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Effect of D_3 dopamine receptors blockade on the cognitive effects of angiotensin IV in rats

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Abstract

Our previous studies showed that D_1 and D_2 dopamine receptors are indispensable for the cognitive effects of angiotensin IV (Ang IV) and its des-Phe^6 derivative des-Phe^6-Ang IV to occur. As most neuroleptics currently used in the treatment of schizophrenia have variable D_2/D_3 dopaminolytic selectivity, in this study we searched for the role of the D_3 dopamine receptors in facilitating learning and improving memory actions of Ang IV and des-Phe^6-Ang IV in rats.

For this purpose, we evaluated the recall of the passive avoidance (PA) behaviour, object recognition (OR) memory, and the spatial working memory (WM) in rats treated with the intraperitoneal (i.p.) nafadotride (N[(*n*-butyl-2-pyrrolidinyl)methyl]-1-methoxy-4-cyanonaphtalene-2-carboxamide), a highly selective D_3 receptor blocker and then by an intracerebroventricular (i.c.v.) Ang IV or des-Phe^6-Ang IV. Separate groups of rats receiving the same treatments were run to check for the possible participation of unspecific motor (open field) or emotioned (elevated "plus" maze) effects of our treatments in the results of the cognitive tests. The results revealed Ang IV to express its improving recall of PA, OR memory and WM action roughly similarly in all groups showing only minor or null significance of the D_3 receptors blockade. Interestingly, in the nafadotride pretreated rats, des-Phe^6-Ang IV beneficial effect on the recall of the PA was weaker than that of Ang IV. Improvement of the spatial WM in an eight-arm radial maze, similar after Ang IV and des-Phe^6-Ang IV, was not significantly affected by nafadotride. There were no motor and only minor anxiogenic effects of Ang IV and des-Phe^6-Ang IV abolished by nafadotride in the former case.

In conclusion, this study points to the minor significance of the D_3 dopamine receptors in the cognitive effects of Ang IV and to the interesting, though unexplained, inhibition by nafadotride of the des-Phe^6-Ang IV effects.

Keywords: Angiotensin IV; des-Phe^6-Ang IV; D_3 dopaminergic receptor; Nafadotride; Memory; Rat

1. Introduction

Angiotensin IV is a neuropeptide possessing potent cognitive effects. Given intracerebroventricularly (i.c.v.), it was shown to stimulate the learning of active and recall of the passive avoidance behaviors (Braszko et al., 1988, 2006; Wright et al., 1993), to improve recognition (Braszko et al., 2006) and spatial memory (Wright et al., 1999). Also, it effectively counteracted scopolamine- and mecamylamine-induced amnesia (Olson et al., 2004) as well as the memory impairment resulting from the perforant path knife lesions (Pederson et al., 1998). Systematic investigations of Mendelsohn's (Zhuo et al., 1998) and Wright's (Roberts et al., 1995) laboratories revealed the presence of the AT_4 receptors in the brain areas involved in the information processing such as hippocampus, entorhinal and pyriform cortices, and the nucleus accumbens. However, in spite of the intense research efforts the mechanisms responsible for the cognitive effects of Ang IV are largely unknown. Obviously, they have to be integrated with the actions of the neurotransmitters classically known to be responsible for the

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memory processes such as acetylcholine (ACh) (Decker and McGaugh, 1991) and dopamine (DA) (Glickstein et al., 2002). The involvement of Ach was supported by Lee et al. (2001) who found that Ang IV is able to increase the depolarization-induced ACh release. As regards the DA, our previous studies showed that in rats functional D_1 and D_2 (Braszko, 2004, 2006) dopamine receptors are necessary for the full expression of the Ang IV cognitive effects. To further explore the participation of the DA system in the Ang IV facilitation of learning and memory in the present study, we addressed the question whether D_3 dopamine receptors have any role in these processes. In an attempt to solve this problem, we blocked the D_3 receptors by pretreatment of rats with nafadotride, a potent and highly selective D_3 receptors inhibitor (Sautel et al., 1995; Audinot et al., 1998) and then assessed their ability to demonstrate the facilitation of learning and improvement of memory in response to the subsequently i.c.v. injected Ang IV. Behavior of these animals was examined by the cognitive (passive avoidance, object recognition and eight-arm radial maze) and auxiliary (open field and elevated "plus" maze) tests. The latter set of the two tests was performed in order to exclude unspecific motor (open field) and emotional ("plus" maze) effects of our treatments that necessarily would affect the results of the cognitive tests.

