The effects of positive allosteric modulators of alpha 7 nicotinic receptors on rats performance in the Odor Span Test

Agnieszka Potasiewicz, Agnieszka Nikiforuk, Piotr Popik

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

INTRODUCTION

It is widely accepted that cognitive deficits are a core feature of schizophrenia. Schizophrenic patients develop a wide range of neuropsychological dysfunctions including deficits in working memory (WM). Specifically, they suffer from shortages in WM span capacity, displaying reduced number of information kept concurrently in the WM.

Nicotinic acetylcholine receptors (nAChRs) play an important role in the regulation of cognitive processes. Particularly, selective activation of α7-nAChRs represents a promising target for the development of pharmacological treatments for cognitive dysfunctions in schizophrenia. It appears however, that positive allosteric modulators (PAMs) of α7-nAChRs may demonstrate a more favorable profile than orthosteric agonists [1].

Current data has demonstrated a positive influence of nicotine on WM span capacity assessed using the odor span task (OST) in rats [2, 3]. However, while the role α7-nAChRs in the nicotine-induced enhancement in span capacity has been suggested, the effects of α7-nAChRs PAMs have not been assessed on that task.

MATERIALS AND METHODS

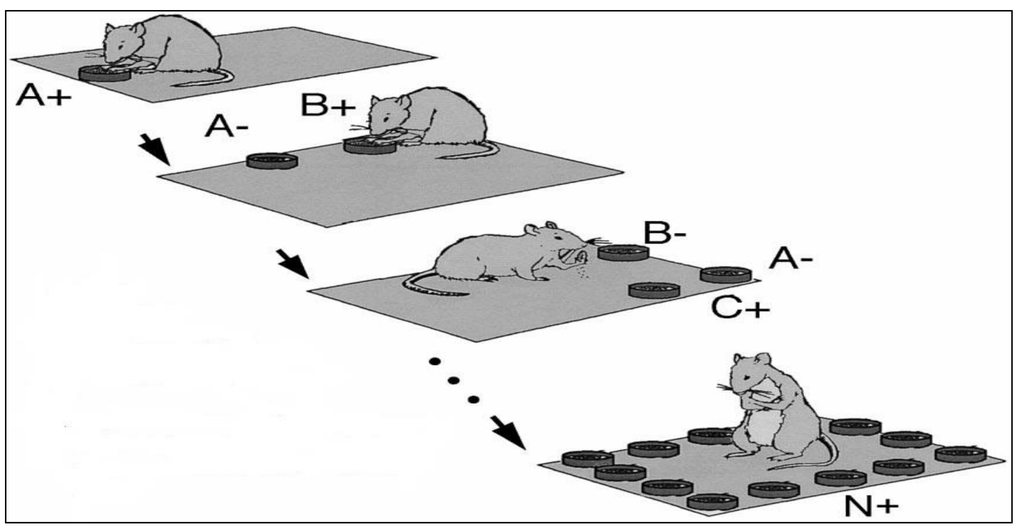
ANIMALS

The subjects were 9 Male Sprague–Dawley rats (Charles River, Germany) weighing 250-280 g at the beginning of training. For one week prior to the testing the rats were mildly food deprived (15g of food pellets per day) and were permitted *ad libitum* access to water. Rats were kept on a 12 hour light/dark cycle and were tested during the light phase of the 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.

DRUGS

Nicotine (0.05 and 0.1 mg/kg) was administered subcutaneously (SC) 10 minutes before the test. **CCMI** (N-(4-chlorophenyl)-a-[[(4-chlorophenyl)amino]methylene]-3-methyl-5-isoxazoleacet-amide) (0.3 and 1 mg/kg) were administered intraperitoneally (IP) 30 minutes before the test. **PNU120596** (1 and 3 mg/kg) was administered SC 30 minutes before the test. The drugs or their vehicle (physiological saline) was administered in a volume of 1 ml/kg of body weight. Drug doses were administered in a Latin square design order.

Figure 1. Schematic of the odor span task [4].



