Interrelation between β-Adrenoceptor Density and Norepinephrine Content in the Cerebral Cortex of Neonatal Rats

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β-Adrenoceptor density in rat cerebral cortex 3-fold increased with the decrease in norepinephrine content over the first week of life. Intracerebral injection of 6-hydroxydopamine to 2-day-old rats decreased the content of norepinephrine and increased the density of β-adrenoceptors in the cerebral cortex measured on the 5th day of life. The data suggest that norepinephrine down-regulates cerebral β-adrenoceptors from the early stages of development of the neurochemical system.

Key Words: *β-adrenoceptors; norepinephrine; ontogeny; brain*

The noradrenergic system in rat brain develops during the late gestational period and the first month of life [2]. Pharmacological interventions in this system during the early ontogeny lead to sustained behavioral and functional disorders [8] probably associated with changes in its neurotransmitter and/or receptor components. Complex regulatory interrelations between adrenoceptors and norepinephrine in adult brain were revealed [3,9]. However, the presence of such interrelations during the early ontogeny, when the concentration of norepinephrine and the density of its receptors are 30-50% of normal, remains unproved. Studies of this problem will clarify the mechanisms of embryogenesis and provide the methods for correction of abnormalities induced by adverse factors during the early ontogeny.

MATERIALS AND METHODS

Experiments were performed on 21-day-old fetuses and 1-16-day-old Wistar rats. 6-Hydroxydopamine (6-OHDA, Sigma) in a dose of 100 μg/5 μl or equivalent volume of solvent (0.1% ascorbic acid in 0.9% NaCl) was administered into the *locus coeruleus* of 2-day-old rats under cold anesthesia. On day 5 of life, the rats were decapitated, and the frontal cortex and brain stem (including the pons and medulla oblongata) were isolated. Norepinephrine content in the brain was measured fluorometrically [5]. The number of β-adrenoceptors was determined by specific binding of ^{3}H-dihydroxyalprenolol (^{3}H-DHA, 67 Ci/mmol, Amersham) in the presence or absence of 10 μM propranolol (Sigma) [1]. Protein concentration was measured by the method of Lowry. Each group consisted of 8-10 animals. The results are expressed as mean±standard error.

RESULTS

Norepinephrine content in rat cerebral cortex gradually decreased over the first 1.5 weeks of life below the perinatal level and increased starting from the second decades (Fig. 1). During the first week of life, the density of β-adrenoceptors in the cerebral cortex increased 3-fold compared to the perinatal level and then remained at the level typical also of adult animals. This

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is consistent with our previous results [1] and published data [2]. During this period of ontogeny, β-adrenoceptors had constant affinity for the ligand. The dissociation constant corresponded to 1 nM DHA. Norepinephrine content decreased with the increase in β-adrenoceptor density in the cerebral cortex and started to increase when the density of β-adrenoceptors attained the normal level. The data suggest that norepinephrine down-regulates the density of adrenoceptors in the brain of neonatal and adult rats [3,9].

The neurotoxin 6-OHDA, which induces degeneration of catecholaminergic endings [12], decreased norepinephrine content in the cerebral cortex of 5-day-old rats (Fig. 2, *a*), but not in the brain stem (the site of localization of bodies of noradrenergic neurons). These results are consistent with previous data [7].

In rat pups treated with 6-OHDA, the number of specific ^{3}H-DHA binding sites (β-adrenoceptors) in

