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Research article

Neurochemical arguments for the use of dopamine D_4 receptor stimulation to improve cognitive impairment associated with schizophrenia

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ABSTRACT

Background: Dopamine (DA) D_4 receptors have been implicated in schizophrenia and the ability of some atypical antipsychotic drugs (APDs) to improve the cognitive impairment associated with schizophrenia (CIAS). Systemic administration of a D_4 agonist, PD168077, at a sub-effective dose, together with a sub-effective dose of lurasidone, an atypical APD which is a weak D_4 receptor antagonist, reversed the deficit in novel object recognition (NOR) in rats treated subchronically with phencyclidine (PCP), a rodent model of CIAS. Atypical APDs potentially stimulate D_4Rs via their ability to enhance DA release in key brain areas related to cognition. However, some atypical APDs are relatively potent D_4 antagonists at clinical dosages, including clozapine, and risperidone. The D_4 antagonist, L745870, blocked the ability of clozapine, but not lurasidone, to reverse the NOR deficit in rats.

Methods: The purpose of this study was to determine the effects of a selective D_4 agonist and antagonist, alone, and as pretreatment with lurasidone, on neurotransmitter efflux in mouse medial prefrontal cortex (mPFC) and dorsal striatum (dSTR), using in vivo microdialysis.

Results and discussion: PD168077 alone, and in combination with sub-effective dose lurasidone, increased DA and acetylcholine (ACh) efflux in mPFC, but only DA efflux in dSTR. L745870 had no effect on neurotransmitter efflux on its own or on the ability of lurasidone to increase cortical or striatal neurotransmitter efflux. These results indicate D_4 receptor agonism alone is sufficient to increase cortical DA and ACh efflux without interfering with the effects of lurasidone and possibly other atypical APDs on extracellular cortical DA and ACh levels. A D_4 agonist may be useful for treating CIAS, especially as augmentation of those atypical APDs which are not potent D_4 antagonists.

1. Introduction

The dopamine (DA) D_4 receptor (D_4R), a member of the DA D_2-like receptor subfamily, is widely distributed in prefrontal cortex (PFC), entorhinal cortex, and hippocampus, regions particularly important for cognition, with less significant distribution on medium spiny neurons in striatum and the thalamus of rodents and humans, and is involved in multiple neuronal signal transduction cascades, including inhibition of adenylate cyclase (Defagot et al., 1997; Gan et al., 2004; Lauzon and Laviolette, 2010; Rondou et al., 2010; Tarazi et al., 2004; Thomas et al., 2009). D_4Rs play roles in disorders of cognitive function, including schizophrenia, attention deficit disorder, addiction and Parkinson's disease (Furth et al., 2013; Rondou et al., 2010; Tarazi et al., 2004; Thomas et al., 2009). A possible role of excessive D_4R stimulation in the pathophysiology of schizophrenia was suggested based on the elevated D_4R density in the brains of patients with schizophrenia (Seeman et al., 1993; Van Tol et al., 1991). However, subsequent evidence from postmortem was inconsistent with this excessive D_4R stimulation hypothesis (Hwang et al., 2012; Tarazi et al., 1998). None of the D_4R antagonists tested in patients with schizophrenia (e.g. L745870 and sonepiprazole) improved psychopathology in schizophrenia, and in one study, worsened the symptoms (Corrigan et al., 2004; Kramer et al., 1997; Reynolds, 1996).

None of these studies examined the effects of D_4R blockade on cognition. Recent studies suggest that D_4R agonism rather than D_4R antagonism might have a pro-cognitive effect (Lauzon and Laviolette,

Abbreviations: ACh, acetylcholine; APDs, antipsychotic drugs; CIAS, cognitive impairment associated with schizophrenia; DA, dopamine; dSTR, dorsal striatum; EPS, extra-pyramidal effects; 5-HT, serotonin; Glu, glutamate; mPFC, medial prefrontal cortex; NE, norepinephrine; NOR, novel object recognition; scPCP, sub-chronic phencyclidine

