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Transcriptional dysregulation causes altered modulation of inhibition by haloperidol

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ABSTRACT

Many neuropsychiatric and neurodevelopmental disorders such as schizophrenia and autism involve interneuron transcriptional dysregulation. The transcriptional coactivator PGC-1α regulates gene expression in GABAergic interneurons, which are important for regulating hippocampal network activity. Genetic deletion of PGC-1α causes a decrease in parvalbumin expression, similar to what is observed in schizophrenia postmortem tissue. Our lab has previously shown that PGC-1$\alpha^{-/-}$ mice have enhanced GABAergic inhibition onto CA1 pyramidal cells, which increases the inhibition/excitation (I/E) ratio, alters hippocampal circuit function, and impairs hippocampal dependent behavior. The typical antipsychotic haloperidol, a dopamine receptor antagonist with selectivity for D2-like receptors, has previously been shown to increase excitation in the CA1 region of hippocampus. We therefore tested whether haloperidol could normalize the I/E balance in CA1 of PGC-1$\alpha^{-/-}$ mice, potentially improving circuit function and behavior. Surprisingly, we discovered instead that interneuron transcriptional dysregulation caused by loss of PGC-1α alters the effects of haloperidol on hippocampal synaptic transmission and circuit function. Acute administration of haloperidol causes disinhibition in CA1 and decreases the I/E ratio onto CA1 pyramidal cells in slices from PGC-1$\alpha^{+/+}$ mice, but not PGC-1$\alpha^{-/-}$ mice. The spread of activity in CA1, assessed by voltage sensitive dye imaging, is increased by haloperidol in slices from PGC-1$\alpha^{+/+}$ mice; however haloperidol decreases the spread of activity in slices from PGC-1$\alpha^{-/-}$ mice. Haloperidol increased the power of hippocampal gamma oscillation in slices from PGC-1$\alpha^{+/+}$ mice but reduced the power of gamma oscillations in slices from PGC-1$\alpha^{-/-}$ mice. Nest construction, an innate hippocampal-dependent behavior, is inhibited by haloperidol in PGC-1$\alpha^{+/+}$ mice, but not in PGC-1$\alpha^{-/-}$ mice, which already have impaired nest building. The effects of haloperidol are mimicked and occluded by a D2 receptor antagonist in slices from PGC-1$\alpha^{+/+}$ mice, and the effects of blocking D2 receptors are lost in slices from PGC-1$\alpha^{-/-}$ mice, although there is no change in D2 receptor transcript levels. Together, our results show that hippocampal inhibitory synaptic transmission, CA1 circuit function, and hippocampal dependent behavior are modulated by the antipsychotic haloperidol, and that these effects of haloperidol are lost in PGC-1$\alpha^{-/-}$ mice. These results have implications for the treatment of individuals with conditions involving PGC-1α deficiency.

1. Introduction

Transcriptional dysregulation in inhibitory interneurons is seen in a variety of neuropsychiatric and neurodevelopmental disorders, including schizophrenia and autism (Lewis and Hashimoto, 2007). Decreased expression of the calcium binding protein parvalbumin, which is found primarily in fast-spiking interneurons, is consistently reported from studies on

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postmortem tissue from schizophrenia patients (Blum and Mann, 2002; Eyles et al., 2002; Knable et al., 2004; Reynolds et al., 2001, 2004). Parvalbumin levels are also reduced in autism (Gandal et al., 2012) and bipolar disorder (Sibille et al., 2011). However, our understanding of the effects of interneuron transcriptional dysregulation and parvalbumin reduction on synaptic and circuit function is incomplete.

PGC-1α (peroxisome proliferator activated receptor γ coactivator 1α) is a transcriptional co-activator that in hippocampus is concentrated in GABAergic interneurons. PGC-1α regulates the expression of parvalbumin (Lucas et al., 2010), and deletion of PGC-1α causes reductions in parvalbumin and other proteins that regulate GABA release, including synaptotagmin 2 and complexin 1 (Bartley et al., 2015; Lucas et al., 2010). PGC-1$\alpha^{-/-}$ mice provide a way to investigate the effects of interneuron transcriptional dysregulation on synaptic and circuit function. Our lab has previously shown that interneuron transcriptional dysregulation caused by loss of PGC-1α causes a frequency-dependent increase in inhibitory synaptic transmission onto CA1 pyramidal cells (Bartley et al., 2015). This increase in the I/E ratio greatly reduces the spread of activation in CA1 and impairs spiking of CA1 pyramidal cells, reducing hippocampal output (Bartley et al., 2015). PGC-1$\alpha^{-/-}$ mice also have enhanced power of gamma oscillations and an impairment in nest building (Bartley et al., 2015), an innate hippocampal-dependent behavioral task (Deacon, 2006), consistent with impaired hippocampal circuit function (Bartley et al., 2015).

Haloperidol, a dopamine receptor antagonist with selectivity for dopamine D2-like receptors, is an antipsychotic used in schizophrenia patients to treat positive symptoms that arise from enhanced dopamine signaling (Davis et al., 1991). Although hippocampal dysfunction contributes to cognitive impairment in schizophrenia (Gastambide et al., 2015), and dopamine receptors regulate inhibition in hippocampus (Gonzalez-Islas and Hablitz, 2001), haloperidol has not been found to be effective for treating the cognitive symptoms in schizophrenia (Furth et al., 2013). It is currently not known how haloperidol will affect hippocampal circuit function altered as a result of interneuron transcriptional dysregulation.

