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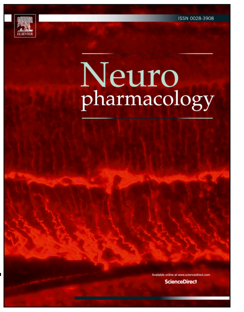

Depolarizing, inhibitory GABA type A receptor activity regulates GABAergic synapse plasticity via ERK and BDNF signaling

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ABSTRACT

γ-aminobutyric acid (GABA) begins as the key excitatory neurotransmitter in newly forming circuits, with chloride efflux from GABA type A receptors ($GABA_AR$s) producing membrane depolarization, which promotes calcium entry, dendritic outgrowth and synaptogenesis. As development proceeds, GABAergic signaling switches to inhibitory hyperpolarizing neurotransmission. Despite the evidence of impaired GABAergic neurotransmission in neurodevelopmental disorders, little is understood on how agonist dependent $GABA_AR$ activation controls the formation and plasticity of GABAergic synapses. We have identified a weakly depolarizing and inhibitory $GABA_AR$ response in cortical neurons that occurs during the transition period from $GABA_AR$ depolarizing excitation to hyperpolarizing inhibitory activity. We show here that treatment with the $GABA_AR$ agonist muscimol mediates structural changes that diminish GABAergic synapse strength through postsynaptic and presynaptic plasticity via intracellular Ca^{2+} stores, ERK and BDNF/TrkB signaling. Muscimol decreases synaptic localization of surface γ2 $GABA_AR$s and gephyrin postsynaptic scaffold while β2/3 non-γ2 $GABA_AR$s accumulate in the synapse. Concurrent with this structural plasticity, muscimol treatment decreases synaptic currents while enhancing the γ2 containing benzodiazepine sensitive $GABA_AR$ tonic current in an ERK dependent manner. We further demonstrate that $GABA_AR$ activation leads to a decrease in presynaptic GAD65 levels via BDNF/TrkB signaling. Together these data reveal a novel mechanism for agonist induced GABAergic synapse plasticity that can occur on the timescale of minutes, contributing to rapid modification of synaptic and circuit function.

keywords: GABA type A receptors; inhibition; neuronal development; synaptic plasticity; muscimol; ERK; BDNF; calcium

1. Introduction

Synaptic development occurs first with the emergence of excitatory GABAergic signals that drive the subsequent establishment of glutamatergic responses (Ben-Ari et al., 2007; Deng et al., 2007). At this time, GABA depolarizes neurons due to a high intracellular chloride level ($[Cl^-]_i$) maintained by the cation-chloride importer NKCC1. This depolarizing response relies on chloride efflux via $GABA_AR$s and leads to an increase in intracellular calcium ($[Ca^{2+}]_i$) through activation of voltage gated calcium channels and removal of magnesium block from NMDA receptors. The transition from a depolarizing to hyperpolarizing response occurs due to a rise in expression of the K-Cl extruder KCC2 that reduces $[Cl^-]_i$ (Kaila et al., 2014), with *in vitro* cultured neuron and brain slice studies reporting the switch occurs in most brain areas (cerebellum, hypothalamus, cortex, hippocampus) during the second week of development (Ganguly et al., 2001; He et al., 2014; Mueller et al., 1984; Obrietan and van den Pol, 1995; Owens et al., 1996; Succol et al., 2012; Tyzio et al., 2007). Depolarizing $GABA_AR$ responses during