Behavioural Brain Research 302 (2016) 73–80

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Nicotinic α7 and α4β2 agonists enhance the formation and retrieval of recognition memory: Potential mechanisms for cognitive performance enhancement in neurological and psychiatric disorders

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HIGHLIGHTS

- Object recognition memory decays to 0 after a 6 h ITI in female hL rats.
- Activation of nicotinic α7 and α4b2 receptors restores this memory.
- Donepezil restores this memory while risperidone is ineffective.

ARTICLE INFO

Article history:
Received 20 July 2015
Received in revised form 25 August 2015
Accepted 27 August 2015
Available online 30 August 2015

Keywords:
Object recognition memory
Female rat
Delay-dependent deficits
α7 Nicotinic receptors
α4β2 Nicotinic receptors

ABSTRACT

Cholinergic dysfunction has been shown to be central to the pathophysiology of Alzheimer's disease and has also been postulated to contribute to cognitive dysfunction observed in various psychiatric disorders, including schizophrenia. Deficits are found across a number of cognitive domains and in spite of several attempts to develop new therapies, these remain an unmet clinical need.

In the current study we investigated the efficacy of donepezil, risperidone and selective nicotinic α7 and α4β2 receptor agonists to reverse a delay-induced deficit in recognition memory. Adult female Hooded Lister rats received drug treatments and were tested in the novel object recognition (NOR) task following a 6 h inter-trial interval (ITI). In all treatment groups, there was no preference for the left or right identical objects in the acquisition trial. Risperidone failed to enhance recognition memory in this paradigm whereas donepezil was effective such that rats discriminated between the novel and familiar object in the retention trial following a 6 h ITI. Although a narrow dose range of PNU-282987 and RJR-2403 was tested, only one dose of each increased recognition memory, the highest dose of PNU-282987 (10 mg/kg) and the lowest dose of RJR-2403 (0.1 mg/kg), indicative of enhanced cognitive performance. Interestingly, these compounds were also efficacious when administered either before the acquisition *or* the retention trial of the task, suggesting an important role for nicotinic receptor subtypes in the formation *and* retrieval of recognition memory.

1. Introduction

Cholinergic dysfunction has been shown to be central to the pathophysiology of Alzheimer's disease and is postulated to contribute to the cognitive deficits observed in various neuropsychiatric disorders, including schizophrenia [10,25]. Indeed, nicotine has been widely reported to improve cognitive function in humans and experimental animals (for review, see Ref. [45], and adds support to the self-medication hypothesis to explain the high rates of smoking in schizophrenia patients [80] although there may be alternative explanations for this (see recent discussion in the Refs. [23,26]. Of the nicotinic acetylcholine receptors (nAChRs), the most prevalent subtypes in the brain are comprised of α4β2 and α7 subunits [61,17] and it has been suggested that they play an important role in cognition [12,28,69]. These receptors are

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http://dx.doi.org/10.1016/j.bbr.2015.08.037
0166-4328/

highly expressed in the hippocampus, cortex, striatum, thalamus and ventral tegmentum [8,24,27]. Both subtypes have been shown to be reduced in post-mortem studies of schizophrenia patients [8,24]. Post-mortem studies of Alzheimer's disease patients have revealed a reduction in the α4β2 subtype [77] while studies showing changes in α7 receptor levels in this illness are conflicting (see [75] for review).

Visual recognition memory is impaired in both schizophrenia [11] and Alzheimer's disease patients [60]. Recognition memory in rats can be tested using the novel object recognition (NOR) task, a spontaneous and ethologically relevant paradigm based on the natural preference of rats to explore a novel object more than a familiar one after a specified time delay [21]. Indeed, NOR has been listed by the TURNS initiative as relevant for studying visual learning and memory deficits in schizophrenia (TURNS.ucla.edu) and may be used to study cognitive deficits occurring in a range of disorders [29]. In our laboratory, we have extensively shown that sub-chronic phencyclidine (PCP) treatment impairs object recognition memory following a 1 min inter-trial interval-ITI [15,16,30,33,55,51,73,72]. We have also demonstrated the efficacy of a wide range of selective receptor targets to reverse these sub-chronic PCP-induced deficits (see Ref. [58] for review) as have other laboratories using the same paradigm (see [57] for review). However, in order to investigate the efficacy of pro-cognitive drugs in a non-disease model we require rats to forget previously experienced situations or objects. In this scenario, the deficit is induced by increasing the ITI following acquisition and prior to the retention trial of the task. Previous studies in our laboratory have shown that, using this approach, female rats can recall objects up to a 4 h ITI [74], an effect that was abolished following a 6 h ITI [53].

