GENERAL PATHOLOGY AND PATHOPHYSIOLOGY

Expression of Vasopressin in the Hypothalamus of Active and Passive Rats with Poststress Depression

V. I. Mironova, E. A. Rybnikova, and V. V. Rakitskaya

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 140, No. 12, pp. 618-621, December, 2005
Original article submitted May 31, 2005

No interstrain differences were revealed in vasopressin concentration in the hypothalamus of control and treated active and passive rats with poststress depression. Changes in vasopressin immunoreactivity corresponded to variations in corticotropin-releasing hormone concentration observed in this model of depression. These data suggest that vasopressin contributes to the development of this experimental psychopathology.

Key Words: *vasopressin; hypothalamus; poststress depression; KHA and KLA rats*

The role of vasopressin (VP) in the pathogenesis of depressions is little studied despite the facts that dysfunction of the pituitary-adrenocortical system (PAS) is one of the major signs of depression and hypothalamic VP, in addition to corticotropin-releasing hormone (CRH), acts as a neurohormonal regulator in PAS. Changes in the synthesis and secretion of hypothalamic CRH play a major role in the development of depression-like disorders [5]. There are data on VP and CRH colocalization in neurons and neurosecretory terminals, stimulating effect of VP on the synthesis and secretion of CRH and affinity of CRH receptors, and synergistic effect of these neurohormones in the regulation of stress reactions and PAS activity [3,8,9]. Colocalization of VP and CRH in neurosecretory terminals serves as a criterion for secretory activity, while VP/CRH ratio in portal blood flow determines the course of adaptation [6]. Little is known about the role of VP and its receptors (particularly V1β-receptors) in dysfunction of PAS during various forms of depression [6].

Laboratory of Neuroendocrinology, I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg. ***Address for correspondence:*** viablos@mail.ru. V. I. Mironova

Here we performed an immunocytochemical study of VP concentration in supraoptic and paraventricular hypothalamic nuclei expressing this neurohormone under conditions of experimental poststress depression in behaviorally active and passive rats. Our previous studies showed that active and passive animals demonstrate different psychopathologies in the learned helplessness paradigm, which can be considered as model analogues of endogenous and reactive depression in KHA and KLA rats, respectively [2].

MATERIALS AND METHODS

Experiments were performed on KHA (n=20) and KLA rats (n=20). These animals were selected at the I. P. Pavlov Institute of Physiology by the rate of learning conditioned active avoidance response. KHA and KLA rats exhibit active and passive strategy of adaptive behavior, respectively. The study was conducted on animals weighing 180-250 g. Learned helplessness served as an experimental model of depression [7]. The rats were exposed to unavoidable electrocutaneous stimulation in cages (13×16×26 cm) with a current-conducting floor. There were intermittent periods of stimulation and rest (60 electroshocks over 1 h). Control animals

0007-4888/05/1406-0668

were maintained in the same cages, but did not receive electrostimulation. Although the development of learned helplessness differed in KHA and KLA animals, persistent behavioral depression was observed in all animals by the 10th day of treatment.

For immunocytochemical study, the rats were decapitated 1, 5, and 10 days after stress. The brain was rapidly removed. The hypothalamus was isolated, fixed in 4% paraformaldehyde for 36-48 h, routinely processed, and embedded into paraffin. Frontal brain sections (6 μ) were prepared. To study VP expression in the hypothalamic paraventricular and supraoptic nucleus, the sections were treated with monoclonal antibodies against VP (ICN Biomedicals, 1:500). Visualization involved the avidin-biotin method with diaminobenzidine. Radioactivity was studied quantitatively using a computerized image analysis system. After evaluation of optical density, VP-immunopositive cells were divided into groups of weakly immunoreactive, moderately immunoreactive, and strongly immunoreactive cells. We estimated the total number of immunoreactive cells and total number of moderately and strongly immunoreactive cells. This approach allowed us to perform qualitative and quantitative study of neurohormone expression. The results were analyzed by Excel-2002 software ($p<0.05$). The data are expressed as $M \pm SEM$.

RESULTS

VP expression in animals of both strains decreased over the first day after stress, but returned to normal on day 10. The degree of changes differed in KHA and KLA rats.

Basal expression of VP in the hypothalamic supraoptic nucleus of KLA rats was slightly higher than in KHA rats. The concentration of VP decreased in KHA and, particularly, in KLA rats over the first day after stress. By the 10th day VP immunoreactivity in the hypothalamic supraoptic nucleus partially returned to normal in animals of both strains (Fig. 1).