Previously it has been shown that acute application of haloperidol to hippocampal slices from wildtype mice causes an enhancement of excitatory synaptic transmission in CA1 (Baskys et al., 1993), suggesting that haloperidol could alleviate the I/E imbalance in CA1 caused by loss of PGC-1α. Here we compared the effects of haloperidol on synaptic transmission, circuit function, and behavior in PGC-1$\alpha^{-/-}$ and PGC-1$\alpha^{+/+}$ mice. We find that acute application of haloperidol reduces feed-forward inhibition and the I/E ratio in CA1 pyramidal cells in slices from PGC-1$\alpha^{+/+}$ mice, and enhances the spread of activation in CA1 as measured by voltage-sensitive dye imaging. Surprisingly, none of these effects were observed in slices from PGC-1$\alpha^{-/-}$ mice, indicating that the ability of haloperidol to cause disinhibition is lost in these mice. Furthermore, haloperidol increased the power of gamma oscillations in PGC-1$\alpha^{+/+}$ slices, but reduced gamma power in PGC-1$\alpha^{-/-}$ slices. Haloperidol significantly impaired nest construction by PGC-1$\alpha^{+/+}$ mice, however haloperidol caused no further effect on nest building behavior in PGC-1$\alpha^{-/-}$ mice, which was already impaired. Blocking D2 receptors with a specific antagonist mimicked and occluded the effects of haloperidol in slices from PGC-1$\alpha^{+/+}$ mice but had no effect in slices from PGC-1$\alpha^{-/-}$ mice, confirming the effects of haloperidol are through D2 receptors. Together, our results show that transcriptional dysregulation in interneurons alters the modulation of inhibition and hippocampal circuit function by the antipsychotic haloperidol.

2. Materials and methods

2.1. Animals

All experimental procedures for the care and use of laboratory animals were approved by the University of Alabama at Birmingham Institutional Animal Care and Use Committee, and were conducted in accordance with the U.S. National Institute of Health *Guide for the Care and Use of Laboratory Animals*. Male and female PGC-1$\alpha^{+/+}$ and PGC-1$\alpha^{-/-}$ mice generated from PGC-1$\alpha^{+/-}$ breeding pairs were used. Mice were maintained on a C57BL/6J genetic background. Mice were housed in cages at 80 °F with food and water *ad libitum*. Mouse genotypes were determined from tail biopsies using real time PCR with specific probes designed for PGC-1α (Transnetyx, Cordova, TN).

2.2. Slice preparation

Male and female mice, postnatal (P) day 25 to P60, were anesthetized with isoflurane and sacrificed by decapitation using a rodent guillotine. The brains were rapidly removed and placed in ice cold dissection solution containing the following: 120 NaCl, 3.5 KCl, 0.75 $CaCl_2$, 4.0 $MgCl_2$, 1.25 NaH_2PO_4, 26 $NaHCO_3$, and 10 glucose, bubbled with 95% O_2/5% CO_2, pH 7.35–7.45, and osmolarity 295-305. 400 μm thick coronal slices (or 300 μm thick horizontal slices for gamma oscillation experiments) of the hippocampus were cut on a vibrating microtome (VT1000S; Leica, Bannockburn, IL) in ice cold dissection solution. Slices were stored in a recovery chamber containing room temperature dissection solution bubbled with 95% O_2/5% CO_2 for at least 1 h before recording, except slices for gamma oscillation experiments and voltage sensitive dye experiments, which were incubated in dissection solution at 32 °C for 1 h before being stored at room temperature. Slices used for experiments with inhibition blocked had area CA3 removed during slice preparation.

2.3. Electrophysiology

2.3.1. Field potential recordings

Extracellular field potential recordings from acute ventral hippocampal slices from PGC-1$\alpha^{+/+}$ and PGC-1$\alpha^{-/-}$ mice were performed at 30 °C in a submerged recording chamber on a Nikon (New York, NY) Optiphot-2. The slices were perfused with external recording solution (ERS) containing the following: 120 NaCl, 3.5 KCl, 2.5 $CaCl_2$, 1.3 $MgCl_2$, 1.25 NaH_2PO_4, 26 $NaHCO_3$, and 10 glucose, bubbled with 95% O_2/5% CO_2, pH 7.35–7.5, osmolarity 295-305. Field postsynaptic potentials (fPSPs) were recorded using an ERS-filled microelectrode in response to extracellular stimulation of Schaffer collateral axons in the stratum radiatum layer of CA1 with a bipolar tungsten microelectrode (FHC, Bowdoinham, ME). In experiments where inhibition was blocked the ERS contained 100 μM picrotoxin (Abcam, Cambridge, MA) to block $GABA_A$ receptors. Haloperidol and L-741,626 were obtained from Abcam.

2.3.2. Whole-cell recordings

Whole-cell patch-clamp recordings were acquired by blindly patching CA1 pyramidal cells in the voltage-clamp configuration on a Nikon (New York, NY) Eclipse E600-FN upright microscope. Patch electrodes were filled with internal solution composed of the following (in mM): 125 Cs-Gluconate, 0.6 EGTA, 1.0 $MgCl_2$, 3 $MgSO_4$, 25 HEPES, 10 Na-ATP, 0.3 GTP, 5 phospocreatine, pH was adjusted to 7.2 with CsOH. The internal solution also contained 10 mM Cs-BAPTA to block depolarization-induced suppression of inhibition (Lenz and Alger, 1999), and 2 mM QX-314 (*N*-(2,6-dimethylphenylcarbamoylmethyl) triethylammonium chloride) to improve space clamp and reduce nonlinear effects caused by