The antagonist of 5-HT7 receptors, SB-269970, and amisulpride both reverse ketamine-induced cognitive inflexibility in rats.

Dominik Rafa, Agnieszka Nikiforuk, Piotr Popik

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

INTRODUCTION

The prefrontal cortex mediates higher-order executive functions, including among other, the cognitive flexibility, i.e., the ability to modify behavior in response to changing task demands. This aspect of executive function is impaired in schizophrenia. Cognitive flexibility may also be assessed in rodents in the attentional set-shifting task (ASST). In this paradigm, rats must select a bowl containing a 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 form an attentional "set" within the same stimulus dimensions. At the extradimensional (ED) shift, 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 animals' performance at the ED phase is impaired in N-methyl-D-aspartate receptor antagonist (e.g., ketamine)-treated animals, regarded as pharmacological model of schizophrenia-like symptoms.

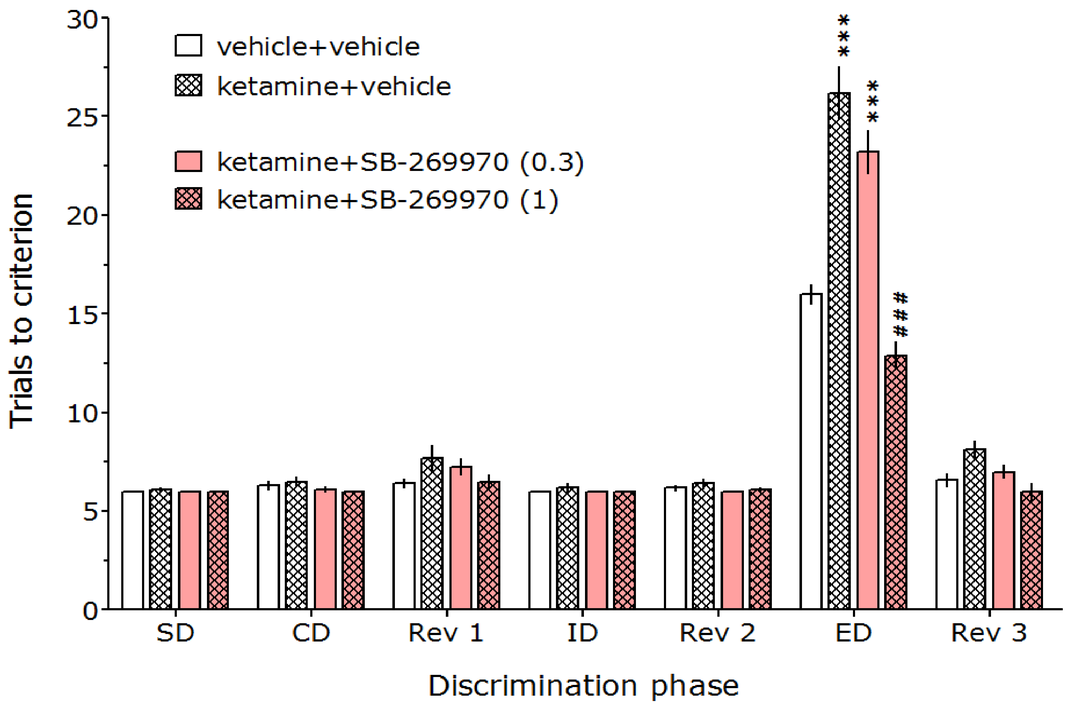
The 5-HT7 (5-hydroxytryptamine 7, serotonin 7) receptor, one of the most recently identified members of the serotonin receptor family, may play important role in the pathophysiology and treatment of many psychiatric disorders. Recent data suggest that the blockade of 5-HT7 receptors may exert procognitive effects in animal models of schizophrenia. This issue might be of special interest, since several atypical antipsychotics, e.g., amisulpride, are characterized by a high affinity for 5-HT7 receptors. Nevertheless, little is known about the efficacy of 5-HT7 antagonists in models of schizophrenia-like cognitive inflexibility.

