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Research Report

Stereochemical and neuroanatomical selectivity of pramipexole effects on sensorimotor gating in rats

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ABSTRACT

Background: In rats, prepulse inhibition (PPI) of acoustic startle is disrupted by systemic administration of dopaminergic agonists, such as the dopamine D3 receptor (D3R)-preferential agonist pramipexole (PPX). PPX has D3R-active (S) and -inactive (R) stereoisomers. Here, we tested the neuroanatomical and stereochemical selectivity of PPX effects on PPI.

Methods: (S)-PRA or (R)-PRA (0, 0.47, 1.42, 4.73 μmol/kg) was injected sc 15 min prior to PPI testing in adult male Sprague Dawley rats. In separate rats, (S)-PPX (0, 3, 10 μg/0.5 μl/side, ic) was infused into the nucleus accumbens (NAc), caudodorsal striatum (CS), or olfactory tubercle/Islands of Calleja (ICj) 15 min prior to PPI testing. D3R expression in these brain regions was assessed using quantitative rt-PCR. The PPI-disruptive effects of systemic (S)-PPX were also tested after pretreatment with the D3R-selective antagonist, U99194 (10 mg/kg).

Results: Systemic administration of PPX stereoisomers demonstrated a dose-dependent effect of (S)-PPX on PPI, while (R)-PPX had no effect on PPI. PPX decreased PPI when infused into the NAc and ICj, but not the CS. Quantitative rt-PCR revealed D3R expression in ICj > NAc > CS. The PPI-disruptive effects of PPX were prevented by U99194.

Conclusion: The PPI-reducing effects of PPX are stereospecific for the D3R-active (S)-isomer, neuroanatomically preferential for the D3R-rich ventral vs. D3R poor caudodorsal striatum, and prevented by pharmacologic D3R blockade. These findings are consistent with the conclusion that PPX disrupts PPI via stimulation of mesolimbic D3Rs.

1. Introduction

Prepulse inhibition of acoustic startle (PPI) is the automatic suppression of startle reflex magnitude that occurs when a weak lead stimulus precedes the startling noise. In rats, PPI is disrupted by systemic treatment with dopamine (DA) agonists such as amphetamine and apomorphine; this DA-mediated loss of PPI has been used to model PPI deficits in neuropsychiatric disorders, such as schizophrenia (Braff et al., 1978) and Tourette Syndrome (Castellanos et al., 1996), and to predict the clinical efficacy of antipsychotic compounds (Swerdlow et al., 1994; cf. Swerdlow et al., 2008). Several studies have assessed the regulation of PPI by specific DA receptor subtypes (Doherty et al., 2008; Peng et al., 1990; Stevenson and Gratton, 2004; Wan and Swerdlow, 1996), and the role of D1, D2 and D3 DA receptors in the regulation of

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PPI differs substantially across rodent strains and species, as well as across different brain regions. We and others have shown that PPI is disrupted by systemic treatment with D3-preferential agonists such as pramipexole (PPX) and PD128907 (Chang et al., 2010b; Weber et al., 2008, 2009; Zhang et al., 2007). PPX is among the most D3-selective agonists that are commercially available, with selectivity for D3 over D2 receptors reported to be between 7:1 and 160:1 (Millan et al., 2002; Piercey et al., 1996; Svensson et al., 1994). We previously reported the sensitivity of PPX-induced PPI deficits to several experimental parameters, including sex, species, stimulus modality, inter-stimulus interval, and startle-eliciting pulse magnitude, and demonstrated that PPX effects on PPI are dissociable from changes in startle magnitude or prepulse-elicited motor responses (Chang et al., 2010b; Swerdlow et al., 2009).

Despite its D3-preferential profile, it is unclear precisely how PPX disrupts PPI in rats. For example, a proposed role of D3 autoreceptor stimulation in suppressing presynaptic DA release (Carlsson, 1975; Chen et al., 2003; Diaz et al., 2000) would not easily account for the PPI-disruptive effects of PPX, since PPI is reduced by higher rather than lower levels of forebrain presynaptic DA release (Swerdlow et al., 1990, 2007). PPX has many other biological properties, beyond its effects on D3 receptors, some of which may have clinical utility. For example, PPX exists as both DA-active (S) and DA-inert (R) stereoisomers, both of which display neuroprotective properties in models of DA neurodegenerative disorders, purportedly acting as an antioxidant in neurons (Ferrari-Toninelli et al., 2010; Gu et al., 2004; Joyce et al., 2004; Le et al., 2000; Ramirez et al., 2003). Interestingly, the DA-inactive dexpramipexole has already advanced through early phase clinical trials for neurodegenerative disorders (cf. Cheah and Kiernan, 2010). Here, we first assessed whether D3 activity is necessary for the observed PPX-disruption of PPI, by comparing the effects of (S)-PPX vs. (R)-PPX on this measure.

