Pharmacology, Biochemistry and Behavior 102 (2012) 6–12

Contents lists available at SciVerse ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

DOI-induced deficits in prepulse inhibition in Wistar rats are reversed by mGlu2/3 receptor stimulation

Lena Wischhof *, Helena E.A. Aho, Michael Koch

University of Bremen, Brain Research Institute, Department of Neuropharmacology, COGNIUM, 28359 Bremen, Germany

ARTICLE INFO

Article history:
Received 13 October 2011
Received in revised form 6 March 2012
Accepted 17 March 2012
Available online 25 March 2012

Keywords:
Serotonin
Glutamate
5-HT_{2A} receptors
LY379268
Sensorimotor gating
Schizophrenia

ABSTRACT

Prepulse inhibition (PPI) of the acoustic startle response (ASR) provides a measure of sensorimotor gating mechanisms that are impaired in schizophrenia patients. Interactions of the serotonin (5-hydroxytryptamine, 5-HT) and glutamatergic systems, especially via the 5-HT_{2A} receptor subtype, have been implicated in the regulation of PPI. The present study investigated the involvement of interactions between 5-HT_{2A} and metabotropic glutamate (mGlu)2/3 receptors in modulating PPI in Wistar and Lister Hooded rats. Systemic administration of the 5-$HT_{2A/2C}$ receptor agonist DOI ((+/−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan hydrochloride; 3 mg/kg) reduced PPI and ASR magnitude in Wistar but not in Lister Hooded rats. In Wistar rats, pretreatment with the mGlu2/3 receptor agonist LY379268 (1 mg/kg) attenuated the DOI-induced disruption of PPI as well as the DOI-elicited reductions of ASR magnitude. LY379268 itself did not alter PPI in both strains and only slightly increased ASR magnitudes in Wistar rats. Taken together, these findings support the notion of functionally antagonistic interactions between 5-HT_{2A} and mGlu2/3 which might be involved in regulating sensorimotor gating mechanisms. Additionally, the data suggest that stimulation of mGlu2/3 receptors may be useful to ameliorate sensorimotor gating deficits resulting from an overstimulation of 5-HT_{2A} receptors.

1. Introduction

Schizophrenia patients exhibit deficits in early information processing as measured e.g. by reduced prepulse inhibition (PPI) of the acoustic startle response (ASR) (Braff et al., 2001; Geyer et al., 2001). PPI refers to the normal suppression of the ASR when the intense startling stimulus (pulse) is shortly (30–500 ms) preceded by a weak non-startling stimulus (prepulse) (Braff et al., 2001; Koch, 1999). This mechanism is thought to reflect information filtering processes that 'gate out' irrelevant and distracting stimuli, thus preventing sensory information overload (Swerdlow et al., 2001). PPI can be assessed in a wide range of species and is commonly regarded as an operational measure of sensorimotor gating processes.

In rodents, PPI is regulated by a cortico-limbic-striato-pallidal circuit that has also been implicated in the pathophysiology of schizophrenia (Koch and Schnitzler, 1997; Swerdlow et al., 2001). Furthermore, in compliance with the dopamine (DA) and glutamate (Glu)-based hypotheses of schizophrenia, administration of direct or indirect DA receptor agonists (Jones and Shannon, 2000; Swerdlow et al., 2000; Zhang et al., 2000) as well as competitive and noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists (Bakshi et al., 1999; Bast et al., 2000; Martinez et al., 2000) has been shown to disrupt PPI in rats. Additionally, several studies demonstrated a complex serotonergic influence implicated in the modulation of PPI (Padich et al., 1996; Sipes and Geyer, 1994). Specifically, both the serotonin (5-hydroxytryptamine, 5-HT)$_{1A}$ receptor agonist 8-OH-DPAT and the 5-$HT_{2A/2C}$ receptor agonist DOI (2,5-dimethoxy-4-iodoamphetamine) disrupted PPI while the selective 5-HT_{2C} receptor agonist mCPP had no effect on sensorimotor gating processes (Sipes and Geyer, 1994, 1995a). The PPI-disruptive effect of DOI has been specifically attributed to its agonist action at the 5-HT_{2A} receptor subtype since it was blocked by the selective 5-HT_{2A} receptor antagonist M100907 (Padich et al., 1996; Sipes and Geyer, 1995b) while both selective 5-HT_{2C} as well as non-selective 5-HT_1 receptor antagonists failed to reduce the DOI-induced PPI disruption (Sipes and Geyer, 1994, 1995b). Furthermore, clinical studies demonstrated that the 5-$HT_{2A/1A}$ receptor agonist psilocybin also causes impairments in PPI and attentional control in healthy humans which could be attenuated by the 5-$HT_{2A/2C}$ receptor antagonist ketanserin (Quednow et al., 2012). However, in contrast to the PPI-disruptive effects of DOI seen in animal studies, the effects of psilocybin in humans seem to depend upon the duration of the interstimulus interval (ISI), i.e. the time between prepulse and pulse (Gouzoulis-Mayfrank et al., 1998; Vollenweider et al., 2007). The idea of 5-HT_{2A} receptors as crucial components in the regulation of PPI has further been strengthened by the finding that polymorphisms of the 5-HT_{2A} receptor gene are associated with deficient sensorimotor gating in schizophrenia patients (Quednow et al., 2009).

