Neuropharmacology 101 (2016) 389–400

Contents lists available at ScienceDirect

Neuropharmacology

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

Positive allosteric modulators of alpha 7 nicotinic acetylcholine receptors reverse ketamine-induced schizophrenia-like deficits in rats

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ARTICLE INFO

Article history:
Received 25 March 2015
Received in revised form
13 July 2015
Accepted 27 July 2015
Available online 29 July 2015

Keywords:
Alpha 7 nicotinic acetylcholine receptors
Positive allosteric modulators
Schizophrenia
Animal models
Cognition
Ketamine

ABSTRACT

Alpha 7 nicotinic acetylcholine receptors (α7-nAChRs) have generated great interest as targets of new pharmacological treatments for cognitive dysfunction in schizophrenia. One promising recent approach is based on the use of positive allosteric modulators (PAMs) of α7-nAChRs, which demonstrate several advantages over direct agonists. Nevertheless, the efficacy of these newly introduced α7-nAChR agents has not been extensively characterised in animal models of schizophrenia.

The aim of the present study was to evaluate the efficacy of type I and II PAMs, N-(5-chloro-2,4-dimethoxyphenyl)-N'-(5-methyl-3-isoxazolyl)urea (PNU-120596) and N-(4-chlorophenyl)-[[(4-chlorophenyl)amino]methylene]-3-methyl-5-isoxazoleacet-amide (CCMI), respectively, and galantamine, an acetylcholinesterase inhibitor (AChE) that also allosterically modulates nAChRs, against ketamine-induced cognitive deficits and social withdrawal in rats. The orthosteric α7-nAChR agonist octahydro-2-methyl-5-(6-phenyl-3-pyridazinyl)-pyrrolo[3,4-c]pyrrole (A-582941) was used as a positive control. Additionally, the antipsychotic activities of the tested compounds were assessed using the conditioned avoidance response (CAR) test.

PNU-120596, CCMI, galantamine and A-582941 reversed ketamine-induced cognitive inflexibility, as assessed in the attentional set-shifting task (ASST). The tested compounds were also effective against ketamine-induced impairment in the novel object recognition task (NORT). PNU-120596, CCMI, and A-582941 ameliorated ketamine-induced social interaction deficits, whereas galantamine was ineffective. Moreover, all tested compounds selectively suppressed the CAR.

The positive allosteric modulation of α7-nAChRs demonstrates preclinical efficacy not only against schizophrenia-like cognition impairments but also positive and negative symptoms. Therefore, the use of α7-nAChR PAMs as a potential treatment strategy in schizophrenia is supported.

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1. Introduction

Alpha 7 nicotinic acetylcholine receptors (α7-nAChRs) play important roles in the regulation of cognitive functions (Buchanan and Schwarcz, 2011; Wallace and Porter, 2011; Young and Geyer, 2013). Moreover, α7-nAChRs have been implicated in the pathophysiology of schizophrenia. The sensory processing deficit in schizophrenia has been genetically associated with the locus of the CHRNA7 gene encoding α7-nAChRs (Freedman et al., 1997). The cholinergic brain abnormalities observed in patients with schizophrenia include decreased mRNA levels of CHRNA7 (Mexal et al., 2010) and reduced protein expression of α7-nAChRs in the frontal cortex (Guan et al., 1999).

As a result, α7-nAChRs have received increasing attention as targets for novel pharmacological treatment of cognitive dysfunction in schizophrenia. The activity of α7-nAChR can be modulated through either orthosteric agonists or positive allosteric modulators (PAMs). The PAM-induced activation of α7-nAChR occurs exclusively in the presence of an endogenous agonist, thereby preserving the temporal integrity of neurotransmission. Thus, α7-nAChR PAMs might offer several advantages over the direct agonist approach (Jones et al., 2012; Pandya and Yakel, 2013b; Williams et al., 2011). Based on the functional properties of modulation, these compounds can be divided into two classes: type I (e.g., CCMI (Ng et al., 2007)) and type II (e.g., PNU-120596 (Hurst et al., 2005)). Type-I α7-nAChR PAMs potentiate the agonist-induced peak current but have no effect on desensitization,

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http://dx.doi.org/10.1016/j.neuropharm.2015.07.034
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whereas the action of type-II α7-nAChR PAMs is accompanied by the profound retardation of the kinetics of desensitization. Thus, type II PAMs are less prone to induce tolerance, which may occur after the chronic administration of nicotinic agonists. Conversely, type I PAMs, which preserve the rapid channel kinetics, may be more beneficial than type II PAMs at minimizing potential Ca2+-induced cytotoxicity (Ng et al., 2007). It has been also proposed that desensitization of α7-nAChR is responsible for the procognitive effects (Buccafusco et al., 2009).

Although several type I and type II α7-nAChR PAMs have recently been developed, a direct comparison of the behavioural effects of both types of modulators has not been systematically assessed. Particularly, the efficacy of these newly introduced α7-nAChR agents has not been extensively characterised in animal models of schizophrenia.

Non-competitive antagonists of the NMDAR such as ketamine and phencyclidine (PCP) produce a behavioural syndrome in healthy humans that closely resembles the symptoms of schizophrenia (Krystal et al., 1994; Murray, 2002). Therefore, NMDAR-based models are commonly used to mimic schizophrenia-like states in laboratory animals (Neill et al., 2010). The acute administration of NMDAR antagonists evokes a broad range of schizophrenia-like symptoms, including cognitive deficits and social withdrawal. Because ketamine is commonly used in the clinic to model transient schizophrenia-like disturbances in healthy volunteers (Kocsis et al., 2013), the ketamine-based animal model, which has translational value, might represent a valuable tool in preclinical research.