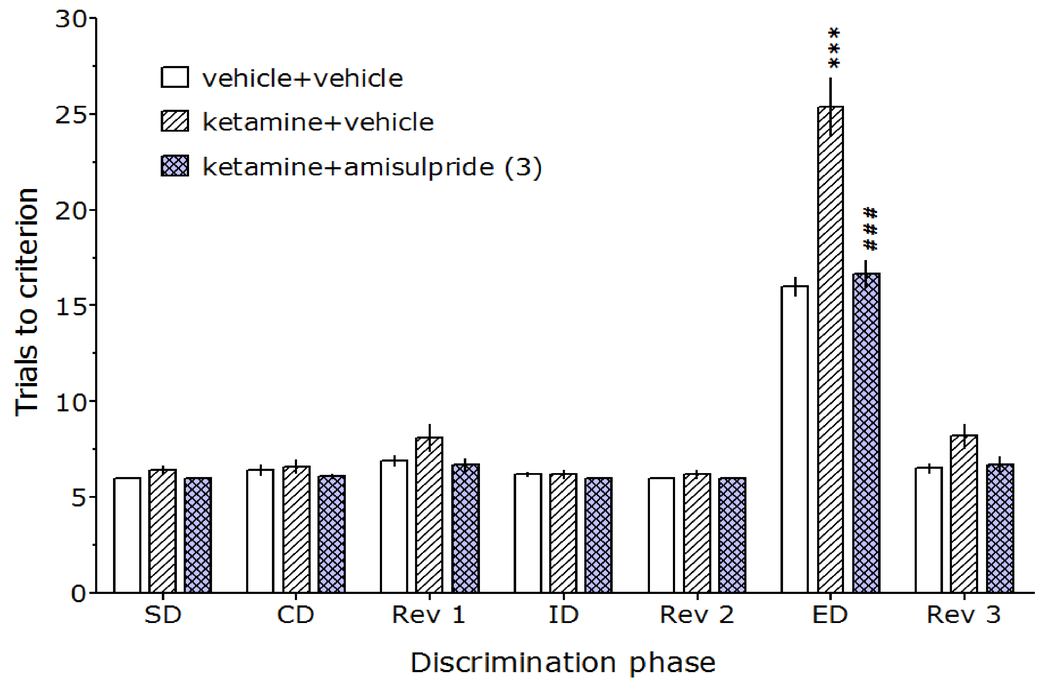
AIM

The aim of the present study was to investigate the role of a potent and selective 5-HT7 receptor antagonist (SB-269970), and amisulpride (an atypical antipsychotic with high affinity to 5-HT7 receptors) on ketamine-induced deficits in the ASST task in rats.

RESULTS

The impact of SB-269970 and amisulpride administration on reversing ketamine-induced cognitive inflexibility in attentional set-shifting task in rats.





SB-269970 (1 mg/kg) and amisulpride (3mg/kg) reversed ketamine-induced cognitive inflexibility. Additionally, SB-269970 at a dose of 1mg/kg also improved ED performance as compared to control rats.

Analyses of variance revealed significant interactions of discrimination phase and treatment: $F[18,204]=26.93$, $P<0.001$ (SB-269970) and $F[12,156]=16.84$, $P<0.001$ (amisulpride).

MATERIALS AND METHODS

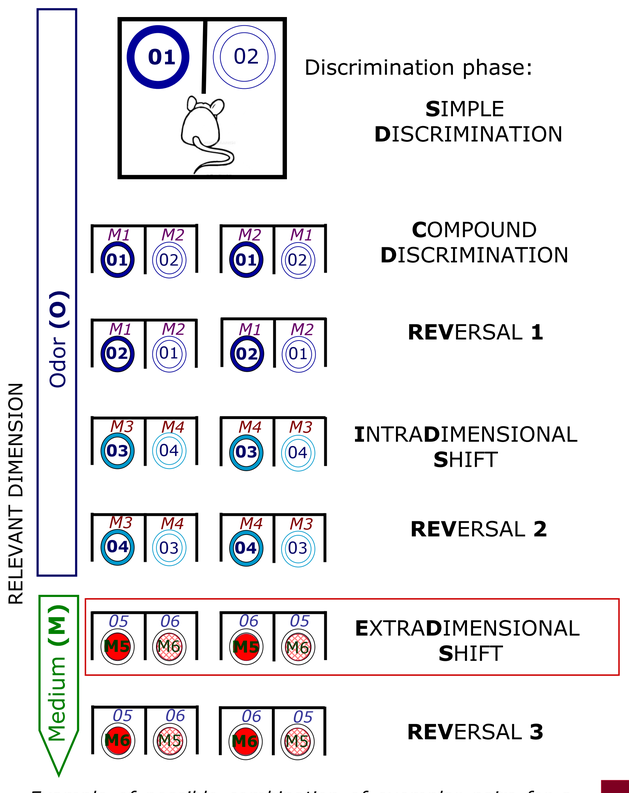
ANIMALS

Male Sprague-Dawley rats (Charles River, Germany) weighing 250-280 g on arrival were used in this study. 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

