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Quetiapine ameliorates stress-induced cognitive inflexibility in rats

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ABSTRACT

The antidepressant action of quetiapine has been demonstrated in clinical and preclinical studies. Nevertheless, little is known about its effectiveness in the treatment of frontal-like cognitive disturbances that may be associated with stress-related disorder.

Therefore, the aim of the present study was to investigate whether quetiapine would prevent and/or reverse stress-induced cognitive impairments in a rat model of prefrontal cortex (PFC)-dependent attentional set-shifting task (ASST). Because quetiapine augmentation to selective serotonin reuptake inhibitors (SSRIs) has recently been proven to be beneficial in neuropsychiatric disorders, a separate experiment was designed to assess the impact of combined administration of inactive doses of quetiapine and escitalopram on ASST performance in rats.

According to our previous studies, 1 h daily exposure to restraint stress for 7 days significantly and specifically impaired extra-dimensional (ED) set-shifting ability of rats. Quetiapine (2.5 mg/kg, PO) given to rats prior to the restraint sessions completely prevented this stress-induced cognitive inflexibility. Similar effect was demonstrated after pretreatment with the α1-adrenoceptor antagonist, prazosin (1 mg/kg, IP). Moreover, acute administration of quetiapine before the test reversed set-shifting deficits in stressed rats (0.63, 1.25 and 2.5 mg/kg, PO) and improved ED performance of cognitively unimpaired control animals (1.25 and 2.5 mg/kg, PO). Finally, the combined administration of inactive doses of quetiapine (0.63 and 0.3 mg/kg in control and stressed rats, respectively) and escitalopram (0.3 mg/kg, IP) facilitated set-shifting performance in either control or stressed rats.

In conclusion, quetiapine administration either prevented or reversed stress-induced cognitive inflexibility in rats. In addition to promoting of set-shifting by itself, quetiapine also enhanced the procognitive efficacy of escitalopram. The potential contribution of the antagonism at α1-adrenoceptors to the mechanisms underlying the protective action of quetiapine requires further evaluation.

These findings may have therapeutic implications for the treatment of frontal-like disturbances, particularly cognitive inflexibility, in stress-related psychiatric disorders.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

Quetiapine is the only atypical antipsychotic approved by the US Food and Drug Administration (FDA) for use as monotherapy in both the manic and depressive phases of Bipolar Disorder (Suppes et al., 2010) as well as adjunctive therapy in Major Depressive Disorder (MDD) (Pae et al., 2010). Moreover, quetiapine demonstrated efficacy as monotherapy in the treatment of patients with MDD (Pae et al., 2010). The antidepressant-like action of quetiapine has also been suggested in preclinical studies. Indeed, quetiapine prevented the anhedonic state in rats exposed to the chronic mild stress protocol (Orsetti et al., 2007) and the major metabolite of quetiapine, N-desalkylquetiapine, exerted antidepressant-like effects in the tail suspension test in mice (Jensen et al., 2008).

Although the procognitive action of quetiapine has been demonstrated in either animal models of schizophrenia (Nikiforuk and Popik, 2012; Tanibuchi et al., 2009) or schizophrenic patients (Purdon et al., 2001), little is known about effectiveness of the drug against frontal-like cognitive disturbances that may be associated with depressive disorder. Depressed patients demonstrate impairments in psychological tasks thought to reflect executive prefrontal functions (Channon, 1996; Merriam et al., 1999). Particularly, deficits reflecting reduced cognitive flexibility have been demonstrated independently of the disease subtype and subjects' motivation, and might persist after the remission of other clinical symptoms (Austin et al., 1992; Robinson et al., 2006).

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Flexibility in modifying behavior in response to the altering relevance of stimuli may be assessed in rodents in the attentional set-shifting task (ASST) (Birrell and Brown, 2000). In this paradigm, rats must select a bowl containing food reward, based on the ability to discriminate the odors 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 dimension. At the extra-dimensional shift (ED), animals must switch their attention to a new, previously irrelevant stimulus dimension and, for example, discriminate between the odors and no longer between the media covering the bait. The ED phase, considered to be an index of cognitive flexibility, is impaired by the lesion of the medial prefrontal cortex (mPFC) (Birrell and Brown, 2000).

