Available online at www.sciencedirect.com
ScienceDirect
Neurobiology of Learning and Memory 87 (2007) 324–331
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

Reinstatement of episodic-like memory in rats by neurokinin-1 receptor antagonism

Emriye Kart-Teke [a], Ekrem Dere [a], Marcus L. Brandão [b], Joseph P. Huston [a], Maria A. De Souza Silva [a,*]

[a] *Institute of Physiological Psychology, Center for Biological and Medical Research, Heinrich-Heine-University of Düsseldorf, D-40225 Düsseldorf, Germany*
[b] *Laboratory of Psicobiology, FFCLRP, University of São Paulo, 14090-901 Ribeirao Preto, SP, Brazil*

Received 27 May 2006; revised 15 September 2006; accepted 17 September 2006
Available online 31 October 2006

Abstract

We previously showed that a systemic administration of the selective non-peptide neurokinin-1-receptor (NK-1-R) antagonist SR140333 increases hippocampal acetylcholine levels and facilitates long term memory. In the present study, we investigated whether systemic SR140333 has beneficial effects on episodic-like memory for unique experiences. Rats received either no injection, a vehicle injection or SR140333 at doses of 1, 3 and 9 mg/kg (i.p.) prior to the acquisition of an object memory for *what, where* and *when*. In line with previous results, untreated rats showed episodic-like memory, while vehicle-injected rats were impaired. A low dose of 1 mg/kg SR140333 reinstated episodic-like memory. This result might be related to the effects of SR140333 on hippocampal cholinergic transmission and/or on the stress-response elicited by the injection procedure. Higher doses of SR140333 (3 and 9 mg/kg) induced psychomotor effects, including stereotypic behaviors and arched posture. Since NK-1-R antagonists have anxiolytic and promestic properties and induce hippocampal acetylcholine release at lower doses, they might be effective in the alleviation of the cognitive deficits and increased anxiety seen in early stages of Alzheimer's disease.

Keywords: SR140333; Acetylcholine; Hippocampus; Object memory; Stress; Cognitive enhancer; Alzheimer's disease

1. Introduction

The neuropeptide substance P is a centrally active neurotransmitter or neuromodulator, which, *inter alia*, has been implicated in nociception (Harrison & Geppetti, 2001), synaptic plasticity (Langosch et al., 2005), learning and memory (Hasenöhrl et al., 2000) brain reward and reinforcement (Nikolaus, Huston, & Hasenohrl, 1999), emotionality (Hasenöhrl, Jentjens, De Souza Silva, Tomaz, & Huston, 1998) and affective disorders (Herpfer & Lieb, 2003).

Substance P stimulates neurokinin-receptors, with the highest affinity to the neurokinin-1-receptor (NK-1-R) (Hokfelt, Pernow, & Wahren, 2001; Quartara & Maggi, 1998). In rats, high densities of the NK-1-R have been found in the neocortex, hippocampal formation, basal forebrain, amygdala and brainstem (Mantyh, Gates, Mantyh, & Maggio, 1989). Antinociceptive, antidepressant as well as anxiolytic effects have been reported after application of NK-1 receptor antagonists to rats (McLean, 2005; Pitcher & Henry, 2004). In line with this evidence, genetic inactivation of the NK-1-R gene in mice reduced the susceptibility to stress in a variety of tasks, similar to mice treated with antidepressants (Rupniak et al., 2001; Santarelli et al., 2001). In terms of learning and memory, NK-1-R knockout mice showed normal trace fear conditioning and a slight improvement in the hidden-platform version of the water maze task. Furthermore, these mice showed increased neurogenesis and brain-derived neurotrophic factor levels in the hippocampus (Morcuende et al., 2003). Similar changes have been reported after chronic treatment with

* Corresponding author. Fax: +49 211 81 12 0 24.
E-mail address: desouza@uni-duesseldorf.de (M.A. De Souza Silva).

1074-7427/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2006.09.007

antidepressants. NK-1-R knockout mice also showed reduced pain sensitivity in the hot plate-test (Mansikka, Shiotani, Winchurch, & Raja, 1999).

SR140333 is a potent and selective non-peptidergic antagonist at the NK-1-R in various species including rats and humans (Emonds-Alt et al., 1993). In vitro, SR140333 blocks substance P-induced endothelium-dependent relaxation of rabbit pulmonary artery and contraction of guinea-pig ileum (Emonds-Alt et al., 1993). In rats, intra-cerebroventricular administration of SR140333 reduces infarct volume after focal cerebral ischemia (Yu, Cheng, Huang, Li, & Cao, 1997). Furthermore, systemic administration of SR140333 blocks the processing of pain stimuli in the thalamus (Emonds-Alt et al., 1993) and inhibits scratching behavior elicited by i.c.v. application of substance P (Jung et al., 1994).

