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Short Communication

Donepezil and the alpha-7 agonist PHA 568487, but not risperidone, ameliorate spatial memory deficits in a subchronic MK-801 mouse model of cognitive impairment in schizophrenia

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HIGHLIGHTS

- Subchronic administration of MK-801 produces long-term memory deficits in mice.
- Memory is restored by an acetylcholinesterase inhibitor or an alpha-7 agonist.
- The atypical antipsychotic risperidone does not ameliorate memory deficits.
- The subchronic MK-801 model has improved face validity for CIAS.
- The current model may be of use for screening new treatments for CIAS.

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ABSTRACT

Cognitive impairment associated with schizophrenia (CIAS) is an important etiological feature of this disorder with implications for symptom severity and quality of life. Acute N-methyl-D-aspartate receptor (NMDAR) blockade using MK-801, a non-competitive antagonist to NMDARs, is assumed to produce temporary cognitive impairments in mice similar to those seen in schizophrenia patients. Less is known, however, about the effects of subchronic MK-801 administration on cognition. In the current study, twenty-eight male C57/BL6 mice received a daily dose of MK-801 (0.1 mg/kg, i.p.) for seven days. Spatial memory was assessed using an object location task prior to MK-801 administration as well as at multiple time points after the treatment. Subchronic treatment with MK-801 caused lasting memory deficits, which were ameliorated by acute doses of an acetylcholinesterase inhibitor (donepezil) and an alpha-7 nicotinic agonist (PHA 568487), but were unaffected by acute administration of the atypical antipsychotic risperidone. Subchronic administration of MK-801 may lend this pharmaceutical model increased face validity, while its resemblance to prodromal schizophrenia makes it suitable for screening new CIAS treatments.

Glutamatergic hypofunction is a well-established feature of schizophrenia and has been used extensively in modeling cognitive impairment associated with schizophrenia (CIAS)[1,2]. Acute treatment with MK-801, a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist, is a common way of creating schizophrenia-like cognitive deficits in rodents [3]. This model has been shown to possess reasonable predictive validity, with no responses to antipsychotics (e.g. risperidone, clozapine) and positive responses to putative cognitive enhancers (e.g. nicotine) mimicking those of human patients [4]. As such, the acetylcholinesterase inhibitor donepezil, which is used as a cognition enhancer, consistently reversed the cognitive deficits induced by an acute dose of MK-801 [4,5], while it has not been successful in improving human CIAS [6,7].

As schizophrenia is a chronic disorder, (sub)chronic treatment with MK-801 might resemble CIAS better. However, less is known about the consequences of subchronic MK-801 administration in rodents. Reports of enduring effects of subchronic MK-801 regimens include locomotor changes [8], changes in affect (increased

Abbreviations: α7nAChR, alpha7 nicotinic acetylcholine receptor; CIAS, cognitive impairment associated with schizophrenia; NMDAR, N-methyl-D-aspartate receptor; OLT, object location task.

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immobility in the forced swim paradigm) [9], and memory performance (in the object recognition test) [10]. Prevention of memory impairments resulting from subchronic NMDA receptor antagonist treatment in the latter task has been suggested to translate as treatment against CIAS in the clinic [11].

In order to explore further the suitability of subchronic MK-801 administration as a preclinical model for testing possible CIAS treatments in rodents, we used a spatial variant of the object recognition task, i.e. the object location task (OLT). We assessed spatial memory prior to, as well as at multiple time points following subchronic MK-801 treatment in mice. In addition, we tested the effects on memory performance of risperidone – an atypical antipsychotic, donepezil – a drug approved for the treatment of cognitive impairment, and PHA 568487 – a putative cognition enhancer. PHA 568487 is an agonist of the alpha7 nicotinic acetylcholine receptor (α7nAChR). α7nAChR agonists have shown positive effects in counteracting acute MK-801-induced memory deficits [12,13] and are currently considered a promising treatment option for CIAS [14].

The OLT was performed as described in Bruno et al. [15]. Briefly, in a first learning trial a mouse is exposed to an arena with two identical objects. Following a 1-h interval, the mouse is placed into the same arena, but with one of the objects placed at a new location. Exploration time for each object is recorded. The preference for the object at the new location in the second trial is considered representative of spatial memory capacity [16]. The main outcome measure is a discrimination index (d2): the difference in exploration time between the displaced and stationary object, divided by the total exploration time for the trial. D2 is a relative measure of discrimination, independent of exploratory activity. A positive d2, significantly different from zero, is considered indicative of successful recall of spatial information (tested using a one-sample *t*-test [17]). All animals were trained until they showed a stable performance at a 1-h interval. Comparisons between treatments were done using one-way analyses of variance (ANOVAs) followed by LSD post hoc tests.

A low dose of MK-801 (Research Biochemicals International/Sigma–Aldrich, Deisenhofen, Germany) was administered daily (0.1 mg/kg dissolved in saline, i.p.) to twenty-eight seven month-old male C57/BL6 mice (Charles River, Sulzfeld, Germany) for seven days. All mice were housed individually in standard Tecniplast IVC system greenline cages, on a sawdust bedding, with a reversed light/dark cycle of 12/12 h (lights off from 7:00 to 19:00). Baseline OLT scores were obtained prior to the subchronic MK-801 regimen. Drug tests were conducted after a seven day washout period. Thirty minutes before the first OLT trial, mice received oral injections of either vehicle (saline; $n = 9$), donepezil (1 mg/kg dissolved in saline, $n = 10$), or risperidone (0.1 mg/kg dissolved in 98% tylose solution (0.5%) with 2% Tween 80, $n = 9$). Injection volume was 2.0 ml/kg. Donepezil and risperidone were a kind gift of Abbott (Weesp, The Netherlands). Both doses were selected as they are known to improve memory (donepezil) and prepulse inhibition performance (risperidone) in rodents [4,5,18]. Since the same group of mice was tested multiple times, allocation to treatment conditions was randomized for the first test and counterbalanced for further tests (see below), such that each mouse was assigned to the vehicle group once for one of three tests. Exploration times were scored manually by an experimenter unaware of the treatment conditions being tested.

