Role of α_{2A}-Adrenoceptors of Locus Coeruleus in Regulation of Plasma Corticosterone Content in Male Rats

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 131, No. 3, pp. 313-315, March, 2001
Original article submitted December 6, 2000

Administration of specific oligonucleotide selectively inhibiting α_{2A}-adrenoceptor gene expression into the locus coeruleus of male rats for 3 days activated the hypothalamic-pituitary-adrenal system, which was manifested in a rise of blood plasma corticosterone content in rats with normal and hypertrophied (after castration) adrenal glands. These data indicate that α_{2A}-adrenoceptors of the locus coeruleus are involved in the regulation of basal plasma corticosterone content.

Key Words: *α_{2A}-adrenoceptors; antisense technique; locus coeruleus; corticosterone; castration*

Brain α_2-adrenoceptors are involved in the regulation of various physiological systems and processes. These receptors are the target for many medicinal preparations, including hypotensive drugs and antidepressants. Molecular genetic studies revealed 3 subtypes of α_2-adrenoceptor (α_{2A}, α_{2B}, and α_{2C} receptors), whose genes were cloned [3,5]. These subtypes of α_2-adrenoceptors are characterized by different distribution in various brain structures, which attests to regional specificity of their functions [3]. The brain stem locus coeruleus (BSLC) modulates stress reactions, including activity of the adrenocortical system and plays an important role in the adaptation to stress and pathogenesis of psychoemotional disorders [10]. BSLC contains bodies of noradrenergic neurons innervating cortical and subcortical structures, whose functions change in response to stress. α_2-Adrenergic autoreceptors (primarily α_{2A}-adrenoceptors [6]) are probably the main regulators of the noradrenergic system. The role of α_{2A}-adrenoceptors, including those localized in BSLC, in the regulation of the adrenocortical system remains poorly understood due to the absence of subtype-specific ligands, which hinders routine pharmacological assays. Here we studied the role of α_{2A}-adrenoceptors of BSLC in the regulation of basal blood corticosterone content using the antisense technique [2]. This method is based on selective blockade of gene expression.

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MATERIALS AND METHODS

Experiments were performed on sham-operated and castrated male Wistar rats kept under natural light-dark conditions and *ad libitum* food and water supply.

The animals were castrated under ester anesthesia. Cannulas were implanted into BSLC under nembutal (40 mg/kg) anesthesia. Four weeks after castration and starting from day 4 after implantation of cannulas, the rats were daily (for 3 days) administered with specific oligonucleotide selectively inhibiting expression of α_{2A}-adrenoceptor gene (antisense), random oligonucleotide of the same composition (daily dose 1 nmol/5 μl), or an equivalent volume of physiological saline. On day 4, the animals were decapitated, and plasma corticosterone concentration was measured by competitive radioligand binding assay [1]. The adrenals were weighted. The results were analyzed by two-way ANOVA using Statistica software.

RESULTS

Previous studies showed that administration of antisense into BSLC decreases the content of α_{2A}-adreno-

0007-4888/03/1313-0263$25.00

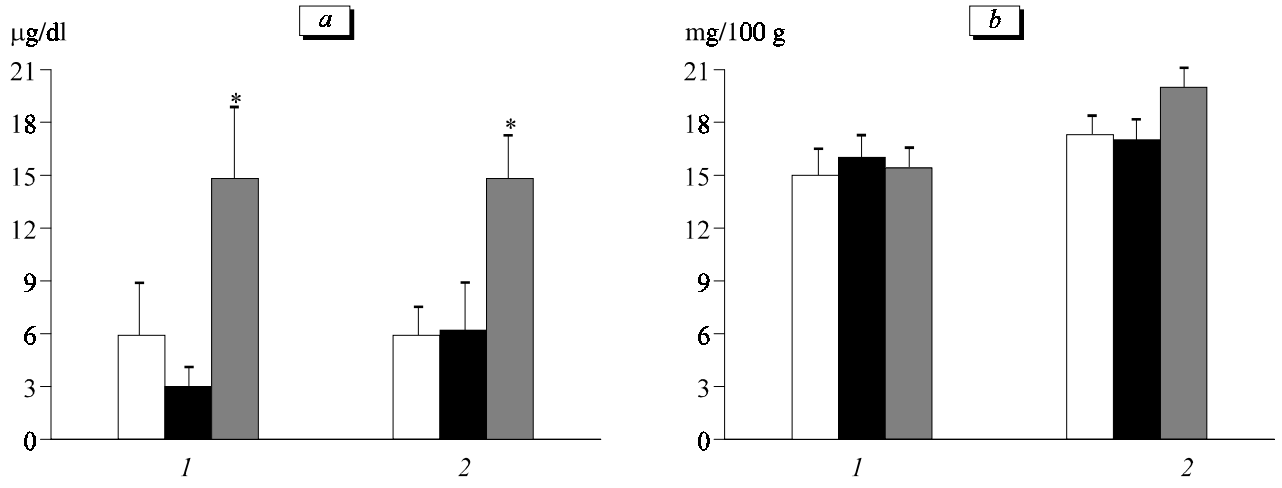

Fig. 1. Corticosterone content in peripheral blood (*a*) and relative weight of the adrenals (*b*) in sham-operated (*1*) and castrated (*2*) adult male rats. Light bars: physiological saline; dark bars: random; and shaded bars: a_{2A}-adrenoceptor antisense. **p*<0.05 compared to other groups.

ceptor mRNA and the total number of receptor molecules in this brain region. In our experiments, antisense significantly increased plasma corticosterone level ($F(2.34)=6.590$, $p<0.01$, Fig. 1, *a*). The inhibition of α_{2A}-adrenoceptor expression in BSLC was accompanied by activation of the hypothalamic-pituitary-adrenal system both in sham-operated and castrated rats. The activation of the hypothalamic-pituitary-adrenal system after castration was confirmed by the development of adrenal hypertrophy in castrated animals ($F(1.39)=13.060$, $p<0.001$, Fig. 1, *b*). These results are consistent with the data on increased content of corticotropin-releasing hormone in the hypothalamus of castrated animals related to androgen deficiency. Replacement hormone therapy abolished the castration-induced changes [4].

The antisense probably activates noradrenergic neurons in BSLC by decreasing the number of presynaptic α_{2A}-adrenoceptors. Systemic [8] and local [9] administration of α_{2A}-adrenoceptor antagonists into BSLC leads to activation of the noradrenergic system, which is manifested in transmitter release and decrease in its content. In our experiments, the antisense reduced the content of transmitter in brain regions containing noradrenergic terminals. Activation of the hypothalamic-pituitary-adrenal system followed by an increase in plasma corticosterone content probably attested to enhanced noradrenergic transmission. Previous studies showed that the administration of α_{2A}-adrenoceptor antagonist yohimbine into BSLC increases blood ACTH content, while α_{2A}-adrenoceptor agonist clonidine decreases hormone concentration [7]. Destruction of BSLC markedly attenuates adrenocorticotropic and adrenocortical reactions to emotional stress [11]. Our results indicate that nonselective α_2-adrenoceptor ligands primarily affect α_{2A}-adrenoceptors.

Our experiments showed that suppression of α_{2A}-adrenoceptor expression in BSLC is accompanied by activation of the adrenocortical system, which is confirmed by the increase in blood corticosterone content. Thus, these receptors play an inhibitory role in the regulation of basal content of adrenocortical hormones in the blood.

The study was supported by the Russian Foundation for Basic Research (grant No. 99-04-50022).

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