Deficits in prefrontal cortical functions are recognised as prominent features of schizophrenia and include reduced flexibility in modifying behaviour in response to the changing relevance of stimuli. This aspect of executive functions can also be assessed in rodents using the attentional set-shifting task (ASST) (Birrell and Brown, 2000). In this paradigm, the rats must select a bowl containing a food reward based on the discrimination of odours and media covering the bait. The ASST requires rats to initially learn a rule and form an attentional "set" within the same stimulus dimensions. At the crucial extra-dimensional shift (ED) stage, the animals must switch their attention to a new, previously irrelevant stimulus dimension—for example, discriminating between odours while ceasing to discriminate between the media covering the bait. Performance at the ED stage is regarded as an index of cognitive flexibility. In a previous study, we demonstrated that either acute (Nikiforuk et al., 2010) or repeated (Nikiforuk and Popik, 2012) administration of ketamine impaired the performance of rats at the ED stage in the ASST. This ketamine-evoked set-shifting could be reversed using antipsychotic drugs, i.e., sertindole, quetiapine or amisulpride (Nikiforuk et al., 2010; Nikiforuk and Popik, 2012; Nikiforuk et al., 2013).

The novel object recognition task (NORT) in rodents has been increasingly used as an ethologically relevant paradigm for the study of visual episodic memory (Ennaceur and Delacour, 1988). This paradigm is based on the spontaneous exploration of novel and familiar objects. Successful object recognition is indicated when an animal spends more time interacting with the novel object in the retention trial. Ketamine administration in rats was previously demonstrated to abolish the ability to discriminate the novel object from the familiar one (Nikiforuk et al., 2013). Moreover, this object recognition deficit was ameliorated through treatment with various antipsychotic drugs (Nikiforuk et al., 2013).

Perturbations in social functioning such as social withdrawal and a sociality represent key items of a cluster of negative symptoms. Social deficits can also be modelled in preclinical paradigms. Specifically, rodents exhibit structured and stable social behaviour patterns associated with well-defined biological functions that can be assessed in laboratory rats using the social interaction (SI) test. Sams-Dodd (Sams-Dodd, 1995) demonstrated that the social behaviours of pairs of unfamiliar rats in the open field arena might represent an ethologically valid approach for the preclinical assessment of social functions (for a recent review, see Gururajan et al. (2010)). According to a previous study (Nikiforuk et al., 2013), the acute administration of ketamine evoked robust decreases in time spent in social interactions, and atypical antipsychotic drugs have been shown to ameliorate ketamine-evoked social withdrawal (Holuj et al., 2015; Nikiforuk et al., 2013).

Therefore, the aim of the present study was to examine the ability of PNU-120596 (Hurst et al., 2005) and CCMI (also known as compound 6, AVL-3288 or XY4083) (Ng et al., 2007) to reverse ketamine-induced cognitive deficits observed in the ASST and NORT and social withdrawal in rats. Additionally, the efficacy of galantamine, an acetylcholinesterase (AChE) inhibitor that also allosterically modulates nAChRs (Maelicke et al., 2001), was assessed. The activities of α7-nAChR PAMS were compared to the orthosteric agonist A-582941 (Tietje et al., 2008).

Moreover, to evaluate the potential antipsychotic activities of the tested compounds, we employed the conditioned avoidance response (CAR) test (Wadenberg and Hicks, 1999). In the CAR, the presentation of a conditioned stimulus (CS) predicts an aversive outcome (a weak electric shock). Animals learn to avoid a foot shock by moving into another compartment (avoidance response). Alternative behaviours include escape (response to CS paired with shock) and escape failure (failure to respond to CS paired with shock). Antipsychotic action is revealed through the selective suppression of avoidance behaviour in well-trained animals. Therefore, the CAR is commonly considered a reliable screening tool for the detection of potential antipsychotic activities, even for compounds that have no direct dopamine D2 receptor blocking properties (Wadenberg, 2010).

2. Materials and methods

2.1. Animals

The experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the II Local Ethics Committee for Animal Experiments at the Institute of Pharmacology, Polish Academy of Science, Krakow, Poland.

Male Sprague–Dawley rats (Charles River, Germany), weighing 200–250 g (ASST, NORT and CAR tests) or 125–150 g (SI test) on arrival, were housed in a temperature-controlled (21 ± 1 °C) and humidity-controlled (40–50%) colony room under a 12/12 h light/dark cycle (lights on at 06:00 h). For the NORT and CAR studies, the rats were group-housed (5 rats/cage) with free access to food and water. For the ASST, the rats were individually housed with a mild food restriction (17 g of food pellets per day) for at least one week prior to testing. For the SI test, the rats were individually housed for 5 days prior to the start of the procedure with free access to food and water. Behavioural testing was performed during the light phase of the light/dark cycle.

2.2. Attentional set-shifting task (ASST)

Apparatus. Testing was conducted in a Plexiglas apparatus (length × width × height: 38 × 38 × 17 cm) with the grid floor and wall dividing half of the length of the cage into two sections. During testing, one ceramic digging pot (internal diameter of 10.5 cm and a depth of 4 cm) was placed in each section. Each pot was defined by a pair of cues along with two stimulus dimensions. To mark each

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