The aim of the current study was to investigate the ability of novel pharmacological agents and established drugs to enhance cognitive performance, with particular focus on targets of relevance to Alzheimer's disease and schizophrenia in this paradigm. The effects of the AChE inhibitor, donepezil, the atypical antipsychotic, risperidone, the α7 nACh receptor agonist, PNU-282987, and the α4β2 nACh receptor agonist, RJR-2403, on deficits in object recognition memory following a 6 h ITI were investigated in female Hooded Lister rats. In order to ascertain whether these receptor mechanisms positively affect the formation or retention of recognition memory, we administered these compounds both before the acquisition trial and in a separate experiment, before the retention trial of the test.

2. Materials and methods

2.1. Subjects and housing conditions

Three cohorts of 20, 30 and 50 female Lister Hooded rats (Harlan, UK) housed in groups of five were used as subjects. Animals initially weighing 220–250 g, were maintained under standard laboratory conditions at a temperature of 21 °C (±2 °C) and humidity of 40–50%. They were maintained on a 12-h light/dark cycle (lights on at 0700 h) and experimental procedures were performed during the light phase. Rats had free access to food (standard laboratory chow, Special Diet Services, Essex, UK) and water. Experiments were conducted in accordance with the Animals (Scientific Procedures) Act UK (1986), and approved by the University of Bradford ethical review process.

Female rats were used in this study as we have previously shown that females can recall information about a particular object for longer than male rats and that stage of the oestrous cycle does not affect cognitive performance in several tasks such as novel object recognition [74] and reversal learning [55].

2.2. Novel object recognition

Rats were tested in the novel object recognition (NOR) task as described in detail by McLean et al. [50–52]. Briefly, rats in home cage groups were habituated to the test box for 20 min on 3 consecutive days. Following a 3-min habituation session on the day of testing, each rat was placed in the NOR chamber (52 cm wide × 40 cm high × 52 cm long) and exposed to two identical objects for a period of 3 min. The objects used were opaque plastic pyramids, small glass jars, cola cans and striped plastic bottles and rats showed equal exploration of these objects in validation experiments in our laboratory (Grayson, unpublished findings). The rats were then returned to their home cage for an inter-trial interval (ITI) of 6 h, the entire box was cleaned, both objects removed and one replaced with an identical familiar copy and one with a novel object. Following the ITI, rats were returned to explore the familiar and a novel object in the test box for a 3-min retention trial. The location of the novel object in the retention trial was randomly assigned for each rat using a Gellerman schedule. All experiments were filmed and video recorded for subsequent behavioural analysis by an experimenter blind to the treatments. Locomotor activity was also recorded, this was evaluated by scoring the number of line crossings by the animal in both acquisition and retention trials. The exploration time (sec) of each object in each trial was recorded manually using two stopwatches and the D1 score was calculated [D1 = (time at the novel object – time at the familiar object)]. The D1 represents the difference in time spent exploring the novel and familiar objects.

2.3. Experimental design and dose selection

In each experiment the drug treatment given to each rat (and within each home cage) was randomised. For experiment 1, 20 rats were used and studies testing the effects of donepezil and risperidone separately were combined, therefore the vehicle group was $n = 20$. The doses of donepezil (1 mg/kg) and risperidone (0.16 mg/kg) were selected based on their efficacy to reverse a sub-chronic PCP-induced deficit in female Lister Hooded rats in reversal learning in our laboratory [50,34]. For experiment 2, 30 rats were used and studies testing the effects of PNU-282987 and RJR-2403 separately were combined, therefore the vehicle group was $n = 17$ (3 rats failed to explore the objects and were excluded from the final analysis). The doses of PNU-282987 were selected based on efficacy to reverse a sub-chronic PCP-induced deficit in reversal learning in our laboratory [51]. The doses of RJR-2403 were selected based on efficacy to improve working memory in the odour span task [67]. In experiments 1 and 2 where animals were re-used, at least one week separated each part of the study to allow drug wash-out, different objects were used for the second part of the study and dosing was fully randomised as described above. Experiment 3 was carried out in a separate cohort of 50 rats, with donepezil (1 mg/kg), risperidone (0.16 mg/kg), PNU-282987 (10 mg/kg) and RJR-2403 (0.1 mg/kg) administered prior to the retention trial. In this experiment only the active doses from the prior experiments were used in an attempt to detemine which specific memory processes are affected by these compounds.

2.4. Drugs

Donepezil hydrochloride monohydrate (Sigma, UK) was dissolved in 0.5% carboxymethylcellulose and given in a volume of 1 ml/kg via the intraperitoneal (i.p.) route. Risperidone (Sigma, UK) was dissolved in a minimum volume of acetic acid, made up to volume with distilled water and pH adjusted to 6 with 0.1 M NaOH. Risperidone was administered in a volume of 1 ml/kg via the i.p. route. PNU-282987 (Tocris, UK) was dissolved in isotonic water and