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Signs of attenuated depression-like behavior in vasopressin deficient Brattleboro rats

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Abstract

Vasopressin, a peptide hormone functioning also as a neurotransmitter, neuromodulator and regulator of the stress response is considered to be one of the factors related to the development and course of depression. In the present study, we have tested the hypothesis that congenital deficit of vasopressin in Brattleboro rats leads to attenuated depression-like behavior in tests modeling different symptoms of depression. In addition, hypothalamic–pituitary–adrenocortical axis activity was investigated. Vasopressin deficient rats showed signs of attenuated depression-like behavior in forced swimming and sucrose preference tests, while their behavior on elevated plus maze was unchanged. Vasopressin deficiency had no influence on basal levels of ACTH and corticosterone and had only mild impact on hormonal activation in response to forced swimming and plus-maze exposure. However, vasopressin deficient animals showed higher level of dexamethasone induced suppression of corticosterone response to restraint stress and higher basal levels of corticotropin-releasing hormone mRNA in the hypothalamic paraventricular nucleus. In conclusion, present data obtained in vasopressin deficient rats show that vasopressin is involved in the development of depression-like behavior, in particular of the coping style and anhedonia. Moreover, behavioral and endocrine responses were found to be dissociated. We suggest that brain vasopressinergic circuits distinct from those regulating the HPA axis are involved in generating depression-like behavior.

Keywords: Vasopressin; Brattleboro rats; Depression; Anxiety; Forced swimming test; Coping strategy; Elevated plus-maze; Sucrose preference; Corticosterone; ACTH

Introduction

The neuropeptide vasopressin is considered to be one of the factors related to the development and course of depression (Dinan and Scott, 2005; Scott and Dinan, 2002). Vasopressin is functioning as a neuromodulator and neurotransmitter in key limbic regions, e.g. hippocampus, amygdala, hypothalamus (de Vries and Miller, 1998; Landgraf and Neumann, 2004) involved in affective functions, cognition as well as stress response (Carrasco and Van de Kar, 2003; Kalia, 2005). Vasopressin signaling has already been found to contribute to memory formation, regulation of aggression, anxiety and social behavior (Alescio-Lautier et al., 2000; Bielsky et al., 2004; Wersinger et al., 2002).

Hypothalamic vasopressin synthesized in parvo and magnocellular divisions of the paraventricular nucleus (PVN) is related to the function of hypothalamic–pituitary–adrenocortical (HPA) axis (Engelmann et al., 2004). Regulatory role of vasopressin becomes apparent particularly under prolonged stress conditions (Makara et al., 2004; Volpi et al., 2004), which are linked to the pathophysiology of depression (Tafet and Bernardini, 2003). In patients with depression, a dysregulation of the HPA axis function has been observed. The alterations include elevated cortisol levels, blunted ACTH response to exogenous corticotropin-releasing hormone (CRH) challenge and disrupted dexamethasone feedback efficacy with aberrant outcome in combined dexamethasone/CRH test (Holsboer and

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Barden, 1996). Enhanced vasopressin action has been proposed to underlie disruptions in challenge tests in patients with depression (Dinan et al., 1999, 2004; von Bardeleben et al., 1985; von Bardeleben and Holsboer, 1989).

The implication of vasopressinergic system in depression is supported by some clinical and preclinical findings. In patients with depression, an increased number of vasopressin expressing neurons in the PVN (Purba et al., 1996), increased expression of vasopressin mRNA in supraoptic nucleus (Meynen et al., 2006), elevated levels of vasopressin in plasma (van Londen et al., 1997) and normalization of blunted ACTH response to CRH by the vasopressin agonist desmopressin (Dinan et al., 1999) were observed. The experimental data are limited as well. In some animal models of depression treatment with a vasopressin receptor antagonist resulted in a reduction of depression-like behavior comparable to the action of clinically effective antidepressants (Alonso et al., 2004; Griebel et al., 2002; Louis et al., 2006; Overstreet and Griebel, 2005). There are some other studies providing indirect evidence (Ebner et al., 2002; Marcilhac et al., 1999) and supporting data obtained in rats bred for high trait anxiety. These rats suffer from genetically determined (Murgatroyd et al., 2004) hyperactivation of hypothalamic vasopressin system associated with increased depression-like behavior and impaired HPA axis activity similar to that seen in depressed patients. In these rats, treatment with an antidepressant as well as vasopressin antagonist can normalize both behavioral and endocrine abnormalities (Landgraf and Wigger, 2003).

Even though the mentioned data suggest the involvement of vasopressin system in depression, it is still not clear whether vasopressin hyperactivity is a pathogenetic factor or just a result of depressive state. Vasopressin deficient Brattleboro rats may provide a tool to answer this question. Brattleboro strain is a natural vasopressin knockout derived from Long Evans rats. Vasopressin deficiency is a result of a single nucleotide deletion in the neurophysin region of the vasopressin gene. Because of this genetic mutation Brattleboro rats synthesize an altered vasopressin precursor, which is unable to enter the secretory pathway (Bohus and de Wied, 1998; Evans et al., 2000).