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2010; Rondou et al., 2010). The D_4R agonists, A-412997, Ro 10-5842, and PD168077, but not the D_4R antagonist, L745870, have been reported to improve cognition in normal (Browman et al., 2005; Newman-Tancredi et al., 2008; Powell et al., 2003; Sood et al., 2011; Woolley et al., 2008), and sub-chronic phencyclidine (scPCP)-treated rats (Sood et al., 2011; Miyauchi et al., 2017). The D_4R agonist-induced improvement in one-trial step-through inhibitory avoidance task was attenuated by both D_1 and D_2R antagonists and potentiated by D_1 and D_2R agonists, indicating both D_1R and D_2R are important for at least some of the domains of cognition for which D_4R may be important (Bernaerts and Tirelli, 2003). Some or all of these DARs may be affected by DA released during brain activity, or the result of drug actions, especially atypical APDs, which enhance cortical, hippocampal, limbic and striatal DA efflux (see Meltzer and Huang, 2008 for review).

The effect of D_4R modulation on cognition is complex with both pro-cognitive and cognitive impairing effects reported (Floresco and Magyar, 2006). Activation of D_4Rs in the PFC elevates cortical acetylcholine (ACh) and DA efflux, as do most atypical APDs, which could contribute significantly to pro-cognitive effects (Woolley et al., 2008). Furthermore, D_4R activation increases gamma oscillations (RH Andersson et al., 2012; Kocsis et al., 2014) which are known to be diminished in schizophrenia and thought to contribute to cognitive impairment associated with schizophrenia (CIAS) because of their central role in cognition (Gandal et al., 2012; Lisman et al., 2008). Atypical APDs, particularly clozapine, also a potent D_4 antagonist, rescue evoked gamma oscillation deficits in rats (Hudson et al., 2016; Wong and Van Tol, 2003). On the other hand, a high dose of a potent and selective D_4R antagonist (NGD94-1) or haloperidol, a D_2R antagonist with some D_4R antagonist properties (Newman-Tancredi et al., 2008), impaired baseline spatial memory performance in monkeys (Jentsch et al., 1999). Moreover, reduced D_4R expression impairs attentional performance in the 5-choice continuous performance test (Young et al., 2011). D_4R knockout mice are significantly less responsive to novelty compared to wild type mice in novel object recognition (NOR) tests, reflecting a decrease in novelty-related exploration (Dulawa et al., 1999). Collectively, these findings suggest D_4R stimulation rather than blockade may have a pro-cognitive effect for treatment of CIAS and thus, represents an attractive drug target to meet the need for additional drug treatment of CIAS.

Lurasidone, an atypical APD, is a potent 5-HT_{2A}/D_2 antagonist, 5-HT_7 antagonist and 5-HT_{1A} partial agonist, with weak affinity for the D_4R (Murai et al., 2014). Lurasidone has been found to improve cognition in patients with schizophrenia and in various rodent models of CIAS, including scPCP treatment (Harvey et al., 2015; Horiguchi and Meltzer, 2012; Miyauchi et al., 2017; Murai et al., 2014). It also has marked ability to enhance cortical and hippocampal DA, ACh, and glutamate (Glu) release in rodents (Huang et al., 2014). The D_4R agonists, Ro 10-5824 and PD168077, increased cognition by themselves, potentiated the pro-cognitive effect of lurasidone, and reversed the effect of clozapine in rat NOR and object retrieval detour task (Murai et al., 2014; Miyauchi et al., 2017). These findings suggest that the lack of D_4R antagonism of lurasidone could also contribute, at least partially, to its greater cognitive-enhancing effect in rat and mouse scPCP models of CIAS. Compared to typical APDs, atypical APDs preferentially increase cortical and hippocampal DA and ACh efflux (Huang et al., 2014; Meltzer et al., 2013), both regions are known to have key roles in cognitive function by initiating signaling cascades in both interneurons and principal neurons (Knox, 2016; Otani et al., 2015). The cognitive deficits of CIAS are the result of impaired function and integration of the activity of multiple brain regions, including, but not limited to cortex, hippocampus, dorsal striatum (dSTR), and the influence of multiple neurotransmitter and neuromodulator systems, such as DA, GABA, Glu, BDNF, VEG-F, and others, ultimately affecting synaptic plasticity (Alshammari et al., 2016; Barch and Ceaser, 2012; de Bartolomeis et al., 2014). In the present study, we investigated the effect of D_4R stimulation and blockade on basal- and lurasidone-induced neurotransmitter efflux, including ACh, DA, serotonin (5-HT), GABA and Glu release in both medial PFC (mPFC) and dSTR, the region related to both cognitive impairment and also extra-pyramidal effects (EPS) liability of lurasidone.

