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Original research article

Telmisartan attenuates cognitive impairment caused by chronic stress in rats

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ABSTRACT

Background: The potential effect of chronic treatment with telmisartan, an angiotensin type 1 receptor blocker (ARB) and partial agonist of peroxisome proliferator – activated receptor γ (PPARγ), on stress-related disorders is a matter of considerable interest. The existing data suggest that angiotensin II (Ang II) plays a major role in exaggerated sympathetic and hormonal response to stress. Enhanced formation of Ang II and increased AT_1 receptor activity is associated with devastating impact of stress on central nervous system, which may trigger many psychiatric disorders such as depression, schizophrenia or post-traumatic stress disorder. Some of the anti-stress effects of ARBs have already been proven but these on the stress-induced cognitive impairment were examined only for candesartan. In this study, we tested a hypothesis that blockade of stress response by another ARB telmisartan alleviates the negative effect of prolonged restraint stress on cognitive functions of male Wistar rats.

Methods: The preventive action of long-lasting treatment with telmisartan (1 mg/kg body weight) against impairment caused by chronic stress (2 h daily for 21 days) on recall was evaluated in a passive avoidance (PA) situation and object recognition test (ORT). Locomotor activity and anxiety behavior were tested respectively, in an open field and an elevated plus-maze.

Results: The results of this study indicate that telmisartan diminishes deleterious effects of chronic restraint stress on memory in a statistically significant manner ($p < 0.01$) in both, PA situation and ORT.

Conclusion: It appears that telmisartan may constitute a new therapeutic option in a stress-related cognitive impairment.

Introduction

The most important outcome of prolonged psychological stress includes impairment of learning and memory that is accompanied by neuronal damage and reorganization in the cognition-related brain structures [1,2]. Despite the well-known involvement of stress as a key factor in development of neuropsychological dysfunctions, no clinically effective therapeutic strategy has yet been found. Since prolonged emotional pressure becomes an inseparable factor of our everyday life, safe and effective prevention against its negative impact is an urgent priority.

Response to stressful stimuli triggers inseparable and correlated activity of the hypothalamic-pituitary-adrenal (HPA) axis, the renin-angiotensin system (RAS) and sympathetic-adrenal medulla system [3]. Angiotensin II (Ang II), the main effector peptide of RAS, apart from being well known vasoconstrictor, is involved in stress-related information signaling [4]. Ang II is highly concentrated in hippocampus [5], a limbic structure associated with the formation and recall of spatial memories [6]. Physiologically, Ang II excites hippocampal CA1 pyramidal neurons [7] and modulates the induction of hippocampal LTP [8]. Pathophysiological response to stressful stimuli exceeding adaptive mechanisms include increased brain Ang II activity, amplified AT_1 receptor expression in the HPA axis which is associated with higher HPA activation, and enhanced peripheral RAS activity [9]. Noteworthy, it has been proven that the expression of Ang II receptors increases after chronic restraint stress [10]. The blockade of brain AT_1 receptors ameliorates the response to stress, decreases sympathetic activation [11], prevents somatic stress disorders such as gastric ulceration [12], and decreases anxiety-related behavior [13].

The preclinical experimental data described above is increasingly supported by clinical evidence. Recently, accumulating data associate decrease of cognitive performance with high blood pressure [14]. Moreover, some clinical trials point to angiotensin

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antagonists i.e. ACEIs and ARBs as potentially beneficial in prevention of cognitive decline [15]. Accordingly, a clinically proven significant reduction in the incidence and progression of memory impairment was archived with ARBs [16].

One of the most commonly used ARB, with constantly increasing popularity, is telmisartan. Because of its well-known pharmacologic properties, including the longest half-life among all ARBs [17], telmisartan might be considered as superior cardioprotective drug in patients with hypertension. Interestingly, telmisartan is also the most lipophilic agent among ARBs, therefore it most readily crosses the brain-blood barrier (BBB) to cause central AT_1 receptor blockade [18]. Due to the fact that systemic ARB treatment, along with intraventricular injection of Ang II, inhibited the central effects of Ang II on blood pressure, vasopressin secretion and the drinking response in spontaneously hypertensive rats [19], it is reasonable to assume that ARB penetrates into the brain. Since BBB permeability increases due to stress [20], the effect of peripherally administered telmisartan on central response to Ang II, might be sufficient to attenuate stress-induced cognitive decline. Moreover, recent in vitro studies indicate that telmisartan is directly neuroprotective [21], but its usefulness in the treatment of inflammatory conditions of the brain needs further support.