2. Materials and methods

2.1. Animals

Male Wistar rats (160–180 g) were housed five in a cage, in a temperature controlled room (22°) on a 12-h light-dark cycle beginning at 07:00 h. They had free access to standard laboratory food and tap water. Each animal was handled daily for three minutes until the day of the experiment (usually 5th). The experiments were conducted between 10:00 and 15:00 h. A 30-min adaptation period in the experimental room proceeded all the behavioural tests. The experimental procedures were carried out in accordance with the "Guidalines for the Care and Use of Laboratory Animals" published by the US National Institutes of Health (NIH publication No. 85–23, revised in 1996) and were approved by the Local Ethics Commission for Animal Experimentation.

2.2. Surgical procedure

Under light ether anaesthesia, a circular piece of skin, 7 mm in diameter, was cut off the scalp and the underlying skull surface was cleaned of soft tissue. A burr hole, 0.5 mm in diameter, was drilled in the skull 2.5 mm laterally and 1 mm caudally from the point of intersection of bragma and the superior sagittal suture on the right side of the head. The operation took about 2 min and, after 72 h recovery, the wound was completely dry and the animal behaved normally. Intracerebroventricular (i.c.v.) injections were made freehand into the right cerebral ventricle with a 10 μl Hamilton syringe, using a KF 730 needle cut 4.5 mm from its base. This procedure allowed the tip of the needle to be lowered about 0.5 mm below the ceiling of the lateral cerebral ventricle. The procedure was relatively non-traumatic as the animal, gently fixed by the left hand of the experimenter, was usually quiet and no vocalization occurred. The injection volume was 2 μl administered over 3 s. Upon completion of each experiment, all rats were sacrificed and the sites of injection were verified microscopically after brain sectioning.

2.3. Passive avoidance

Passive avoidance behavior was studied in a one-trial learning, step-through situation, which utilizes the natural preference of rats for a dark environment (Ader et al., 1972). The experiment was conducted exactly as described previously (Braszko et al., 2006).

2.4. Object recognition

Object recognition was tested in a plastic box 62 cm long, 38 cm wide and 20 cm high covered with a wire mesh lid. The objects to be discriminated were made of glass or porcelain and existed in duplicate. They appeared to have no natural significance for the rats and they had never been associated with reinforcement. Their weight was such that they could not be displaced by the rats. The procedure was similar to that described previously (Ennaceur and Meliani, 1992) and may be summarized as follows. All rats were submitted to two habituation sessions, with a 1-h interval, whereby they were allowed 3 min exploration of the apparatus. Twenty-four hours later testing began. The experimental session consisted of two trials, each lasting for 3 min. In the first trial (T1), rats were exposed to two identical objects A_1 and A_1. Immediately post trial, the animals were injected i.c.v. In the second trial (T2), performed 60 min later, rats were exposed to two objects, one of which was duplicate of familiar objects A (A′), in order to avoid olfactory traits, and a new object B. From rat to rat, the role (familiar or new object) as well as the relative position of the two objects were counterbalanced and randomly permuted during trial T2. These precautions were taken in order to reduce object and place preference effects. The basic measure was the time spent by the rat in exploring objects during trials T1 and T2. Exploration of an object was defined as touching it with the nose. Turning around or sitting on the object was not considered exploratory behaviour. From this measure, the following variables were defined: A, the time