Within the cerebral cortex, 5-HT_{2A} receptors show a strikingly overlapping distribution with metabotropic Glu (mGlu)2/3 receptors

* Corresponding author at: University of Bremen, Brain Research Institute, Department of Neuropharmacology, Centre for Cognitive Science, COGNIUM, PO Box 330440, 28359 Bremen, Germany. Tel.: +49 421 218 62975; fax: +49 421 218 62984.
E-mail address: lena_wischhof@yahoo.de (L. Wischhof).

0091-3057/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2012.03.011

(Jakab and Goldman-Rakic, 1998; Ohishi et al., 1998) and several studies demonstrated functionally antagonistic behavioral interactions between these two receptor subtypes. For example, mGlu2/3 receptor agonists have been shown to suppress excitatory postsynaptic potentials in the medial prefrontal cortex (mPFC) induced by 5-HT_{2A} receptor stimulation, and to attenuate behavioral responses following hallucinogenic drug treatment (Gewirtz and Marek, 2000; Klodzinska et al., 2002). Moreover, González-Maeso et al. (2008) recently demonstrated that on cortical pyramidal cells 5-HT_{2A} and mGlu2 receptors share direct molecular interactions via specific transmembrane domains resulting in the formation of a heteroreceptor complex. The authors further hypothesized that these 5-HT_{2A}–mGlu2 receptor complexes may trigger a unique cellular response serving to integrate 5-HT and Glu signaling which might be crucial for the regulation of sensory gating mechanisms (González-Maeso et al., 2008).

Reversal of pharmacologically induced PPI deficits is considered indicating potential antipsychotic properties and recent research suggests that compounds acting at the mGlu2/3 receptor subtype may be beneficial for the treatment of psychiatric disorders such as schizophrenia (Moghaddam and Adams, 1998; Monn et al., 1997). For example, mGlu2/3 receptor agonists have been shown to attenuate phencyclidine (PCP)-induced locomotor hyperactivity (Cartmell et al., 2000; Moghaddam and Adams, 1998; Rorick-Kehn et al., 2007) and attentional deficits following intra-cortical infusions of (R)-CPP (3-(R)-2-carboxypiperazin-4-propyl-1-phosphonic acid) (Pozzi et al., 2011). However, mGlu2/3 receptor agonists like LY314582 and LY379268 failed to reverse PPI deficits caused by either amphetamine or PCP treatment (Galici et al., 2005; Henry et al., 2002). In addition, stimulation of mGlu2/3 receptors did not improve (Ossowska et al., 2000; Schlumberger et al., 2009) or even exacerbated (Amitai and Markou, 2010) cognitive impairments caused by NMDA receptor agonism. Thus, mGlu2/3 receptor agonists appear to have only limited capability to attenuate NMDA receptor antagonist-induced disruptions in cognitive functioning but they might be more effective in ameliorating cognitive deficits resulting from a hyperserotonergic state.

The present study investigated the functional relevance of 5-HT_{2A} and mGlu2/3 receptor interactions in the regulation of sensorimotor gating mechanisms and tested whether the PPI-disruptive effects of the hallucinogenic 5-HT_{2A} receptor agonist DOI can be attenuated by pre-treatment with the mGlu2/3 receptor agonist LY379268. Furthermore, several studies reported rat strain differences in the mediation and modulation of PPI as well as in drug-responsiveness (Varty and Higgins, 1994, 1995b; Weiss et al., 2000). However, most of these studies are limited to a comparison between Wistar and Sprague–Dawley rats while the results obtained in Lister Hooded rats are fairly rare. Since we used this rat strain in our previous studies (Wischhof et al., 2011; Wischhof and Koch, 2012) and in order to consider possible strain differences, all experiments were carried out with both Wistar and Lister Hooded rats.