ATTENTIONAL SET-SHIFTING: PROCEDURE

The procedure was adopted from Birell and Brown and entailed three days for each rat:
Day 1, habituation: rats were habituated to the testing area and trained to dig in the bowls filled with sawdust to retrieve the food reward.
Day 2, training: the rats were trained on a series of simple discriminations (SD), to a criterion of six consecutive correct trials. For these trials, the rats had to learn to associate the food reward with an odor cue and/or digging medium
Day 3, testing: in a single test session the rats performed a series of increasingly difficult discriminations in the order outlined in Table 1. The first four trials at the beginning of each discrimination stage were a discovery period (not included in six trials to criteria), in which the rat was allowed to dig in both bowls regardless of where it first began to dig. In the subsequent trials an incorrect choice terminated the trial. Testing was continued at each stage until the rat reached a criterion of six consecutive correct trials, after which testing proceeded to the next stage.

Table 1. Order of discriminations performed



Example of possible combination of exemplar pairs for a rat shifting from odor to digging medium as the relevant dimension. The correct exemplar is shown in bold, and was paired with either of two exemplars from the irrelevant dimension across trials within each discrimination problems. On every trial except the SD, the pair of exemplars differed on both the relevant and irrelevant dimensions. In the ID and ED, there were novel pairs of exemplars of each dimension.

ATTENTIONAL SET-SHIFTING: APPARATUS

Testing was conducted in modified wired rat housing cage (length x width x height: 42 x 32 x 22cm) with a white plywood wall dividing half of the length of the cage into two sections (choice area). During the testing one digging bowl was placed in each section. These stimulus bowls consisted of ceramic pots, with an internal diameter of 10.5 cm and the depth of 4 cm. Each pot was defined by a pair of cues along 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 immediately prior to use. The bait (a one third of Honey Nut Cheerio, Nestle®) was placed in the bottom of the "positive" pot and buried with the digging medium.

DRUGS

Ketamine (10 mg/kg) was administered to Sprague-Dawley rats subcutaneously 75 min prior to the test. SB-269970 or amisulpride were given intraperitoneally 15 min before ketamine injection.

DATA ANALYSIS

The number of trials required to achieve the criterion of 6 consecutive correct responses was recorded for each rat and for each discrimination phase. Data were calculated using two-way mixed-design ANOVAs followed by the Newman-Keuls post-hoc test.

CONCLUSION

Present study demonstrated the efficacy of the 5-HT7 antagonist, SB-269970, and amisulpride in ameliorating frontal-like deficits relevant to the psychopathology of schizophrenia. It thus seems likely that the antagonism of 5-HT7 receptors may represent a useful pharmacological approach for cognitive enhancement in schizophrenia.

Acknowledgements

This study was supported by the Statutory Funds of the Institute of Pharmacology, Polish Academy of Sciences and project "Prokog," UDA-POIG.01.03.01-12-063/09-00, co-financed by the European Union from the European Fund of Regional Development (EFRD)

REFERENCES

(1) Birrell, J.M., Brown, V.J., 2000. Medial frontal cortex mediates perceptual attentional set shifting in the rat. J Neurosci 20, 4320-4324.
(2) Nikiforuk, A., Golembiowska, K. and Popik, P., 2010. Mazindol attenuates ketamine-induced cognitive deficit in the attentional set shifting task in rats. Eur Neuropsychopharmacol 20,37-48.
(3) Horiguchi, M., Huang, M., Meltzer, H. Y., 2011. The role of 5-hydroxytryptamine 7 receptors in the phencyclidine-induced novel object recognition deficit in rats. J Pharmacol Exp Ther 338, 605-14.

INNOVATIVE ECONOMY
NATIONAL COHESION STRATEGY

EUROPEAN UNION
EUROPEAN FUND OF
REGIONAL DEVELOPMENT