimuli, the researchers focused on three features of their firing patterns: the response magnitude, duration, and polarity (an increase or decrease in firing rate). About half the neurons responded selectively to a particular modality, whereas only about a quarter responded selectively to specific items, or types of stimuli, within a modality. The authors surmised from their analysis that modality is encoded in the early part of the spike train, with items being encoded later in the train. Somewhat surprisingly, the multisensory neurons were found distributed throughout the nuclei of the amygdala, supporting the idea that neurons from different amygdala nuclei are not readily distinguishable from one another by their electrophysiological responses to stimuli. Because the stimuli were not intrinsically emotionally salient, the work also suggests that amygdala neurons do not respond only to emotional stimuli. Future studies may focus on how the amygdala integrates this multisensory information with emotional valence.

This Week in The Journal was written by Stephani Sutherland, Ph.D.
https://doi.org/10.1523/JNEUROSCI.twij.39.19.2019.