Because prolonged stress has been regarded as a major risk factor for depression, stress-based animal models represent a useful instrument to mimic depressive-like symptomatology (Anisman and Matheson, 2005). In particular, the repeated restraint stress produced morphological (Cook and Wellman, 2004; Radley et al., 2006), physiological (Cerqueira et al., 2007; Liu and Aghajanian, 2008) and functional (Liston et al., 2006) alternations in the rat mPFC, and therefore may provide an appropriate model to study clinically relevant frontal-like cognitive deficits. Our previous study demonstrated that rats restrained for 1 h daily for 7 consecutive days exhibited a long-lasting (up to 3 weeks) mPFC-dependent cognitive deficit as indicated by the selective impairment of ED set-shifting in the ASST (Nikiforuk and Popik, 2011). Therefore, the first aim of the present study was to investigate whether quetiapine administration prior to restraint sessions would prevent the stress-induced set-shifting deficit as assessed in the ASST task in rats. Our previous study demonstrated that acute administration of quetiapine before testing reversed the ED set-shifting deficit in the *N*-methyl-D-aspartate receptor (NMDAR)-based rat model of schizophrenia (Nikiforuk and Popik, 2012). Therefore, a separate experiment was conducted to evaluate the effectiveness of acute treatment with quetiapine in alleviating stress-induced cognitive inflexibility.

Experimental data suggest that α1-adrenoceptor stimulation in the PFC contributes to stress-induced impairments in PFC cognitive functions (Birnbaum et al., 1999). Consequently, high affinity of quetiapine for the α1-adrenoceptor (Richelson and Souder, 2000) suggests that its protective action against the stress-induced ED deficit may be due to antagonism at the α1-adrenoceptor. To further explore this hypothesis, the next experiment investigated whether pretreatment with the α1-adrenoceptor antagonist, prazosin, before each stress session would prevent cognitive inflexibility.

The combination of quetiapine with selective serotonin reuptake inhibitors (SSRIs) has recently been proven to be beneficial in neuropsychiatric disorders, such as depression and schizophrenia (Chertkow et al., 2009; Devarajan et al., 2006). Nevertheless, little is known about the influence of this augmentation strategy on cognitive functioning. Thus, the last experiment was designed to assess the impact of combined administration of inactive doses of quetiapine and escitalopram on ASST performance in rats.

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 06:00 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). Behavioral 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 13:00 and 16:00 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 current ASST experiments were performed on 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

2.3.1. Apparatus

Testing was conducted in a modified wire rat housing cage (length- × width × height: 42 cm × 32 cm × 22 cm) with a white plywood wall dividing half of the length of the cage into two sections (Nikiforuk and Popik, 2011, 2012). 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 pot with a distinct odor, 5 μl of a flavoring essence (Dr. Oetker®, Poland) was applied on a piece of blotting paper fixed to the external rim of the pot immediately prior to use. A different pot was used for each combination of digging medium and odor; only one odor was ever applied to a given pot. The bait (one-third of a Honey Nut Cheerio, Nestle®) was placed at the bottom of the "positive" pot and buried in the digging medium. 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 smell.

2.3.2. Attentional set shifting: procedure

The procedure was adopted from Birrell and Brown (2000) and entailed three days for each rat.

Day 1, habituation: rats were habituated to the testing area and were trained to dig in the pots filled with sawdust to retrieve the food reward. Rats were transported from the housing facility to the testing room where they were presented with one unscented pot (filled with several pieces of cereal) in their home cages. After the rats had eaten the Cheerio from the home cage pot, they were placed in the apparatus and given three trials to retrieve the reward from both of the sawdust-filled baited pots. With each exposure, the bait was covered with an increasing amount of sawdust.

Day 2, training: rats were trained on a series of simple discriminations (SD) to a criterion of six consecutive correct trials. For these trials, rats had to learn to associate the food reward with an odor cue (e.g., arrack vs. orange, both pots were filled with sawdust) and/or a digging medium (e.g., plastic balls vs. pebbles, no odor). All rats were trained using the same pairs of stimuli. The positive and negative cues for each rat were presented randomly and equally. These training stimuli were not used again in later testing trials.

Day 3, testing: rats performed a series of discriminations in a single test session. The first four trials at the beginning of each discrimination phase were a discovery period (not included in the six criterion trials). In subsequent trials, an incorrect choice was recorded as an error. Digging was defined as any distinct displacement of the digging media with either the paw or the nose; the rat could investigate a digging pot by sniffing or touching without displacing material. Testing was continued at each phase until the rat reached the criterion of six consecutive correct trials, after which testing proceeded to the next phase.

In the simple discrimination (SD) involving only one stimulus dimension, the pots differed along one of two dimensions (i.e., a digging medium). For the compound discrimination (CD), the second (irrelevant) dimension (i.e., an odor) was introduced but the correct and incorrect exemplars of the relevant dimension remained constant. For the reversal of this discrimination (Rev 1), the exemplars and relevant dimension were unchanged but the previously correct exemplar was now incorrect and vice versa. The intra-dimensional (ID) shift was then presented, comprising new exemplars of both the relevant and irrelevant dimensions with the relevant dimension remaining the same as previously. The ID discrimination was then reversed (Rev 2) so that the formerly positive exemplar became the negative one. For the extra-dimensional (ED) shift a new pair of exemplars was again introduced, but this time a relevant dimension was also changed. Finally, the last phase was the reversal (Rev 3) of the ED discrimination problem. The exemplars were always presented in pairs and varied so that only one animal within each treatment