# Effect of Nonselective β-Adrenoblockers on the State of Sympathoadrenal System and Ratio of Neuroactive Amino Acids in Rat Medulla Oblongata

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Experiments on rats showed that injection of propranolol into the medulla oblongata increased the contents of epinephrine, norepinephrine, dopamine, and L-DOPA by 3.76, 1.4, 2.0, and 1.7 times, respectively. These propranolol-induced changes in the levels and ratio of neurotransmitters were not accompanied by variations in serotonin content. Propranolol had no significant effects on the content of excitatory amino acids, except marked increase in aspartate content. The level of inhibitory amino acids increased mainly due to an increase in GABA content. The balance between excitatory and inhibitory amino acids was shifted towards inhibitory compounds.

**Key Words:** *medulla oblongata; propranolol; catecholamines; neuroactive amino acids*

Antihypertensive preparations of central action moderate the central sympathetic activity and prevent blood pressure rise by affecting adrenergic receptors in interneuronal synapses of the brainstem vasomotor centers [8,9]. Highly lipophilic β-adrenoblockers (alprenolol, metoprolol, oxprenolol, and propranolol) interact with cardiac $\beta_1$-adrenoceptors and cross the blood-brain barrier. They reduce anxiety, excitement, fear, cardiovascular disorders, and autonomic and somatic abnormalities [4]. β-Adrenoblockers moderate heart rate, decrease the contractile force of the myocardium, reduce myocardial oxygen demand, inhibit automaticity of the atrioventricular node and ectopic foci of myocardial excitation, and improve tolerance to physical exercise [11]. Activation of adrenergic pathways in the brain can stimulate the sympathetic system in humans, because surplus of norepinephrine in the internal jugular vein positively correlates with the conductance of peripheral sympathetic nerves [8].

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Our aim was to study the effects of propranolol, a highly lipophilic agent easily crossing the blood-brain barrier according to the data of positron emission tomography [5], on the state of sympathoadrenal, serotonin-, and GABA-ergic systems of the brainstem in rats.

## MATERIALS AND METHODS

The study was carried out on male rats ($n$=14) weighing 180-200 g. The rats were randomly divided into control and experimental groups (7 animals per group) and maintained under vivarium conditions on a standard ration and unrestricted water.

The rats were fixed in a stereotaxic apparatus. The rostral surface of the ventrolateral medulla oblongata was scanned. Amiodarone (0.001 mg) and artificial liquor (in mM: 150 $Na^+$, 3.0 $K^+$, 1.4 $Ca^{2+}$, 0.8 $Mg^{2+}$, 31.0 $PO_4^{2-}$, 155 $Cl^-$, pH 7.4) were injected bilaterally with a Hamilton microsyringe to experimental and control rats, respectively [2]. The medulla oblongata was placed in liquid nitrogen. Then it was minced on ice. Biogenic amines, glycine, GABA, glutamate, and aspartate were assayed in medulla oblongata homo-

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**TABLE 1**. Effect of Propranolol on Content and Ratio of Biogenic Amines and Neuroactive Amino Acids in Rat Medulla Oblongata (*M*±*m*)

| Parameter | Group | |
|---|---|---|
| | control | propranolol |
| Epinephrine, nmol/mg protein | 3.75±0.62 | 14.1±5.2* |
| Norepinephrine, nmol/mg protein | 5.20±1.1 | 7.3±2.6* |
| Dopamine, nmol/mg protein | 3.6±0.8 | 7.3±1.8* |
| L-DOPA, nmol/mg protein | 4.16±0.21 | 7.0±0.7* |
| Serotonin, nmol/mg protein | 0.05±0.01 | 0.044±0.013 |
| Norepinephrine+epinephrine | 8.95±1.68 | 21.3±7.4* |
| Norepinephrine/epinephrine | 1.38±0.01 | 0.51±0.08* |
| Norepinephrine/(norepinephrine+epinephrine) | 0.57±0.03 | 0.33±0.03* |
| Dopamine/(norepinephrine+epinephrine) | 0.38±0.01 | 0.34±0.05 |
| Aspartate, μmol/g wet tissue | 2.88±0.31 | 4.93±0.38* |
| Glutamate, μmol/g wet tissue | 7.1±0.5 | 7.2±0.3 |
| Glycine, μmol/g wet tissue | 1.22±0.16 | 1.86±0.33 |
| GABA, μmol/g wet tissue | 3.4±0.2 | 6.84±0.37* |
| (Aspartate+glutamate)/(glycine+GABA) | 2.21±0.22 | 1.41±0.14* |

**Note.** *$p<0.05$ compared to the control.

genate [3]. The data were processed statistically using Statistica software and Student's $t$ test at $p<0.05$.