After establishing that D3-active properties are required for the PPI-disruptive effects of PPX, we next examined whether the PPI-disruptive effects of systemically-administered PPX could be reproduced via intracerebral infusion into discrete forebrain DA terminal regions. Previous studies have demonstrated that infusion of the D2/D3 agonist quinpirole into the nucleus accumbens (NAc) core and shell regions dose-dependently reduces PPI (Wan et al., 1994). D3 receptors are localized within mesolimbic and limbic regions; highest densities are found in the NAc and Islands of Calleja (ICj) in rats and primates, including humans (Landwehrmeyer et al., 1993; Levesque et al., 1992; Sokoloff et al., 2006). In addition to being implicated in the regulation of PPI, many of these brain regions are also of particular relevance to schizophrenia pathology and/or therapeutics. Here, we assessed changes in PPI in Sprague Dawley rats after infusion of PPX into 3 brain regions: 1) the NAc, based on the prominent role of the NAc in mediating DAergic PPI deficits, and the high D3 receptor expression levels in this brain region; 2) the ICj, based on its reported high levels of D3 receptor expression; and 3) the caudodorsal striatum (CS), a region known to regulate PPI, but which has little or no D3 receptor expression. Levels of D3 expression in these three target regions were confirmed via quantitative rt-PCR of tissue collected from drug-naïve rats. Finally, the PPI-disruptive effects of PPX were assessed in rats after blockade of D3Rs using the D3R-selective antagonist, U99194, which has a 13-fold selectivity for D3 over D2 receptors (Audinot et al., 1998).

2. Results

2.1. (S)-PPX vs. (R)-PPX effects

Repeated measures ANOVA of %PPI showed significant main effects of stereoisomer ($F=14.27$, df 1,22; $p<0.002$), PPX dose ($F=7.68$, df 3,66; $p<0.0003$), trial block ($F=5.89$, df 1,22; $p<0.03$), and prepulse intensity ($F=108.07$, df 2,44; $p<0.0001$), and a significant PPX dose × stereoisomer interaction ($F=5.91$, df 3,66; $p<0.002$). There were no other significant two- three- or four-way interactions involving stereoisomer, except for stereoisomer × prepulse intensity ($F=4.85$, df 2,44; $p<0.02$) and stereoisomer × prepulse intensity × PPX dose ($F=3.26$, df 6,132; $p<0.006$). Both of these interaction effects appeared to reflect a lack of any PPX effect on %PPI in the (R)-PPX treated group. Post-hoc tests revealed that %PPI was significantly reduced by the middle and high doses of (S)-PPX ($p<0.009$, $p<0.0001$, respectively), but were not reduced by any doses of (R)-PPX (Fig. 2A).

Startle magnitude to PULSE-ALONE trials also demonstrated significant main effects of PPX dose ($F=3.48$, df 3,66; $p<0.03$) and block ($F=8.30$, df 1, 22; $p<0.009$), but interestingly, no effect of stereoisomer ($F<1$), and no significant interactions. Thus, statistically, both isomers reduce startle magnitude. However, inspection of the data suggests an orderly effect of PPX dose on startle magnitude in the DA-active, but not DA-inactive drug groups (Fig. 2B). As in previous studies (Chang et al., 2010b; Swerdlow et al., 2009; Weber et al., 2008, 2009), to understand the relationship between the startle- and PPI-reducing effects of (S)-PPX, difference scores were calculated between startle magnitude after vehicle and after active drug doses, and an ANOVA was conducted with a median split of these difference scores in each stereoisomer group. The PPI-disruptive effects of PPX did not differ among groups that exhibited high vs. low PPX-induced startle reduction ($F<1$), nor was there a median split × stereoisomer interaction ($F<1$).

2.2. Quantitative rt-PCR

As expected, highest levels of DRD3 expression were observed in the ICj, and expression levels in other brain regions were calculated as a percentage of ICj expression. NAc expressed 28% and CS expressed 8% as much DRD3 as the ICj.

2.3. Intracerebral infusion of (S)-PPX

Repeated measures ANOVA of %PPI showed significant main effects of PPX dose in the NAc ($F=5.39$, df 2,13; $p<0.02$) and ICj ($F=10.63$, df2,17; $p<0.0005$) but not the CS ($F=2.85$, df 2,12; NS) (Fig. 3A). In all groups, there was a significant main effect of intensity ($p<0.0001$), but no other main effects and no significant interactions. Post-hoc tests revealed that, within the NAc and ICj infusion groups, PPI was significantly decreased at both active PPX doses ($ps<0.05$–0.01). PPX sensitivity appeared very comparable after infusion into the NAc and ICj; for example, the PPI-reducing effects of the low dose of