Basal expression of VP in the gigantocellular part of the hypothalamic paraventricular nucleus in nonstressed active rats was higher than in passive animals. VP expression and total number of immunoreactive cells decreased in animals of both strains on day 1 after stress. The total number of VP-immunoreactive cells and VP expression in individual cell populations decreased in passive and, particularly, in active rats (Fig. 2). VP expression returned to normal on day 5 and remained unchanged by the 10th day after unavoidable uncontrolled stress.

Basal expression of VP in the parvocellular part of the hypothalamic paraventricular nucleus in KHA rats was lower than in KLA rats. The number of immunoreactive cells in KHA rats slightly increased over the 1st day after stress, which was associated with changes in the count of weakly immunoreactive cells. The concentration of VP in KLA rats decreased due to a decrease in the relative number of weakly immunoreactive cells (Fig. 3).

Our results show that VP expression in the hypothalamus little varied in active and passive rats. However, the concentration of VP in most nuclei decreased significantly 24 h after treatment (Figs. 1 and 2). The decrease in hypothalamic VP concentration probably reflects the reaction of this system to stress and is associated with depletion of neuro-

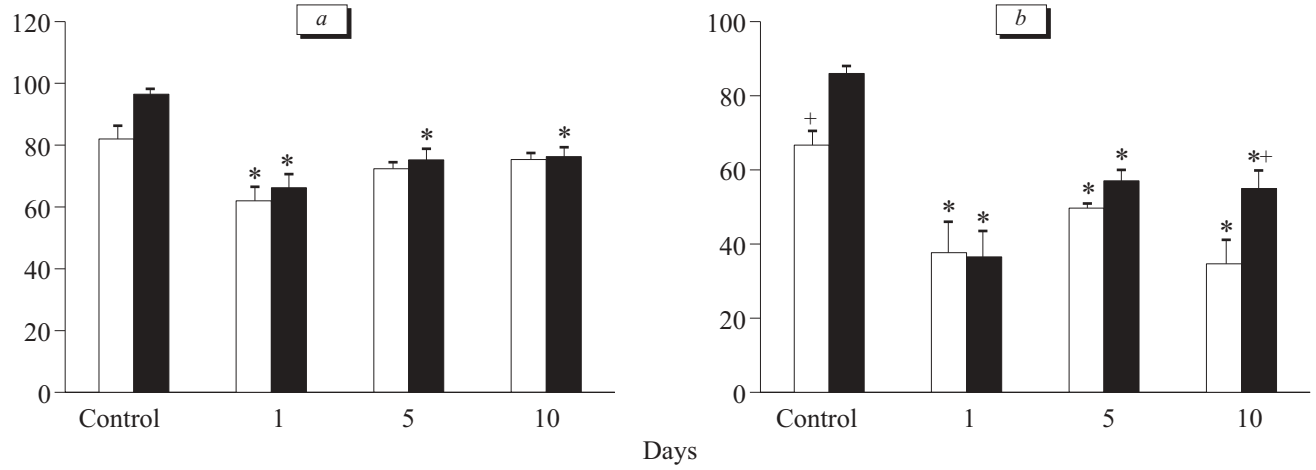

Fig. 1. Vasopressin concentration in the supraoptic nucleus of KHA (light bars) and KLA rats (dark bars) with poststress depression. Here and in Figs. 2 and 3: ordinate, number of immunoreactive cells. Total number of cells (*a*); and total number of moderately and strongly immunoreactive cells (*b*). $p<0.05$: *compared to the control; +compared to KHA rats.

