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Research Report

NC-1900, an arginine–vasopressin analogue, ameliorates social behavior deficits and hyperlocomotion in MK-801-treated rats: Therapeutic implications for schizophrenia

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Abstract

We previously reported that chronic administration of *N*-methyl-D-aspartate (NMDA) antagonists reduced the density of vasopressin V_{1a} receptors in several brain regions in rats that demonstrated social interaction deficits and increased locomotor activity. These observations indicate the ability of arginine–vasopressin (AVP), or its analogues, to modulate behavioral abnormalities associated with blockade of NMDA receptors. The present study was performed to investigate the effect of NC-1900, an AVP analogue, on social behavior and locomotor activity in rats treated with MK-801, a non-competitive NMDA receptor antagonist. Male Wistar rats were administered MK-801 (0.13 mg/kg/day ip) or saline for 14 days. Social behavior and locomotor activity were measured 45 min after the injection of NC-1900 (10 ng/kg sc) or saline together with the last MK-801 or vehicle administration. Social interaction was quantified by an automated video-tracking system, and stereotyped behavior and ataxia were manually measured. Acute administration of NC-1900 partially reversed MK-801-induced hyperlocomotion and deficits in social interaction, while NC-1900 itself did not affect these behavioral measures in animals chronically treated with vehicle saline. These results suggest that the central AVP system may interact with glutamatergic and dopaminergic transmissions, and indicate potential therapeutic effects of AVP analogues on positive and negative symptoms of schizophrenia.

Theme: Disorders of the nervous system
Topic: Neuropsychiatric disorders

Keywords: MK-801; Social interaction; Automated analysis; Vasopressin; NC-1900; Schizophrenia

1. Introduction

Schizophrenia is a relatively common and often debilitating neuropsychiatric disorder. Its symptoms include positive (e.g., delusions, hallucinations, bizarre thoughts) and negative (e.g., affective flattening, poor volition, poverty of speech, impaired interpersonal relationships) symptoms, as well as cognitive deficits such as mild impairment of memory [6,21]. Minor impairments of social or cognitive function are often observed during the premorbid stage of the illness [9,21]. Although treatment with antipsychotic drugs has been shown to ameliorate positive symptoms, only second generation antipsychotics, such as clozapine, are partially effective to treat negative symptoms [22,21].

NMDA antagonists, such as phencyclidine (PCP) and ketamine, have been demonstrated to evoke a worsening of positive and negative symptoms of schizophrenia and induce

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schizophrenia-like symptoms in healthy individuals [4,15]. Animals treated with NMDA antagonists, such as PCP and MK-801, exhibit several types of behavior related with a range of symptoms in schizophrenia, e.g., hyperlocomotion [40], decreased social behavior [28], impaired performance on cognitive tasks [17], and deficits in sensorimotor gating [36]. Mice with reduced NMDA receptor expression have been shown to express behavioral abnormalities, including increased locomotor activity and deficits in social interactions [24]. Similarly, mutant mice lacking the $\varepsilon 1$ subunit of the NMDA receptors exhibited increased locomotor activity and impairment of latent learning in a water-finding task [20]. These findings suggest that abnormal NMDA receptor-mediated neurotransmissions may contribute to the pathophysiology of schizophrenia [4,23].

Arginine–vasopressin (AVP), an antidiuretic hormone, is thought to play an important role in social and emotional behavior, as well as aspects of cognition in rodents [14]. Thus, intracerebroventricular (icv) administered AVP increases affiliative behavior in male prairie voles [41]. Infusion of AVP into the lateral ventricle facilitates learning and memory process, while MK-801, an NMDA receptor antagonist, impairs this cognitive performance [39]. Genetic deficiency of vasopressin in rats, resulting from a null mutation of the vasopressin gene, causes alterations of performance on attention and cognition tasks in adulthood [16].

We previously reported that chronic treatment with PCP or MK-801 results in impaired social interaction and hyperlocomotion, as well as reduced density of vasopressin V_{1a} receptors labeled by [^{125}I]-linear AVP in several brain regions of rats [37]. These observations point to a role for the central AVP system in modulating behavioral abnormalities associated with blockade of NMDA receptors.

NC-1900, a novel AVP analogue, has been shown to enhance cognitive functions, especially learning and memory, via activation of V_{1a} receptors in rodents. Thus, treatment with NC-1900 ameliorated deficits in place learning in rats with selective lesions of the hippocampal formation produced by transient forebrain ischemia [13]. Memory retention and retrieval in the step-through passive avoidant task was facilitated by NC-1900 in mice [33,34]. NC-1900 also facilitated memory performance in the eight-arm radial maze or passive avoidance task in non-amnesic or CO_2-amnesic mice [33], and ameliorated scopolamine-induced impairment of spatial memory in rats [19,33]. V_{1a} antagonists, but not V_2 antagonists, have been demonstrated to suppress the effects of NC-1900 on these behaviors [19,33,34].

This study was designed to test the hypothesis that treatment with AVP agonists would reverse behavioral changes induced by chronic administration of NMDA antagonists. For this purpose, we sought to determine whether acute injection of NC-1900 ameliorates hyperlocomotion and deficits in social interaction behavior in rats chronically treated with MK-801.

2. Materials and methods

2.1. Animals

Male Wistar rats (Japan SLC Inc., Hamamatsu, Japan) weighing 265–348 g at the time of testing were used. They were housed in groups of four in a plastic cage at 24 ± 2 °C under a 12:12-h light/dark cycle (light on from 05:00 to 17:00). Food and water were available ad libitum. All procedure was in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals, and was reviewed and approved by the Committee of Animal Research, Toyama Medical and Pharmaceutical University.

2.2. Drugs

(+)-MK-801 maleate (Tocris Cookson Ltd., Bristol, UK) was dissolved in sterile saline and was administered intraperitoneally 0.13 mg/ml/kg once daily for 14 days. This dose of MK-801 was based on previous reports and was expected to cause social interaction deficits with minimal emergence of stereotyped or ataxic movement [29,37].

NC-1900 (Nippon Chemiphar Co. Ltd., Saitama, Japan) was dissolved in sterile saline and was injected subcutaneously 10 ng/ml/kg at the time of the last MK-801 administration. Vehicle solution was always sterile saline 1 ml/kg.

2.3. Procedure

The animals were purchased 19 days before testing and randomly assigned to one of the four groups: chronic vehicle + acute vehicle group (n = 24); chronic vehicle + acute NC-1900 group (n = 24); chronic MK-801 + acute NC-1900 group (n = 24); or chronic MK-801 + acute vehicle group (n = 24). MK-801 administration was started 6 days after the arrival of rats at the laboratory.

The animals were injected MK-801 or vehicle intraperitoneally once daily for 14 days. On the 14th day of MK-801 administration, NC-1900 or vehicle was injected subcutaneously together with the final injection of chronic MK-801 or vehicle. Injections were made between 17:15 and 18:00. This protocol was based on previous studies [27,29,37]. The animals in each group were housed with the same cage mates at all times, and all rats within a given cage received identical treatment. Seven days prior to testing, half of the rats within a group were dyed with black hair color on the rear part of the body to facilitate recognition in the social interaction test. All rats were subjected to the social interaction test on the 14th day of drug administration, 45 min after the final injection. The social interaction tests were performed at the beginning of the dark phase (between 18:00 and 19:00). The rats were never tested more than once.