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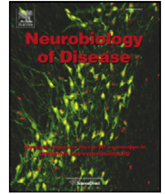

Modulation of serotonin dynamics in the dorsal raphe nucleus via high frequency medial prefrontal cortex stimulation

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A B S T R A C T

The subcallosal cingulate (SCC) region, or its rodent homologue the medial prefrontal cortex (mPFC), and midbrain dorsal raphe (DR) are crucial nodes of the widespread network implicated in emotional regulation. Stimulation of the SCC is being explored as a potential treatment for depression. Because modulation of the 5-HT system is the most common pharmacological means of treating depression, we sought to establish 5-HT's role in the mPFC-DR projection. Using anaesthetized mice, we recorded neuronal activity in 49 neurons of the DR before, during, and after high frequency stimulation (HFS) of the mPFC. The majority of DR cells (74%) significantly decreased firing rate during HFS ($p < 0.001$, 65.7 ± 9.4% of baseline, 14 mice). To see the effect of mPFC-HFS on 5-HT neurons, we used transgenic mice with expression of the channelrhodopsin fusion protein directed to the 5-HT neuronal population. Neurons were categorized as 5-HT based on their excitatory response to blue light stimulation ($p < 0.05$, $n = 11$). Our main finding was that identified 5-HT neurons in the DR were clearly inhibited by HFS, albeit non-selectively. Lastly, we used fast scan cyclic voltammetry (FSCV) to investigate the effects of mPFC-HFS on the release and reuptake of electrically stimulated 5-HT in the DR of C57BL/6 J mice. Serotonin clearance was significantly faster following 5 min HFS (2.3 ± 1.0 s, $n = 5$, $p < 0.05$) when compared to control levels (3.7 ± 1.0 s, $n = 5$), indicating less release or more efficient 5-HT reuptake. Taken together, these findings imply that mPFC stimulation alters 5-HT activity dynamics in the DR. Such altered 5-HT dynamics may modulate the potential therapeutic mechanisms of SCC/mPFC stimulation.

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1. Introduction

While understanding the etiology of debilitating neurological and psychiatric diseases is at a nascent stage, recent neurophysiological studies have begun to uncover the mechanisms that underscore the clinical symptoms of these disorders (Lozano and Lipsman, 2013). Researchers now believe that dysfunctional neural brain circuits controlling motor, mood, and cognitive function bring about clinical manifestations seen in patients with Parkinson's disease (PD), depression, and Alzheimer's disease (AD), (Dickerson and Eichenbaum, 2010; Price and Drevets, 2010; Shin and Liberzon, 2010; Wichmann et al., 2011). Neural pathologies that bring about circuit dysfunctions include damaged pathways, lack or abundance of neurotransmitter release, improper firing and disordered oscillations. While some disorders are thought to be primarily caused by a localized lesion to one brain region, depression is believed to encompass downstream projections and multiple areas (Price and Drevets, 2012). Application of high frequency electrical deep brain stimulation (DBS) has allowed clinicians and researchers the unique opportunity to treat the underlying disorders by alleviating the symptoms, but also to investigate the functions of these circuits (Hariz, 2012; Holtzheimer and Mayberg, 2011).

DBS employs the delivery of a focal electrical current to the brain tissue through surgically implanted pulse-generating electrodes (Benabid et al., 1994; Lujan et al., 2008). DBS of the subcallosal cingulate (SCC) region is being investigated as a potential treatment for refractory forms of depression (Kennedy et al., 2011; Lozano et al., 2008; Mayberg et al., 2005). We have recently reported that local high frequency stimulation (HFS) of the SCC may exert therapeutic effects by mediating local plasticity in depression patients (Srejic et al., 2014). However, the mechanisms underlying downstream effects of DBS are still not well understood. The central unifying principle of DBS therapy is stimulating specific neuronal populations to reverse maladaptive activity, thus influencing local and up- and downstream projections from the pathological focus (Lozano and Lipsman, 2013). The amelioration of pathological symptoms and stabilization of patterns of electrical and metabolic activity in coupled regions by DBS may be partly due the result of distal

