Psychoneuroendocrinology (2014) 40, 119—122

Available online at www.sciencedirect.com

ScienceDirect

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

SHORT COMMUNICATION

Ketamine prevents stress-induced cognitive inflexibility in rats

Agnieszka Nikiforuk, Piotr Popik *

Department of Behavioral Neuroscience and Drug Development, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland

Received 29 August 2013; received in revised form 6 November 2013; accepted 12 November 2013

KEYWORDS
Stress;
Cognitive deficit;
Prefrontal cortex;
Ketamine;
NMDA receptors;
Set-shifting

Summary Chronic stress produces both morphological and functional alternations of the rat medial prefrontal cortex (mPFC). N-methyl-D-aspartic acid (NMDA) glutamate receptor inhibition may alleviate such stress-induced dendritic reorganization in the mPFC. However, it is unknown whether administration of a NMDAR antagonist would also prevent alterations in PFC-mediated cognitive functions. Here, we investigated whether administration of ketamine, the noncompetitive antagonist of NMDA receptors before each stress session would prevent cognitive impairments in a rat model of prefrontal cortex (PFC)-dependent attentional set-shifting task (ASST), a measure of cognitive flexibility. Repeated restraint stress (1 h daily for 7 days) significantly and specifically impaired extra-dimensional (ED) set-shifting ability of rats. Pretreatment with ketamine (10 mg/kg, IP) completely and specifically prevented this stress-induced cognitive inflexibility. The present study demonstrates procognitive efficacy of ketamine in an animal stress model, which confirms and extends the role of the NMDA receptors in mediating stress-evoked prefrontal dysfunctions.

1. Introduction

It is widely accepted that chronic stress, considered as a risk factor for several neuropsychiatric disorders, may have detrimental effects on cortical functions. In animal models, chronic stress produced morphological, physiological and functional alternations in the rat medial prefrontal cortex (mPFC) (Liston et al., 2006; Liu and Aghajanian, 2008).

The attentional set-shifting task (ASST) evaluates cognitive flexibility, a component of executive control subserved by the prefrontal cortex (Birrell and Brown, 2000). In this task, rats must select a bowl containing a food reward by discriminating the odours and the media covering the bait. The ASST requires rats to initially learn a rule and to form an attentional "set" within the same stimulus dimensions. At the extra-dimensional (ED) shift stage, the essential phase of the task, animals must switch their attention to a new, previously irrelevant stimulus dimension and, for example, discriminate only between the odours and no longer between the media covering the bait. The animals' performance at the ED stage, regarded as an index of cognitive flexibility, is impaired by lesions of the mPFC (Birrell and Brown, 2000) and by chronic stress (Nikiforuk and Popik, 2011). Liston et al. (2006) demonstrated that rats subjected to

* Corresponding author at: Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-343 Krakow, Poland. Tel.: +48 12 6623374; fax: +48 12 6374500.
E-mail addresses: nikifor@if-pan.krakow.pl, nfpopik@cyf-kr.edu.pl (P. Popik).

0306-4530/$ — see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psyneuen.2013.11.009

chronic restraint stress exhibited a decrease in mPFC dendritic arborization that predicted impaired ED set-shifting performance. In parallel to this rodent model, chronic psychosocial stress-induced disruption of prefrontal functional connectivity in human subjects predicted the decline in attentional set-shifting ability (Liston et al., 2009).

An exposure to stressors results in a variety of neurochemical changes. For example, stress preferentially increased glutamate concentration in the prefrontal cortex (Moghaddam, 1993). According to the recent study of Martin and Wellman (2011), glutamatergic transmission at N-methyl-D-aspartic acid (NMDA) receptors may play a role in the stress-induced dendritic reorganization in the mPFC. These authors demonstrated that administration of the competitive NMDA receptor antagonist, ±3-(2-carboxypiperazin-4yl)propyl-1-phosphonic acid (CPP) prevented stress-induced mPFC dendritic atrophy. This finding raises the possibility that the neurochemical consequences of stress involving NMDA receptors, may also alter PFC-mediated functional processes, such as the ability to shift attention.