Previously, we showed that systemic post-trial SR140333 injections in rats had minor facilitative effects on inhibitory avoidance learning and behavioral habituation to a novel environment. Systemic application of SR140333 also dose-dependently increased extracellular acetylcholine levels in the hippocampus as measured by in vivo microdialysis in anesthetized rats (Kart et al., 2004). It is well established that modulation of hippocampal cholinergic neurotransmission influences synaptic plasticity (Ovsepian, Anwyl, & Rowan, 2004) and learning performance in rats (Sarter & Parikh, 2005). Therefore, the promnestic effects of SR140333 might be related to increased cholinergic neurotransmission in the hippocampus.

Recently, we developed an episodic-like memory task for rats, in which different versions of the novelty-preference paradigm have been combined in order to simultaneously assess object, place and temporal order memory (Kart-Teke, De Souza Silva, Huston, & Dere, 2006). This task is highly sensitive to the memory impairing effects of stress, e.g. a single i.p. saline injection impaired the acquisition of a memory for *what, where and when* in rats. Given that NK1-R antagonism has moderate promnestic effects, counteracts the behavioral effects of various stressful stimuli and increases hippocampal acetylcholine release, we hypothesized that systemic injections of SR140333 would also reinstate episodic-like memory in mildly stressed rats.

2. Materials and methods

2.1. Animals

Seventy-five male Wistar rats weighting 270–320 g were used, and were group housed with $n = 5$ per cage. They were maintained in a temperature and humidity controlled room (20–22 °C) and kept on a reversed 12 h light–dark cycle with lights off at 07:00 a.m. Animals had free access to rodent chow and tap water. Testing occurred during the dark phase. Before testing the animals were handled for 5 days. All experiments were performed according to the guidelines of the German Animal Protection Law and were approved by the North Rhine Westphalia State Authority.

2.2. Apparatus

Episodic-like memory was tested in an open-field. The open-field was a rectangular acryl box (60 × 60 × 39 cm), with an open roof, so that the rats could perceive distal visual cues. Four 75 W bulbs provided an illumination intensity of 11 lx in the corners and 17 lx in the center of the open-field. A video camera was placed 1.6 m above the center of the open-field to record sample and test trials. Video recordings were used for off-line data collection. The open-field was placed in a sound attenuating chamber. Masking noise was delivered by a white noise-generator.

2.3. Object stimuli

Four exact copies of three distinct translucent glass objects were used, which had no ethological significance to the rats. The objects varied in shape (octagon, rectangular and square), texture (plain or grooved), color and height (22–25 cm). The objects had sufficient weight to ensure that the rats could not displace them. Previous work ensured that Wistar rats could discriminate the two objects, and there was no per se preference for one of these objects (see Kart-Teke et al., 2006). For each animal two of these three objects were randomly chosen, and the order of presentation during the sample trials was randomized.

2.4. Experimental procedure

Each animal was subjected to three habituation trials (each lasting 10 min) to the open-field for three consecutive days. On the fourth day, animals received two sample trials followed by the test trial. The rats were always placed in the central part of the open-field. Each trial lasted 5 min. The inter-trial interval was 50 min. After each trial, the objects and the open-field were thoroughly cleaned with 0.1% acetic acid solution in order to remove odor cues. The open-field was virtually divided into nine squares by 2 × 2 parallel lines. The central square was not used for object placement. For each animal, four out of eight squares were randomly chosen to position the four copies of the "old familiar" object in the first sample trial (Fig. 1). The second sample trial was identical to the first except that four copies of another object ("recent familiar") were present. Two copies of the "recent familiar" object were randomly placed onto positions that had been occupied in the first sample trial and two copies were positioned in new positions, that were randomly chosen from the remaining four peripheral positions. In the test trial (trial 3), two copies of both objects were present in either stationary or displaced positions, i.e. one of the copies of each object was presented in a position encountered in the respective sample trial, i.e. sample trial 1 ("old familiar-stationary" object, A1) or sample trial 2 ("recent familiar-stationary" object, B1). The remaining objects were presented in new positions ("old familiar-displaced", A2 and "recent familiar-displaced", B2). All four objects were placed onto positions previously encountered in the sample trials (Kart-Teke et al., 2006).

2.5. Drugs and application procedure

SR140333 ((*S*)1-{3-(3,4-dichloro-phenyl)-3-[2(4-phenyl-1-aza-bicyclo[2.2.2]oct-1-yl]-ethyl]-piperidin-1-yl}-2-(3-isopropoxy-phenyl)-ethanone benzenesulfonate) was a gift from Sanofi-Aventis, Chilly-Mazarin,

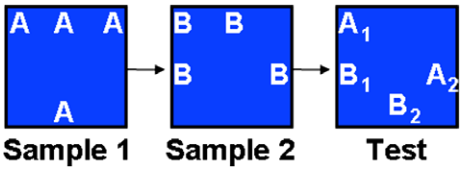

Fig. 1. Episodic-like object memory in rats. Experimental design. The schematic drawing shows an example of a possible object arrangement for the what, where, and when task. The rats received three 5 min trials with a 50 min inter-trial interval. During the test trial two "old familiar" and two "recent familiar" objects known from the sample trials were presented at familiar and novel locations relative to the respective sample trials. A1: "old familiar-stationary"; A2: "old familiar-displaced"; B1: "recent familiar-stationary" and B2: "recent familiar-displaced".