Present study in Brattleboro rats was designed to test the hypothesis that vasopressin is at least partially responsible for the development of depression-like behavior. We predicted that congenital deficit of vasopressin would lead to attenuated depression-like behavior in tests modeling different symptoms of depression, namely passive coping strategy (forced swimming test), anhedonia (sucrose preference) and anxiety (elevated plus-maze). To investigate endocrine state related to behavioral measures, we examined HPA axis responsiveness and feedback efficacy (dexamethasone test). In addition, gene expression of CRH was measured in the PVN and amygdala of Brattleboro rats.

Methods

Animals and experimental conditions

Male Brattleboro rats were maintained at the Institute of Experimental Medicine in a colony started from breeder rats from Harlan, Indianapolis, IN. USA. We compared the vasopressin deficient homozygous (di/di) rats with congenital diabetes insipidus to heterozygous (di/+) control rats from the same litters (Bohus and de Wied, 1998; Zelena et al., 2003a). Rats were kept in controlled environment (23±1 °C, 50–70% humidity, 12 h light starting at 07.00) and given commercial rat chow (Charles River, Hungary) and tap water ad libitum. Due to high level of urination in di/di rats sawdust bedding was changed daily. The animals were isolated at least 3 days prior to testing (individual cage size: 42.5×26.6×18.5 cm, 1291 Eurostandard Type III/h). All studies were carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC) and were reviewed and approved by the Animal Welfare Committee of the Institute of Experimental Medicine, Budapest, Hungary.

Experiments were performed in the morning between 9:00 and 12:00. If not stated otherwise, rats were tested in their home animal room brightly lit by standard neon ceiling lamps (producing approximately 200 lx). Each behavioral test was performed in a separate group of naive animals. All experimental animals were undisturbed till the test day, except rats used in forced swimming test, which were equipped by jugular vein catheter 2 days prior the behavioral measurement.

Testing general behavioral profile

Locomotor activity

General locomotor activity was assessed in two identical series. Behavior of animals was tested in a plastic cage with rectangle floor (36×40 cm) and walls (40 cm) covered with aluminium tinfoil. The cage was placed in animal room brightly lit by standard neon ceiling lamps (producing approximately 200 lx). Floor of the cage was divided into nine equal squares of 12×13.3 cm. The rat was placed in the middle square and its activity was videotaped by camera positioned above the cage. Each measurement lasted 7 min. Floor of cage was washed with water and dried prior next animal was introduced. All recordings were analyzed by the same observer afterwards. Number of squares entered (all four paws in the square) and number of rears was counted to determine the level of horizontal and vertical activity, respectively.

Muscle strength and psychomotor coordination

Wire suspension (a measure of animal muscle strength): Forepaws of the rat were placed on a horizontal stainless-steel wire (40 cm long and 2 mm in diameter) stretched 1.5 m above the mat-covered floor. Latency of suspended animal to fall was recorded.

Stationary beam (a measure of psychomotor coordination and the integrity of the vestibular system): animals were successively placed in the center of a fixed plastic rough rod (50 cm long, 7 mm in diameter) positioned 90 cm above landing platform covered with a thick sheet of soft plastic. Latency to fall off the rod was recorded.

Rotarod (a measure of motor coordination, balance, and resistance to fatigue): The rod consisted of a longitudinally rotating wooden beam (6 cm in diameter, 50 cm long, rotation speed: 4/s) covered by a layer of sticky plaster in order to ensure a firm grip. Following three pre-test trials the day before the test, rats were placed on the centre of the rod and its latency to fall was recorded.

Wire suspension, stationary beam and rotarod falling latencies were counted by stop-watch directly during the test. In each particular test, results represent averages of the data obtained in three consecutive trials of 90 s at 15-min intervals (Jeljeli et al., 2003).

Testing depression-like behavioral displays

Copying strategy: forced swimming test (FST)

Test was performed in two separate, identical series in brightly lit room adjacent to animal facility. Rats equipped with jugular vein catheter were brought to test room in their home cages and immediately tested. They were individually placed in a glass cylindrical tank 40 cm tall and 14 cm in diameter filled with tap water (21±1 °C) at a height of 25 cm. The animals were forced to swim for a 10-min period (pre-test) and 24 h later were subjected to a 10-min swimming session (test; modified version of Porsolt et al. (1977)). Both swimming sessions were videotaped by camera positioned in front of the water tanks and subjected to analyses later on. Behavior was scored over the first 5 min of the test (measurement over this time interval was introduced in the original Porsolt paper and it is still being used as a standard for testing antidepressant drug activity in rats) and during the entire pre-test and test sessions (exactly 9