Following subchronic MK-801 administration, the vehicle treated group did not show a preference for the displaced object (d2 not different from zero; $t(8) = 1.31$, $p = 0.227$), suggesting memory impairment associated with MK-801 exposure (Fig. 1). This was further supported by a paired samples *t*-test, which revealed a significant decrease in d2 from the pre-MK-801 treatment baseline for the vehicle treated animals [$t(8) = 2.332$, $p < 0.05$]. The one-way ANOVA showed no treatment effect [$F(2, 25) = 1.149$, ns], however

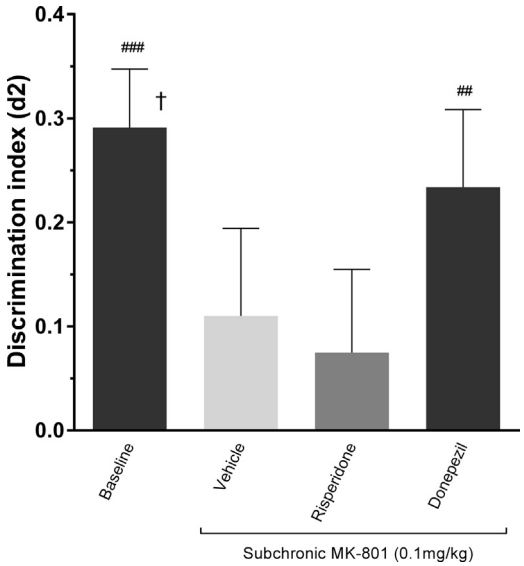

Fig. 1. Effects of risperidone (0.1 mg/kg) and donepezil (1 mg/kg) on MK-801-induced spatial memory deficits measured by the discrimination index (d2) of the object location task at baseline ($n = 28$) and at seven days after subchronic MK-801 (0.1 mg/kg; injected daily for seven days) treatment (means ± SEM). A difference from zero is represented by hashes (one-sample *t*-tests: $^{\#\#}p < 0.01$; $^{\#\#\#}p < 0.001$). $^{\dagger}p < 0.05$ difference between baseline and vehicle (paired-samples *t*-test).

the memory deficit was partly ameliorated by a single dose of donepezil as donepezil-treated mice showed a preference for the displaced object [comparison with zero using a one-sample *t*-test: $t(9) = 3.144$, $p = 0.012$]. The d2 score of the risperidone group was not different from zero [$t(8) = .939$, $p = .375$], indicating that risperidone had no effect at all on spatial memory at this dose.

Twenty-four days after the end of the subchronic MK-801 treatment, mice were tested again on the OLT 30 min after receiving oral injections of either saline ($n = 9$), or one of two doses of the α7nAChR agonist PHA 568487 (0.3 mg/kg, $n = 10$; 1 mg/kg, $n = 9$; PHA 568487 was a kind gift from Forum pharmaceuticals, Boston, USA), dissolved in saline in an injection volume of 2.0 ml/kg. The same test was conducted five days later, i.e. twenty-eight days after the end of the subchronic MK-801 treatment, with a saline treated ($n = 9$) group and two additional groups treated with lower doses of the α7nAChR agonist (0.03 mg/kg, $n = 9$; 0.01 mg/kg, $n = 10$).

At both time points d2 remained non-significantly different from zero for the vehicle groups [$t(8) = 1.18$, $p = .272$ and $t(8) = .109$, $p = .916$ resp.], and paired-samples *t*-tests revealed significant d2 reductions from baseline for each vehicle condition [$t(8) = 2.637$, $p = 0.03$; and $t(8) = 3.145$, $p = 0.014$, resp.]. This indicates clear memory impairment at both time points. Testing d2 scores in the treatment groups against zero showed that PHA 568487 ameliorated the MK-801-induced memory deficit at doses of 0.1 mg/kg [$t(9) = 4.65$, $p = 0.001$], 0.3 mg/kg [$t(9) = 5.421$, $p < 0.001$], and 1 mg/kg [$t(8) = 4.22$, $p = 0.003$], but not at the lowest dose of 0.03 mg/kg [$t(8) = 1.913$, $p = .092$]. One-way ANOVAs revealed significant treatment effects on both test days [$F(2, 25) = 4.013$, $p = 0.031$; and $F(2, 25) = 3.639$, $p = 0.041$ resp.]. Post hoc LSD comparisons showed significant differences between the treatment and the local vehicle condition at doses of and 0.1 mg/kg ($p = 0.013$), 0.3 mg/kg ($p = 0.021$), and 1 mg/kg ($p = 0.02$), suggesting notable memory improvement at these doses [19] (Fig. 2).

In summary, low-dose subchronic MK-801 administration induced a lasting memory deficit in mice, which persisted at least 28 days after the last drug administration. This deficit was ameliorated by donepezil and an agonist to the α7nAChR. The atypical antipsychotic risperidone was not effective at the dose of 0.1 mg/kg. The predictive validity of the subchronic MK-801 model of CIAS is