Effect of *Hypericum* Extract on the Hypothalamic-Pituitary-Adrenal System in Rats

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We studied the effect of *Hypericum* extract on activity of the hypothalamic-pituitary-adrenal system in rats. In rats exposed to stress after a 30-day daily oral treatment with *Hypericum* extract, the weight of the adrenals and ACTH concentration were lower than in controls. Hence, treatment with *Hypericum* extract improved resistance to stress and prevented exhausting of the hypothalamic-pituitary-adrenal system.

Key Words: *Hypericum; stress, adrenals; ACTH*

St. John wort (*Hypericum perforatum*) has been used as antidepressant for many years [6,15]. However, the mechanism of its effect is still poorly understood. Among bioactive substances contained in this plant, the leading part in the realization of its antidepressant effect is played by hyperforine. This substance inhibits synaptosomal uptake of serotonin, norepinephrine, and dopamine [13,14]. The selectivity of this effect is comparable to the effects of selective serotonin and norepinephrine re-uptake blockers [5,10]. The antidepressant effect of *Hypericum* extract (HE) results from elevation of serotonin and norepinephrine concentrations, which are reduced during depression [2].

Depressive states are associated with impaired stress tolerance. However, the effect of St. John wort on the hypothalamic-pituitary-adrenal system predominating in adaptive reactions was not studied. We simulated a possible effect of *Hypericum* on adaptation to a stress exposure proceeding from the fact that neurotransmitters (serotonin, dopamine, and norepinephrine) modulate the production of corticotropin releasing hormone (CRH) [1]. Opinions on the effects of these neurotransmitters on CRH production are contradictory. Some authors reported an inhibitory effect [7,9], while others observed increased production of CRH [3]. In any case, the increase in serotonin and norepinephrine concentrations after blockade of their re-uptake modulates the state of the hypothalamic-pituitary-adrenal system.

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MATERIALS AND METHODS

Experiments were carried out on male Wistar rats (200 g). Experimental animals (6 rats per group) were fed HE (BioDom) for 30 days in daily doses of 3 or 6 mg (the doses of HE were calculated on the basis of its therapeutic doses [6,15]). This duration of treatment was chosen because the antidepressant effect usually appeared after 1-1.5 months of regular oral treatment [14].

Control rats (n=6) were kept under similar conditions but received no HE.

After the end of treatment all rats were exposed to stress (10-min wheel running), after which they were decapitated, blood was collected for hormone assay, the adrenal was removed and weighed. ACTH was measured and the mean value for each group was estimated. The measurements were carried out at Hormone Laboratory, St. Petersburg Medical Academy.

The data were statistically processed using nonparametric Mann—Whitney U test or Student's t test.

RESULTS

Daily administration of HE to experimental rats had no effect on their behavior.

In rats receiving HE in a daily dose of 3 mg the relative weight of the adrenal decreased in compa-

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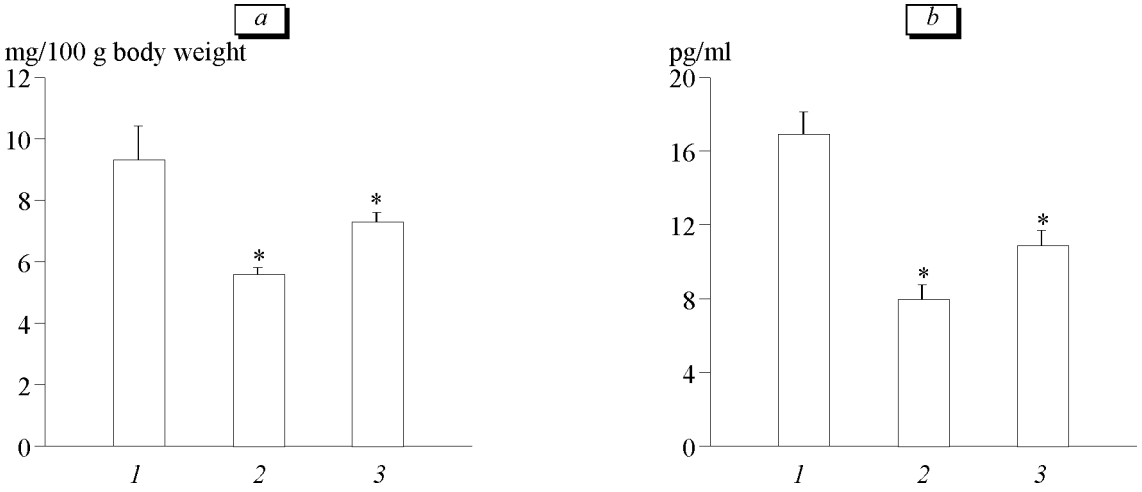

Fig. 1. Changes in the adrenal weight (*a*) and ACTH level (*b*) in rats receiving *Hypericum* extract in daily doses of 3 (*2*) and 6 mg (*3*) for 30 days. *$p<0.05$ *vs.* the control (*1*).

rison with the control (Fig. 1, *a*). Group 1 rats had the lowest concentration of ACTH (47% of the control) (Fig. 1, *b*). This can be attributed to the inhibitory effect of neurotransmitters on CRH production in the hypothalamus, which, in turn, led a decrease in the adrenal weight. Changes in ACTH level and the reaction of the adrenals to stress in experimental animals were less expressed than in controls. Hence, HE therapy protects the organism from overstrain during stress.

In rats receiving HE in a daily dose of 6 mg, the weight of the adrenals and ACTH level decreased to 60% and 56% of the control, respectively (Fig. 1). Hence, this dose was less effective.

Our results indicate that chronic treatment with HE moderately inhibited the hypothalamic-pituitary-adrenal system. The most pronounced effect was produced by HE in a dose of 3 mg/day. Treatment with a higher dose led to adaptation of the hypothalamic-pituitary-adrenal system, probably due to the decrease in β-adrenoreceptor and type 2 serotonin receptor sensitivity [12], however the effect was still protective.

Adrenal weight can change due to alteration of their blood content and due to hypertrophy of its structural elements directly responding to ACTH. In our experiment, the weight of the adrenal was used as an integral characteristic of prolonged HE treatment and stress. The difference in the adrenal weight between the experimental and control groups is largely determined by lower secretory activity of the adrenals under conditions of low ACTH concentration.

Hence, long-term treatment with HE reduced activity of the hypothalamic-pituitary-adrenal system during stress. However it remains unclear what is more physiologically beneficial for the organism: hyper- or hypofunction of the hypothalamic-pituitary-adrenal system during stress [8,11]. Presumably, there is a certain range of system activity providing optimal response of the organism to stress. In our experiment the animals treated with HE were most likely at the lower boundary of this range, which was physiologically more beneficial for the organism.

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