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Ontogeny of cortical synaptic depression underlying olfactory sensory gating in the rat

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Abstract

Sensory gating is the ability to filter irrelevant or redundant sensory input and is a critical function of all sensory systems that allows efficient processing of important stimuli. The present results demonstrate that a form of activity-dependent synaptic depression recently found to be involved in both cortical and behavioral olfactory sensory gating, is functional by at least the first postnatal week in the rat piriform cortex, and shares a common metabotropic glutamate receptor mechanism.

Keywords

Metabotropic glutamate receptor; Piriform cortex; Synaptic depression; Sensory gating; Autism

Sensory gating is the ability to filter irrelevant or redundant sensory input and is a critical function of all sensory systems that allows efficient processing of important stimuli. Sensory gating abnormalities have been described in several clinical disorders including autism and autism spectrum disorder [9,12,13], Fragile X syndrome [8], and schizophrenia [11]. Acute disruption of sensory gating could lead to reduced habituation, repetitive behaviors or thoughts, or general cognitive decline. However, tonic disruption of sensory gating, especially during early development, could produce more dramatic effects on both neural architecture and local circuit function. For example, given the importance of synaptic competition in shaping cortical circuit structure and function [14], a disruption of adaptation and sensory gating early in development could lead to abnormal dendritic pruning and/or cell survival.

Our recent work in rats suggests that intense activation of mitral/tufted cell pre-synaptic terminals in the piriform cortex induces two forms of synaptic depression that may contribute to olfactory cortical sensory gating. One very rapidly recovering (<20 s) depression appears to be mediated by transmitter depletion, while a second intermediate duration (<2 min) depression is mediated by pre-synaptic group III metabotropic glutamate receptors (mGluR). The mGluR-mediated mechanism underlies both piriform cortical and behavioral short-term adaptation (sensory gating) to odors. Specifically, the infusion of the group II/III mGluR antagonist (*RS*)- α -Cyclopropyl-4-phosphonophenylglycine (CPPG) into the anterior piriform cortex (aPCX) blocks both cortical and behavioral odor adaptation, without disrupting normal odor responses [2,3]. CPPG antagonizes pre-synaptic group III mGluRs on mitral/tufted cell axons projecting to the piriform cortex and blocks activity-dependent intermediate duration synaptic depression at this synapse.

In our efforts to develop a model of developmental sensory gating disorders, the present experiments served two purposes. First, although behavioral odor habituation is expressed to a similar extent and time course throughout development [6,7], we wanted to confirm that the

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cortical synaptic depression believed to underlie odor habituation was also expressed throughout the postnatal period. Second, we wanted to confirm the role of group III mGluRs in this synaptic depression throughout development. Although the olfactory system undergoes major postnatal developmental changes in cell number and circuitry [4], the mitral/tufted cell projection via the lateral olfactory tract (LOT) to the aPCX is present and functional near birth [7,15,16], and rats are reliant on olfactory information for survival from birth [17].

Male Long Evans hooded rats obtained from Harlan Lab Animals (Indianapolis, IN) were maintained on a 12 h light/dark cycle, housed with the mother. Date of birth was considered postnatal day 0 (PN0). Animal care and experimental procedures conformed to US Public Health Service Policy on Humane Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee. Coronal 400- μ m-thick slices including the aPCX were prepared as previously described [2]. In all procedures described below, a concentric bipolar stainless steel stimulating electrode was placed on the lateral olfactory tract (LOT) and field potentials were recorded from layer I of the aPCX using tungsten microelectrodes (A-M Systems). Amplified and bandpass (5 Hz–1 kHz) filtered signals were acquired at 5 kHz and analyzed using Spike2 software (CED, Inc). To investigate the possibility of age-dependent differences on aPCX synaptic depression in rats, we used slices from PN7, PN16 and PN24 rats. Electrophysiology was performed in a static interface chamber filled with aCSF. Test stimuli (0.1 ms duration, 5–100 μ A) were delivered at 10 s intervals for 5 min to determine a baseline level of response prior to a 50 s train burst designed to mimic odor-driven LOT activity (8 pulses, 100 Hz trains repeated at 2 Hz for the 50 s total duration). Recovery from depression was assessed by recording similar test stimuli for at least 5 min following the end of the train. The magnitude of responses was determined using slope measurements from the initial falling portion of the negative evoked wave that correlates with monosynaptic activation by LOT afferent synapses, and response slope values were normalized to baseline for analyses. A repeated measures ANOVA (age $\times$ time post-trains) was used to determine the effects of age on induced synaptic depression.