In this study we tested a hypothesis that telmisartan can protect rats against chronic stress induced cognitive impairment using passive avoidance and object recognition tests. The unspecific influence of potential effects of telmisartan on locomotor activity and anxiety was evaluated in open field and elevated plus-maze, respectively.

Materials and methods

Animals

The experiments were conducted on male Wistar rats, weighing approximately 150 g at the beginning. Animals were housed five to a cage in a temperature (22 °C) and humidity (50–60%) controlled room, on a 12 h:12 h light/dark cycle with light on from 6:00 a.m. Free access to standard laboratory food and tap water was provided. All animals were handled daily for 2 min each until the day of experiment. All the procedures were conducted between 1:00 and 6:00 p.m. A 30 min adaptation period in the experimental room preceded all the tests. All procedures involving animals were approved by the local Ethics Commission for Animal Experimentation.

Drugs

The specific AT_1 receptor antagonist – telmisartan (Boehringer Ingelheim, Germany) was suspended in 0.5% methylcellulose (vehicle) at concentration of 1 mg/ml. Telmisartan or its vehicle was dosed by oral gavage at 1 mg/kg body weight, considered to be a nonhypotensive dose in rats [22,23].

Seventy-two male Wistar rats were randomly assigned to four groups: (1) 18 control rats – receiving 0.5% methylcellulose as a vehicle; (2) 18 rats receiving telmisartan suspended in 0.5% methylcellulose; (3) 18 rats receiving 0.5% methylcellulose subjected to a repeated restraint stress procedure; (4) 18 rats receiving telmisartan suspended in 0.5% methylcellulose subjected the repeated restraint stress procedure. The subjects received either telmisartan or vehicle each day immediately before the stress procedure.

Stress procedure

Two groups of animals (18 rats each) were subjected to chronic restraint stress [24,25] 2 h daily for 21 days. The restraint was imposed during the light phase from 13:00 to 15:00 p.m. The restrainer was made of transparent perforated plastic tube, 20 cm long, and 7 cm in diameter. A rat was eased into the restrainer, head first, and once in the tube it was closed with a plexiglass lid. The animals fit tightly into the restrainers and it was not possible for them to move or turn around. Not stressed control rats were at the same time briefly handled and returned to their home cages. All the animals subjected to stress were checked for gastric ulceration on the next day after ending the behavioral tests. Rats were anaesthetized with the mixture of ketamine (50 mg/kg) and xylazine (7.5 mg/kg) injected intraperitoneally and sacrificed. Exposed gastric mucosa was visually examined under the 5× magnification lens for gastric ulceration. No visible signs of injury were found.

Behavioral tests

All rats underwent behavioral testing next day after ending the chronic drug treatment and repeated stress procedure. Thirty six subjects (assigned to 4 groups) participated in the open field test followed by the passive avoidance test. Performance of another group of 36 rats was estimated in elevated plus-maze which was executed right after object recognition test.

Passive avoidance

Passive avoidance (PA) behavior was studied in one trial learning, step-trough situation [26], which utilizes the natural preference of rats for dark environment. The apparatus consisted of the platform (250 mm × 80 mm) connected to a dark compartment – a metal box (400 mm × 400 mm × 400 mm) with an opening (60 mm × 100 mm) in the middle of the front wall. After a 2 min habituation to the dark compartment, the rat was placed on the illuminated platform and allowed to enter the dark compartment. Two more approach trials were given on the following day with a 2 min interval. At the end of the second trial unavoidable scrambled electric foot-shock (0.3 mA, AC, 2 s) was delivered through the grid floor of the dark compartment (learning trial). Retention of the passive avoidance response was tested 24 h, 48 h and 72 h later by placing the animal on the platform and measuring the latency to re-enter the dark compartment to a maximum of 300 s.

Object recognition

Object recognition was tested in a wooden 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 [27] 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, lasting for 3 min and 5 min. In the first trial (T1), rats were exposed to two identical objects A1 and A2. In the second trial (T2), performed 60 min later, rats were exposed to two objects, one of which was duplicate of the familiar object 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