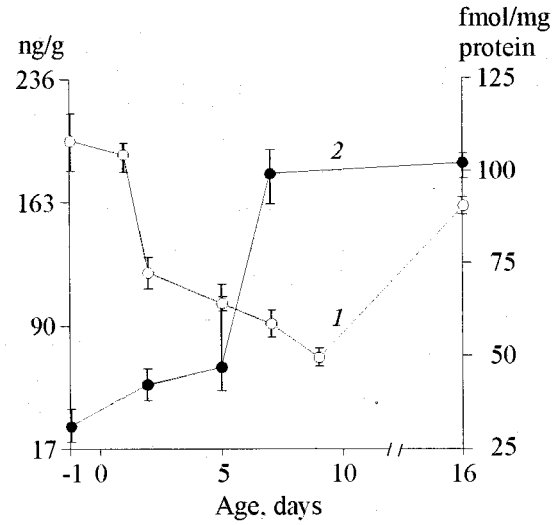

Fig. 1. Content of norepinephrine (left ordinate, *1*) and β-adrenoceptors (right ordinate, *2*) in the cerebral cortex of neonatal rats.

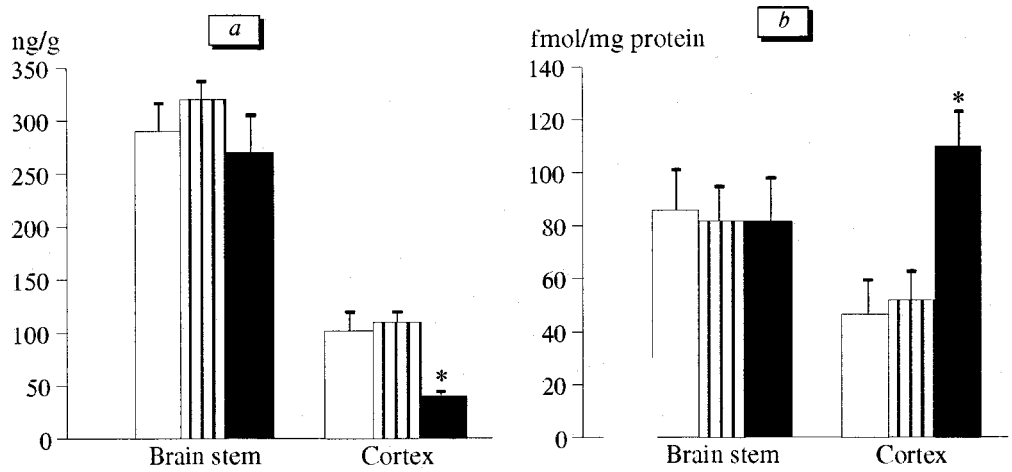

Fig. 2. Norepinephrine concentration (*a*) and β-adrenoceptor density (*b*) in the cerebral cortex and brain stem of 5-day-old rats: intact rats (light bars) and rats injected with physiological saline (shaded bars) and 6-OHDA (dark bars) on day 2 of life. *$p<0.05$ compared with intact rats and animals receiving physiological saline.

the cerebral cortex increased compared with the control (Fig. 2, *b*), while in the brain stem this parameter remained unaffected.

Down-regulation of β-adrenoceptor density with norepinephrine in the neurochemical system of adult brain is well established. Destruction of norepinephrine-containing nerve endings increases the number of β-adrenoceptors in the cerebral cortex of adult animals [11]. After administration of 6-OHDA during the early ontogeny, the decrease in norepinephrine content is manifested by an increase in the density of postsynaptic β-adrenoceptors in the brain of 2-week-old rat pups [7] and adult rats [4,6,10]. Our findings indicate that although the content of norepinephrine and the density of β-adrenoceptors in the cerebral cortex of 5-day-old rats constitute only $^1/_3$ and $^1/_2$ of their normal levels, respectively, the mechanism of down-regulation of β-adrenoceptor density with norepinephrine is present in these animals. Upregulation of β-adrenoceptor density by 6-OHDA is related to down-regulation of norepinephrine concentration, because receptor density in the brain stem at a constant concentration of this neurotransmitter remains unchanged.

The data indicate that norepinephrine down-regulates the density of β-adrenoceptors in the brain from the early stages of development of the neurochemical system. This mechanism underlies the development of neurotransmitter and receptor components of the noradrenergic system and should be taken into account when planning drug interventions during the early ontogeny.

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