APPARATUS AND MATERIALS

Training and testing took place on a black, plexiglass arena (55x70x30 cm). Platform locations were numbered around the perimeter from 1 to 24. To mark each cup with a distinct odor, essential oil was applied on a piece of blotting paper fixed to the internal rim immediately prior to use. The bait (one Honey Nut Cheerio, Nestle®) was placed at the bottom of the cup and covered with woodchips.

ODOR SPAN TEST PROCEDURE

The procedure was adopted from Dudchenko et al., [5]:
Day 1-3, habituation: rats were habituated to the testing area and trained to dig in the cups filled with woodchips to retrieve the food reward.
Day 4-7, nonmatching to sample (NMTS): The rat was presented with a cup of odorized woodchips. Once the animal retrieved the cereal reward, it was removed from the arena and the cup was moved to a new random location. Second bowl marked with a new odor, was added to the platform. The animal had to ignore previous cups and choose a new one in order to gain the reward. After a correct response, the first cup was removed, but the third new odor was introduced. The animal was given 10 NMTS trials during the session until it reliably selected the new odor.
Day 8-21, odor span task(OST): Trial began identically to NMTS. The difference between these two stages was that the previously presented cups were not removed from the platform but moved to another location (Figure 1).

DATA ANALYSIS

Span length, considered as a number of correct and consecutively chosen cups minus 1, as well as the number of errors were counted during the session.
Data were calculated using the main effect-design ANOVAs followed by the Newman-Keuls post-hoc test.

Acknowledgements:

Supported by the Project "Prokog" UDA-POIG.01.03.01-12-063/09-00, co-financed by European Union from the European Fund of Regional Development (EFRD).

INNOWACYJNA GOSPODARKA
NARODOWA STRATEGIA SPÓJNOŚCI

UNIA EUROPEJSKA
EUROPEJSKI FUNDUSZ ROZWOJU REGIONALNEGO

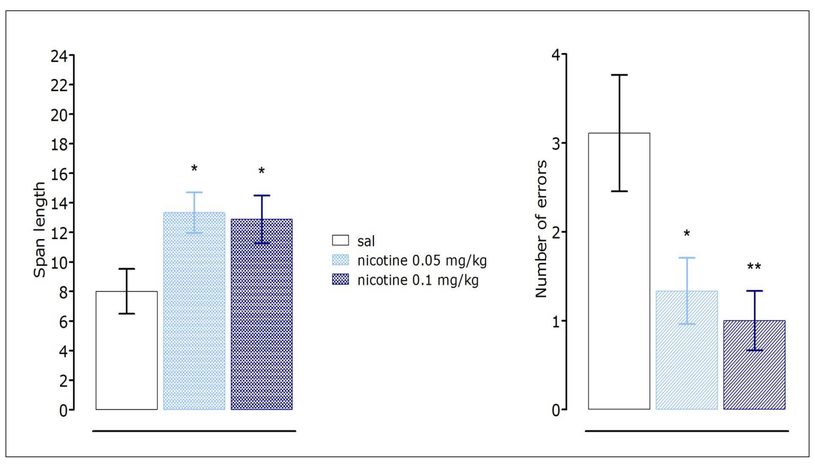
REFERENCES

1. Hurst, R.S., Hajos, M., Raggenbass, M., Wall, T.M., Higdon, N.R., Lawson, J.A. et al., 2005. A novel positive allosteric modulator of the alpha7 neuronal nicotinic acetylcholine receptor: in vitro and in vivo characterization. J Neurosci. 25:4396-4405
2. Rushforth, S.L., Allison, C., Wonnacott, S., Shoaib, M., 2010. Subtype-selective nicotinic agonists enhance olfactory working memory in normal rats: a novel use of the odour span task. Neurosci Lett 471:114-118.
3. Rushforth, S.L., Steckler, T., Shoaib, M., 2011. Nicotine improves working memory span capacity in rats following sub-chronic ketamine exposure. Neuropsychopharmacology 36:2774-2781.
4. Turchi, J., Sarter, M., 2000. Cortical cholinergic inputs mediate processing capacity: effects of 192 IgGsaporin-induced lesions on olfactory span performance. Eur J Neurosci. 12: 4505–4514.
5. Dudchenko, P.A., Wood, E.R., Eichenbaum, H., 2000. Neurotoxic hippocampal lesions have no effect on odor span and little effect on odor recognition memory but produce significant impairments on spatial span, recognition, and alternation. J Neurosci 20:2964-2977