2. Materials and methods

2.1. Animals

A total of 19 adult Lister Hooded and Wistar rats (250–300 g) obtained from Harlan (Borchen, Germany) were used in this study. They were housed in groups of five in Macrolon cages (type IV) under controlled ambient conditions (22 °C, 12 h light/dark cycle, lights on at 7:00 a.m.). The animals received free access to tap water and were maintained on their experimental body weight by controlled feeding of 12 g rat chow (Nohrlin GmbH, Bad Salzuflen, Germany) per rat per day. Behavioral testing was done during the rats' light cycle between 09:00 a.m. and 05:00 p.m. The experiments were performed in accordance with the National Institutes of Health ethical guidelines for the care and use of laboratory animals for experiments and were approved by the local authorities.

2.2. Drugs

The selective 5-$HT_{2A/C}$ receptor agonist DOI ((±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan hydrochloride) was purchased from Sigma-Aldrich (Chemie GmbH, Steinheim, Germany) and dissolved in 0.9% saline. The selective mGlu2/3 receptor agonist LY379268 ((1R,4R,5S,6R)-4-Amino-2-oxabicyclo[3.1.0]hexane-4,6- dicarboxylic acid) obtained from Biozol (Diagnostica Vertrieb GmbH, Eiching, Germany), was dissolved in 0.9% saline with a few drops of 1.2 M NaOH. After adjusting the pH to approximately 7.4 with 2 M HCl, aliquots of stock solutions were made and stored at −20 °C until use.

2.3. Apparatus

PPI and short-term habituation of the ASR were assessed using a three-unit automated SRLab startle system (San Diego Instruments, San Diego, CA, USA). Startle-boxes consisted of non-restrictive Plexiglas cylinders (9 cm in diameter) resting on a piezo-sensitive platform inside a sound-attenuated, illuminated and ventilated chamber. Acoustic stimuli were delivered over 60 dB broadband background noise through loudspeakers in the ceiling of the box. Each test session began with a 5 min acclimation period before a total of 70 trials with an average intertrial interval (ITI) of 25 s were delivered. The first and last five trials consisted of single 20 ms pulse-alone broadband noise stimuli with an intensity of 105 dB sound pressure level. The middle 60 trials consisted of random delivery of ten 105 dB pulse-alone trials, 30 prepulse-pulse trials, ten pre-pulse trials (76 dB) and ten no-stim trials during which no stimuli were presented. Prepulse–pulse trials consisted of a single 105 dB pulse preceded by 100 ms by a white noise prepulse of either 68, 72 or 76 dB (duration 20 ms, 0 ms rise/fall time). Vibration of the cylinder caused by whole body ASR of the rat to the acoustic stimuli were transduced into analog signals and then digitized and stored by a computer using the SRLab software (San Diego Instruments, San Diego, USA). The percentage of PPI induced by each of the three prepulse intensities was calculated as: $100-[(\text{ASR magnitude on prepulse–pulse trials})/(\text{ASR magnitude on pulse alone trial})\times 100]$. Within-session habituation was determined using the ASR magnitudes of the first five, middle ten and last five pulse alone trials. One PPI session lasted for approximately 30 min.

2.4. Experimental design

Before the start of drug testing, a pre-PPI session was conducted to acclimatize the animals to the PPI procedure. The pre-PPI session was done according to an identical protocol as the drug-trials but the rats did not receive any drug treatment. For drug testing, rats were randomly injected with either vehicle (1 ml/kg) or LY379268 (LY, 0.5 mg/kg or 1 mg/kg; intraperitoneally) 20 min prior to DOI (3 mg/kg; subcutaneously) or vehicle. Drug doses and routes of administration were based on previous studies and have been reported to be effective (Gewirtz and Marek, 2000; Padich et al., 1996; Varty and Higgins, 1995a). Ten minutes after the second injection, rats were placed into the PPI chambers. In a pseudo-randomized cross-over protocol all rats received all treatment combinations. To minimize the effects of external factors, the animals were put into the same chambers for each experiment. Three days were allowed between individual testing days to allow the drugs to be washed out.

2.5. Statistics

The descriptive statistics is based on means and variance is indicated by the standard error of the mean (±SEM). The effects of systemic drug administration on PPI were analyzed using a three-way repeated measures analysis of variance (ANOVA; within-subject repeated measures factors: prepulse intensity (68 dB, 72 dB, 76 dB), pre-treatment (Veh, LY0.5, LY1) and treatment (Veh, DOI)). ASR magnitudes were calculated