Abstract

Tonic and phasic inhibitory mechanisms mediating sensorimotor plasticity in the goldfish auditory startle circuit

by

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This work describes related studies of cellular and synaptic signaling mechanisms involved in the balance of excitation and inhibition in the goldfish auditory startle circuit. The general purpose of these experiments was to identify novel mechanisms that contribute to action selection and inhibition among units of the motor control hierarchy. The method developed to achieve this goal tested the effects of selective antagonists for target receptor systems on sound-evoked excitation and inhibition of startle.

Chapter 2 describes a study of a poorly-understood serotonergic mechanism, the 5-HT$_{5A}$ receptor, that was not previously functionally characterized in native tissues or associated with neural or behavioral processes. Treatment with a selective 5-HT$_{5A}$ antagonist caused a 26.41±3.98% reduction in sound-evoked excitation of startle. Subsequent experiments revealed that the 5-HT$_{5A}$ antagonist significantly reduced post-synaptic excitability in the Mauthner-cell (M-cell) neurons that initiate startle. Despite these effects, prepulse inhibition (PPI) of the startle response remained robustly intact after treatment with the 5-HT$_{5A}$ antagonist. The 5-HT$_{5A}$ receptor is thus not a likely mechanism for PPI, but does act as a selective modulator of startle excitability. A final
A series of experiments confirmed that the 5-HT$_{5A}$ antagonist reduced M-cell excitability by increasing Cl$^-$ conductance, likely by activating Cl$^-$ channels.

Chapter 3 presents experiments focused on the inhibitory neurotransmitters that directly mediate the phasic inhibitory process elicited during PPI. Strychnine, a glycine receptor (GlyR) antagonist, caused an 87.43 ± 21.53% increase in sound-evoked excitation of startle, but PPI remained robustly intact, despite this. GlyRs thus likely mediate a tonic inhibitory process that was blocked by strychnine treatment, but glycineergic components of sound-evoked inhibition decayed too rapidly (<50 ms) to contribute to the prolonged time-course of PPI.

In a parallel series of experiments, treatment with bicuculline, the GABA$_{A}$R antagonist, caused similar increases in sound-evoked excitation (by 133.8 ± 10.3%) of startle, but the GABA$_{A}$R antagonist also significantly reduced auditory PPI at inter-stimulus intervals of 100 ms and less. In sum, these findings indicate that glycine and GABA tonically inhibit the M-cell startle circuit, but GABA is also the primary effector mechanism for inhibitory signaling during PPI.

In summary, three goals were accomplished. First, the thorough functional characterization of 5-HT$_{5A}$ provided a fully integrated serotonergic mechanism, and this appears to provide an ideal tool for selective modulatory control. Next, experiments with strychnine emphasize a short-lived role of GlyRs in sound-evoked (feed-forward) inhibition, and also act as mediators of a tonic inhibitory process that controls startle excitability. Last, experiments with bicuculline identify GABA as the inhibitory neurotransmitter that directly mediates PPI.