AIM

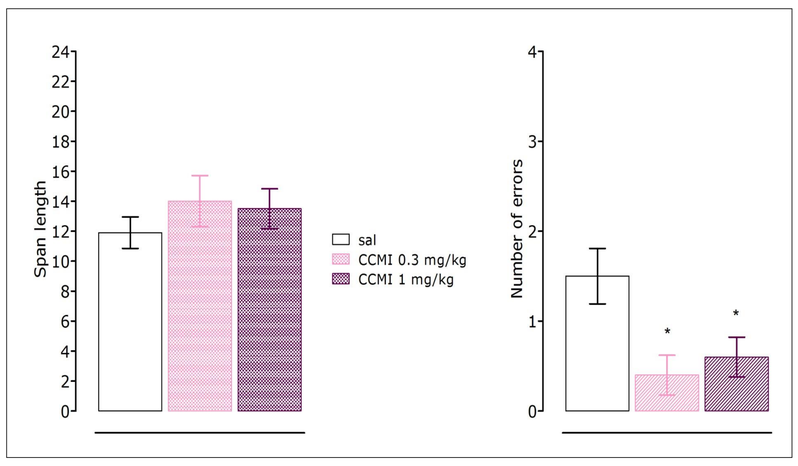
To investigate the effects of α7-nAChRs PAMs: CCMI (type I) and PNU-120596 (type II) in comparison to nicotine on the WM capacity in the OST in rats.

RESULTS

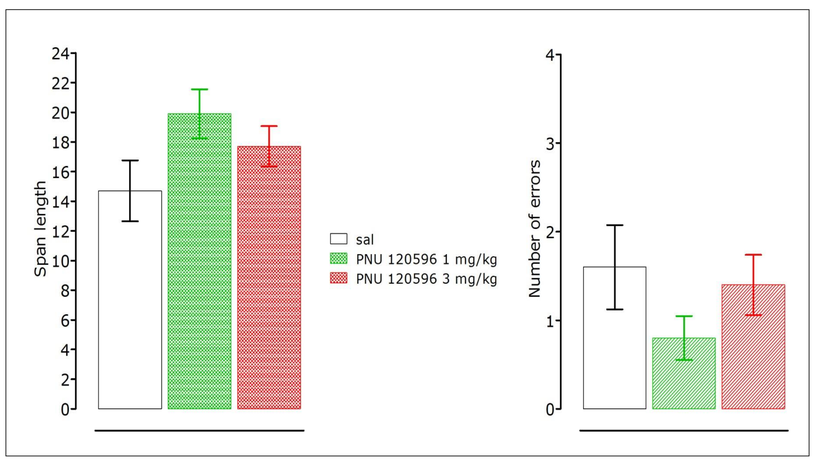


❖ Nicotine (0.05 and 0.1 mg/kg), caused a statistically significant improvement of the span length ($p<0.05$). It also significantly decreased a number of errors ($p<0.05$ and $p<0.001$ for a dose of 0.05 and 0.1 mg/kg, respectively).

❖ CCMI did not affect the span length statistically but it decreased the number of errors ($p<0,05$).



❖ Neither span length nor a number of errors was changed significantly by PNU 120596.



Data are presented as the mean ± S.E.M. N=9 rats per group. Symbols: * denotes $p<0.05$, ** denotes $p<0.01$ when compared to saline, Newman–Keuls post-hoc test.

CONCLUSIONS

Although the α7-nAChRs PAMs represent a promising alternative to orthosteric ligands, their behavioral activity is still poorly understood especially with regard to the differences between type I and type II compounds. Hence, despite the limited efficacy of CCMI and PNU120596 on the span capacity in cognitively unimpaired animals, it seems interesting to further investigate α7-nAChRs PAMs in the models of schizophrenia-like OST deficits.