## RESULTS

Injection of β-adrenoblocker dramatically elevated the content of epinephrine (by 3.76 times, Table 1). Norepinephrine content increased to a lesser extent (1.4-fold). The norepinephrine/epinephrine ratio was shifted towards epinephrine, and the norepinephrine/norepinephrine+epinephrine ratio decreased. The level of dopamine and L-DOPA (dopamine precursor) increased by 2 and 1.7 times, respectively. Most part of norepinephrine is transported by neuronal reuptake. The changes in the content of biogenic amines induced by propranolol suggest that injection of β-adrenoblocker modulates regulation of dopamine β-hydroxylase activity and possibly tyrosine hydroxylase, so that norepinephrine metabolism surpasses its synthesis. This results in a decrease of norepinephrine level relatively to that of epinephrine. During these processes, the ratio between sympathoadrenal and dopaminergic regulation is not disturbed: the compensatory mechanisms are very potent, and they are capable to compensate shifts in the levels of individual biogenic amines and to prevent disturbance of the entire range of regulatory mechanisms.

Injection of isoproterenol, a nonselective β-adrenoceptor agonist, into the lateral cerebral ventricle increases cardiac indices, elevates blood pressure, and induces body temperature rise [5]. By contrast, propranolol, a nonselective β-adrenoceptor antagonist, diminishes these parameters. These data suggest that β-adrenoceptors elevate sympathetic tone, and this effect can be related to systemic β-adrenoblockade. Systemic administration of propranolol could underlie pronounced $\beta_1$- and $\beta_2$-adrenoreceptor blockades in the brain [6,7]. The doses of propranolol used in this study were sufficient to block completely cardiac β-adrenoceptors [10]. When injected intravenously in the specified doses, propranolol inhibits lipolysis in skeletal muscles induced by isoproterenol [11]. Probably, long-term pharmacotherapy leads to chronic changes in the central β-adrenergic neuronal traffic. However, chronic administration of carvedilol to patients with severe cardiac insufficiency did not inhibit systemic and cardiac norepinephrine turnover [11].

During local application of propranolol, the changes in the level and ratio of neurotransmitters were not accompanied by the changes in serotonin content.

These data attest to necessity of studies of these processes in animals with arterial hypertension under conditions of initial pathological shifts in sympathoadrenal and dopaminergic regulation including conditions of complete exhaustion of these systems.

## REFERENCES

1. P. A. Kaliman, N. G. Sergienko, N. A. Luchko, and N. N. Brovina, *Vopr. Med. Khim.*, No. 2, 69-73 (1983).
2. A. Yu. Turovaya, A. Kh. Kade, A. P. Galenko-Yaroshevskii, *et al.*, *Ibid.*, Suppl. 2, 89-93 (2001).

3. A. Yu. Turovaya, A. Kh. Kade, P. A. Galenko-Yaroshevskii, *et al.*, *Ibid.*, Suppl. 2, 63-65 (2002).
4. V. N. Shtok, *Ros. Med. Zh.*, No. 9, 3-10 (1999).
5. H. E. de Werdener, *Physiol. Rev.*, **81**, No. 4, 1599-1658 (2001).
6. K. Ezure, Y. Oku, and I. Tanaka, *Brain Res.*, **632**, 216-224 (1993).
7. M. T. Kailasam, R. J. Parmer, J. H. Cervenka, *et al.*, *Hypertension*, **26**, 143-149 (1995).
8. J. P. Koepke and G. F. Dibona, *Ibid.*, **8**, 133-141 (1986)
9. S. Z. Lander, *Biochem. Pharmacol.*, **23**, 1793-1800 (1974).
10. K.Y. Rahn, M. Barenbrock, and M. Hausberg, *J. Hypertens.*, **17**, Suppl. 3, S11-S14 (2000).
11. J. Tank, A. Diedrich, C. Schroeder, *et al.*, *Hypertension*, **38**, No. 6, 1377-1381 (2001).