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neurotransmitter release (Figee et al., 2014; Hamani et al., 2010). In order to shed light on these processes, animal research has focused on stimulating a region homologous to the SCC, the medial prefrontal cortex (mPFC) (Challis et al., 2014; Hamani and Nóbrega, 2010; Juckel et al., 1999; Puig et al., 2005; Veerakumar et al., 2014). Converging evidence from both human and animal work has shown that the mPFC mediates emotional and thought regulation (Fuster, 2001), which are impaired in mood disorders such as depression (Austin et al., 2001). Stimulation of the rodent mPFC induces an antidepressant-like effect, as measured in animal models of depression, where serotonin (5-HT) may play an important role (Cohen et al., 2015, 2012; Hamani et al., 2010; Warden et al., 2012; Zhou et al., 2015). 5-HT is one neurotransmitter in a complex system that exerts modulatory effects on a wide variety of physiological processes including those that regulate affiliative and antagonistic behaviors (Dayan and Huys, 2009). 5-HT-producing neurons in the midbrain dorsal raphe (DR) provide the majority of serotonergic projections to forebrain areas, such as the mPFC, basal ganglia, and amygdala (Jacobs and Azmitia, 1992). Likewise, activation of 5-HT neurons in the DR is thought to facilitate learned defensive behaviors (Zangrossi et al., 2001), while their inhibition exerts anxiolytic effects (Thiébot et al., 1980).

Optogenetic strategies for controlling neuronal function have been broadly implemented to analyze the connectivity and function of serotonergic cells within complex brain circuits (Cohen et al., 2015, 2012; Liu et al., 2014; Warden et al., 2012). Toward this end, we used a transgenic line of mice expressing channelrhodopsin (ChR2) under the control of cell-type specific promoter elements to enable functional activation of 5-HT-positive neuronal populations with 450–490 nm blue light (Zhao et al., 2011). 5-HT-specific optogenetic targeting coupled with microelectrode recordings in anaesthetized mice enabled us to identify 5-HT neurons and characterize the effects of high frequency stimulation (HFS) of the mPFC on 5-HT and non-5-HT cells in the DR.

To see the effect of mPFC-HFS on 5-HT release and reuptake in the DR in real time, we used fast scan cyclic voltammetry (FSCV). FSCV is a powerful in vivo electrochemical technique that identifies unique reduction-oxidation profiles of specific biogenic monoamines quickly enough to discriminate release and uptake (Hashemi et al., 2009; Stamford et al., 1984). FSCV delivers a rapid series of potential waveforms that oxidize and reduce specific analytes near the carbon-fiber electrode, without changing the overall milieu of the tissue (Dankoski and Wightman, 2013). FSCV has previously uncovered detailed differences between the regulation of dopamine and serotonin in vivo (Hashemi et al., 2012) and provided evidence of two independent serotonin reuptake mechanisms (Wood et al., 2014). Furthermore, FSCV showed rapid, acute SSRI-induced 5-HT reuptake inhibition as an index of 5-HT clearance (Wood and Hashemi, 2013). Here, we demonstrate that acute stimulation of the mPFC robustly releases 5-HT in the DR, while long-train repetitive mPFC-HFS increases the rate of 5-HT reuptake, likely a response to the now increased extracellular 5-HT.

2. Materials and methods

2.1. Animal surgeries

Animal experiments were conducted using male C57BL/6J mice and TpH2-ChR2-YFP BAC transgenic mice weighing (22 to 25 g) in compliance with the ethics protocol of the University Health Network Animal Care Committee (UHN ACC) and the Guide for the Care and Use of Laboratory Animals, approved by the Institutional Animal Care and Use Committees (IACUC) of the University of South Carolina. Every effort was made to reduce the number of experimental animals used and to minimize their discomfort. Mice were housed in the animal care facility at the Toronto Western Hospital and the University of South Carolina with food and water ad libitum. Experiments were performed in the light phase of a 12 to 12-hour light–dark cycle. After 1.2 mg/kg urethane (25% dissolved in 0.9% NaCl solution, Hospira, Lake Forest, IL) was injected intraperitoneally, stereotaxic surgery (David Kopf Instruments, Tujunga, CA) was performed. Urethane anaesthesia allows for continuous monitoring of cortical electrophysiology over a prolonged period with minimal cardiovascular and respiratory complications (De Wildt et al., 1983). Furthermore, spontaneous potentials measured in rats anaesthetized with urethane have similar characteristics to those generated in the conscious animal (Ebenezer, 1986). A heating pad maintained mouse body temperature around 37 °C (Braintree Scientfic, Braintree, MA).