2. Materials and methods

2.1. Animals and drugs

Male C57BL/6J mice (Jackson Laboratories, Bar Harbor, Maine, USA) weighing 20–25 g were group housed (five per cage) in a controlled environment held at 21 ± 2 °C and 50 ± 15% relative humidity on a 14:10 h light–dark cycle (lights on 5 am). Food and water were available ad libitum. All experiments were conducted during the light phase. All experimental procedures were approved by and performed in accordance with Institutional Animal Care and Use Committee of Northwestern University, Chicago, IL.

Lurasidone was provided by Sumitomo Dainippon Pharma Co., Ltd. (Osaka, Japan). PD168077 and L745870 were obtained from Tocris bioscience (Minneapolis, MN, USA). Lurasidone and PD168077 were dissolved in 0.5% methylcellulose and 0.2% Tween 80. L745870 was dissolved in sterile distilled water. Compounds and vehicle were administered intraperitoneally (ip) in a volume of 10 mL/kg body weight to randomly assigned mice. Calculations of drug dosage were referred to the free base.

2.2. Microdialysis

Mice were randomly assigned to experimental groups (N = 8–10 per group). Surgical implantation of guide cannula was performed under isoflurane anesthesia and mice were allowed to recover for 2 days prior to the dialysis experiment as previously reported (Huang et al., 2015). Guide cannula (21 G) with dummy probes (Synaptech Co., Marquette, MI, USA) were placed and fixed with cranioplastic cement such that the final probe placements terminated at the mPFC (A + 2.0, L + 0.5 (10° inclination), V − 3.0 mm) and dSTR (A + 1.0, L − 1.5, V − 4.5 mm; relative to bregma) (Paxinos and Franklin, 2004). Concentric-shaped dialysis probes (Synaptech Co., Marquette, MI, USA) with a non-glued, semi-permeable membrane surface (2.0 mm; molecular weight cut off 20 kDa) were implanted on the morning of the experimental day. Perfusion of Dulbecco's phosphate-buffered saline solution through the microdialysis probe was set at a rate of 1.0 μL/min for 2 h prior to collection of baseline samples. Following this 2 h, 4 baseline samples were collected every 30 min prior to administration of test substances. The effect of the drug(s) on neurotransmitter efflux was monitored for another 180 min. Samples were stored in − 80 °C after collection until assayed.

2.3. Assay for neurotransmitters

Assay samples for all the neurotransmitters in our lab by using UPLC and MS/MS based on the reported method (Song et al., 2012) with some modification (Huang et al., 2014). The neurotransmitters measured include ACh, DA, 5-HT, norepinephrine (NE), DOPAC (3,4-dihydroxyphenylacetic acid), HVA (homovanillic acid), 5-HIAA (5-hydroxyindoleacetic acid), Glu and GABA. Internal standard (200 μM amino acids and DOPAC, HVA, 5-HIAA; and 2 μM 5-HT, NE and DA) was derivatized with $^{13}C_6$ benzoyl chloride using the same procedure as ^{12}C reagent, then diluted 100-fold in DMSO containing 1% acetic acid. Internal standard for ACh was d4-ACh (C/D/N isotopes Inc., Pointe-Claire, Canada) was diluted into the reaction mixture to a final concentration of 100 nM. Ten μL of standard or sample was mixed with 5 μL of borate buffer (sodium tetraborate, 100 mM) first and then mixed with 5 μL of benzoyl chloride (2% in acetonitrile, v/v), after that, 5 μL of internal standard and 1 μL of internal ACh standard were added and mixed well before LC-MS/MS analysis.