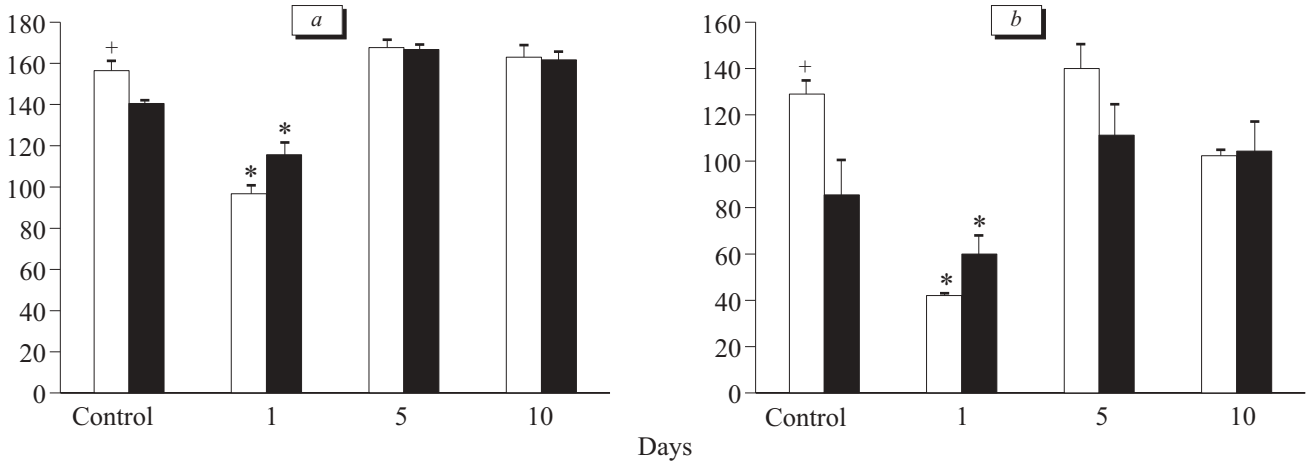

Fig. 2. Vasopressin concentration in the gigantocellular paraventricular nucleus of KHA (light bars) and KLA rats (dark bars) with poststress depression.

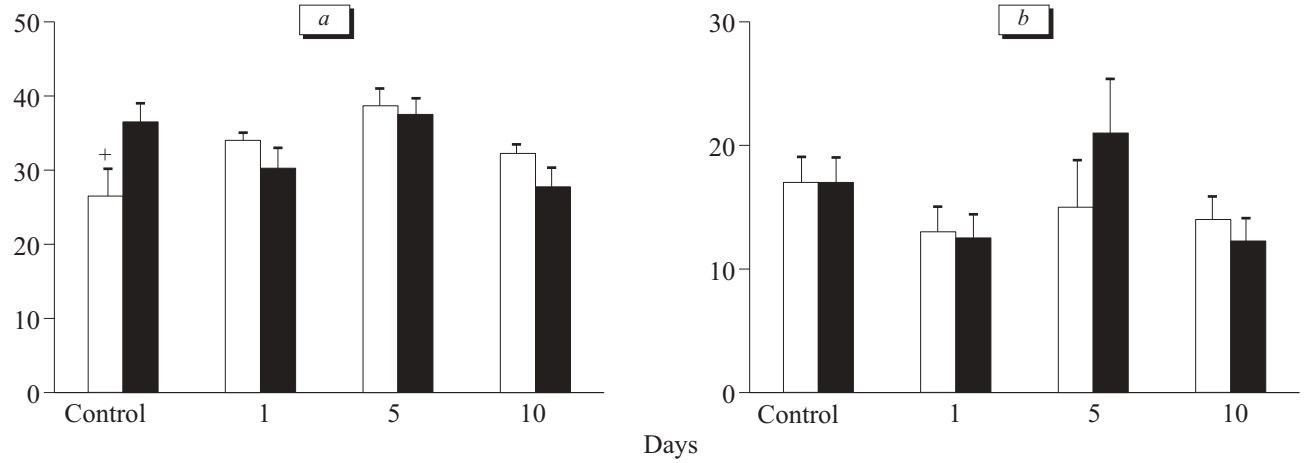

Fig. 3. Vasopressin concentration in the parvocellular paraventricular nucleus of KHA (light bars) and KLA rats (dark bars) with poststress depression.

hormone reserves after its massive release under stress conditions.

The concentration of this neurohormone in hypothalamic nuclei returns to normal in the delayed period after the appearance of depression-like symptoms. It can be hypothesized that VP does not modulate the development of poststress depression and dysfunction of PAS in active and passive rats [1,4]. Hypothalamic VP is probably involved in the primary response to unavoidable uncontrolled aversive stress. Despite the development of various depressive disorders in active and passive rats, we revealed no interstrain differences in the reaction of the VP system to stress. These data suggest that hypothalamic VP plays a role in the nonspecific stress response, which is mediated by the general mechanism and does not depend on individual stress reactivity.

The pattern of changes in VP immunoreactivity in some nuclei corresponded to variations in the concentration of the major stress hormone CRH [2]. It should be emphasized that CRH concentration underwent less significant changes. A slight decrease in VP concentration during behavioral depression can accompany variations in the expression of hypothalamic CRH. VP is colocalized with CRH and serves as a cotransmitter for this hormone.

In terms of PAS activity and behavioral characteristics, the paradigm of learned helplessness in active and passive animals serves as an experimental model of melancholic and reactive depression, respectively. Expression of hypothalamic VP changes only in the acute poststress period, but returns to normal in the delayed period (stage of behavioral depression). Hypothalamic VP probably plays little role in the development of these experimental disorders in rats.

This work was supported by the Russian Foundation for Basic Research (grant No. 02-04-49460) and Foundation to Support Russian Science.

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