2.2. Extracellular recordings of dorsal raphe neurons

Extracellular recordings were performed with three microelectrodes assembled from Parylene-C-insulated tungsten wires (Micro Probe, Gaithersburg, MD, USA), with a 20 μm tip length. To decrease the initial impedance of 1 MΩ for recording, the electrode tips were electroplated in 24 karat yellow gold electroplating solution (Krohn Technical Products, Carlstadt, NJ, USA) and followed by platinizing solution (VWR Scientific Products, Mississauga, ON, Canada) using a Stimulus Isolator (Sarasota, FL, USA; A360 World Precision Instruments) and 1 μA of cathodal direct current applied to the electrode for approximately 10 s, giving final impedances of 200 to 400 kΩ. Finally, the microelectrodes were insulated by a sleeve of polyimide Kapton (Micro ML Tubing, Midway, MA, USA).

The microelectrodes were positioned on the midline just posterior to the sagittal sinus, 5.5 mm posterior to Bregma. To reach the dorsal raphe, the trajectory was adjusted and microelectrode angled 18° anterior in the parasagittal plane, and advanced 2.6–3.2 mm below dura. The recorded signals were digitized at 12.5 kHz with a CED 1401 data acquisition system (Cambridge Electronic Design, Cambridge, UK) and saved to a computer hard-drive running Spike2 software (v. 7, Cambridge Electronic Design). The acquired neuronal signals were monitored continuously during acquisition by computer display.

2.3. Optogenetic methods

In order to reliably classify neurons as 5-HT or non-5-HT, we used mice hemizygous for the TpH2-ChR2-YFP BAC transgene, with expression of the mhChR2::YFP fusion protein directed to serotonergic neuronal populations by the mouse tryptophan hydroxylase 2 (*Tph2* or TpH2) promoter/enhancer regions on the BAC transgene (Jackson Labs, Bar Harbor, ME). The mhChR2::YFP fusion protein is composed of a mammalian codon-optimized *Chlamydomonas reinhardtii*-derived channelrhodopsin-2 that was modified to harbor a gain-of-function H134R substitution (mhChR2; also called hChR2-H134R) fused inframe with an enhanced yellow fluorescent protein (EYFP). The mhChR2 is designed to cause larger stationary photocurrents compared to ChR2. The opsins are retinal-binding proteins that provide light-dependent ion transport and sensory functions to a family of green algae; and this mhChR2 functions as a blue light-driven cation channel that depolarizes the cell and causes action potentials. As such, illuminating mhChR2-expressing neurons with blue light (450–490 nm) leads to rapid and reversible photostimulation of action potential firing/neural activity in these cells.

Optogenetic in vivo stimulation was done using a fiber optic cable (200 μm diameter) (PlexBright, Plexon) affixed to the triple-electrode probe with fast-bonding epoxy, placed 200–500 μm above the tips of the tungsten microelectrodes. The fiber optic cable was coupled to a blue light source (PlexBright Table-top LED Module, Plexon), which was powered by PlexBright LD-1 Single Channel LED Driver (Plexon). The optrode was stereotactically lowered into the DR according to same coordinates as during regular extracellular recordings (AP −5.5, ML 0, DV −2.6 to −3.2 mm relative to bregma). For each neuron, we delivered 10 light pulses, each 2 s long, at 450–490 nm at 20–25 mW/mm^2, before the standard mPFC-HFS protocol.

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