To determine whether synaptic depression at early stages of development is mediated by group III mGluR activation, in vitro electrophysiology was performed on superfused slices from PN7 rats in a perfusion chamber. A within-slice design was used to assess the effects of pharmacological manipulation using the group II/III mGluR antagonist CPPG obtained from Tocris Cookson (Ellisville, MO). Under each condition, field potential recordings were taken for 5 min to determine baseline responses as above. We attempted to induce synaptic depression in each slice using the above protocol in the presence of aCSF and in the presence of 500 μ M CPPG in aCSF. A repeated measures ANOVA (drug condition $\times$ time post-trains) was used to determine the effects of CPPG.

The synaptic depression of LOT afferent synapses to the aPCX was found to be independent of age (Fig. 1). Slices from PN7, 16 and 24 rats all showed a similar extent and time course for recovery of synaptic depression. There was no significant effect of age on the extent of depression between the different age groups (ANOVA main effect of age, $F(2,19) = 1.63$; not significant).

The group II/III mGluR antagonist CPPG has previously been shown to block the late phase (>10 s) of LOT synaptic depression in the aPCX of mature rats [2]. The initial several seconds of depression may reflect synaptic neurotransmitter depletion [2]. Similarly, CPPG blocked the late phase of LOT synaptic depression at PN7 (Fig. 2). There was no significant difference between aCSF and CPPG treated slices prior to depression induction ($F(5,45) = 0.74$, N.S.). However, CPPG significantly reduced synaptic depression compared to aCSF controls (ANOVA main effect of drug, $F(1,10) = 13.50$; $P < 0.01$). Post hoc Fisher tests revealed that time points after 10 s were significantly different between CPPG and aCSF ($P < 0.05$).

The present results demonstrate that a form of activity-dependent synaptic depression recently found to be involved in both cortical and behavioral olfactory sensory gating [2,3] is functional by at least the first postnatal week in the rat aPCX and shares a common mGluR mechanism. aPCX pyramidal cell dendritic branching [18], aPCX cell survival [10] and synaptic and membrane properties of piriform pyramidal cells [1,5] are all odor experience dependent in the rat. Thus, the present results suggest that a developmental disruption of olfactory cortical sensory gating during early development could produce dramatic changes in cytoarchitecture and circuit function within the aPCX that could lead to lifelong changes in sensory processing and cognition. Given that rats rely heavily on olfaction for social interaction and intraspecific communication, such a disruption could also directly impact on these behaviors as well. We are currently developing this paradigm as a model of developmental disorders associated with sensory gating deficits.

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Fig. 1.

Ontogeny of afferent synaptic depression in the in vitro aPCX. (Top) Representative waveform averages (average of 4 responses each) from PN7 slices before, immediately after and following recovery from synaptic depression. Arrowheads mark the stimulus artifact. Vertical hash-marks on the first response denote the location at which slope measurements were made. (Bottom) aPCX synaptic depression occurs to a similar degree and expresses a similar recovery time course at all ages tested following 50 s of pre-synaptic activation.

Fig. 2.

The group II/III mGluR antagonist CPPG blocks the intermediate (>10 s) phase of afferent synaptic depression by at least PN7, similar to previous reports in mature rats. The initial rapidly recovering depression component was unaffected, as previously reported in adults. Asterisks mark significant difference between CPPG and aCSF.