To explore this hypothesis, the present study investigated whether pretreatment with the noncompetitive antagonist of NMDA receptors, ketamine, before each stress session would prevent cognitive inflexibility. While acute administration of ketamine has been widely used to model some symptoms of schizophrenia including the cognitive impairment in rats (Nikiforuk et al., 2010) and mice (Kos et al., 2011), this compound also demonstrated the efficacy against stress-induced synaptic and behavioural alternations (Li et al., 2011).

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Charles River, Germany) weighing 250—280 g on arrival were used in this study. They were housed in a temperature- (21 ± 1 °C) and humidity- (40—50%) controlled colony room under a 12/12-h light/dark cycle (lights on at 0600 h). Individual housing was maintained for the entire duration of the experiment. For one week prior to testing, rats were mildly food restricted (15 g of food pellets per day). Behavioural testing was performed during the light phase of the light/dark cycle. The experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Ethics Committee for Animal Experiments, Institute of Pharmacology.

2.2. Restraint stress procedure

The stress paradigm consisted of 1-h daily restraint stress for 7 consecutive days (Nikiforuk and Popik, 2011). Rats were transferred from a housing facility to the stress-room, separate from the testing-room. Animals were placed into perforated plastic tubes (6.5 cm inner diameter) of adjustable length. The restraint allowed for normal breathing and limited movements of the head and the limbs. After the stress session, animals were removed from the restrainers and returned to their home cages for a 1-h rest period before having been transported back to the housing facility. The rats were restrained between 1300 h and 1600 h. The non-restrained controls were handled daily for 7 consecutive days.

This stress procedure has previously been shown to produce a long-lasting (at least up to 21 days) impairment of ED set-shifting (Nikiforuk and Popik, 2011). To avoid the acute effects of restraint exposure and to be able to evaluate the long-term consequences of repeated stress, the present ASST experiments were performed on the 14th day after the last stress session. Animals were left undisturbed during this period, except for the last 5 days before the start of the testing procedure when all animals were handled daily.

2.3. Attentional set-shifting task

A detailed description of the apparatus and procedure has been provided previously (Nikiforuk, 2012; Nikiforuk et al., 2010). Briefly, rats were presented with two ceramic pots but only one pot is "positive", i.e., it is baited with a food reward (Honey Nut Cheerio, Nestle®). Animals had to retrieve the Cheerio on the basis on their ability to discriminate the odours (the pot is marked with) or the digging media (that cover bait in the pot). The digging (any distinct displacement of the digging media with either the paw or the nose) in the "negative" pot was defined as an error. A small amount of powdered Cheerio was added to the digging media in the unbaited pot to prevent the rat from trying to detect the buried reward by its smell.

The procedure entailed three days for each rat: habituation, training and testing. During a single test session, rats performed a series of 7 discriminations: simple discrimination (SD), compound discrimination (CD), reversal 1 (Rev1), intradimensional shift (ID), reversal 2 (Rev 2), extradimensional shift (ED), reversal 3 (Rev 3). The first four trials at the beginning of each discrimination phase were a discovery period (not included in six trials to criteria). In subsequent trials, an incorrect choice was recorded as an error. Table 1 outlines the progressions through ASST phases including exemplars of odours and media used and their assignment into pairs.

2.4. Drug administration

Ketamine (aqueous solution of 100 mg/ml, Vetoquinol Biowet, Gorzów Wielkopolski, Poland) was diluted in distilled water to the appropriate concentration. Ketamine or vehicle (physiological saline) was administered in a volume of 1 ml/kg of body weight. Rats received intraperitoneal injections of ketamine (0 and 10 mg/kg) immediately before the restraint during 7 daily stress sessions ($n = 6—8$ rats per group). Animals were submitted to the ASST on the 14th day after stress termination. Unstressed controls received ketamine or vehicle for 7 consecutive days in the housing facility and were tested on 14th day after the last drug injection ($n = 6$ rats per group). The dose of ketamine was chosen on the basis of the previous report demonstrating its efficacy against stress-evoked dysfunctions in rats (Li et al., 2011).

2.5. Statistical analysis

The number of trials required to achieve the criterion of 6 consecutive correct responses was recorded for each rat