GENETICS

Age-Related Alterations in Brain α_1-Adrenoreceptors of Hypertensive Rats: Their Possible Role in the Development of Arterial Hypertension

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The binding of labeled agonist (^{3}H-prazosin) to α_1-receptors in the frontal cortex, hypothalamus, and medulla oblongata of hypertensive (NISAG) and normotensive (Wistar) rats of different age is studied to elucidate the role of these receptors in the development of hereditary stress-induced arterial hypertension. It is found that the density of α_1-adrenoreceptors in the hypothalamus of 30-day-old and adult NISAG rats is decreased, while in the medulla oblongata the number of these receptors, starting from the first week of life, is greater than in Wistar rats of the same age. From a comparison of these findings with the development of hypertension in NISAG rats it is concluded that α_1-adrenoreceptors of the medulla oblongata are involved in this process.

Key Words: *hereditary hypertension; α_1-adrenoreceptors; brain structures; postnatal development*

The noradrenoergic system of the brain plays an important role in the regulation of arterial pressure (AP). Many drugs used for the treatment of hypertension are ligands of adrenoreceptors (AR). They operate via different subtypes of AR, whose role in the pathogenesis of hypertension is unclear. Previously it was found that adult rats of the hypertensive NISAG strain, which was created by selecting normotensive Wistar rats with elevated blood pressure under emotional stress [2], differ from Wistar rats in the number of AR in some brain structures [4]. However, it is unknown whether these alterations are genetically determined and are involved in the expression of hypertension or whether they are secondary to the AP rise. The statistically significant positive correlation between AP and the number of α_1-AR in the medulla oblongata and hypothalamus observed in segregating hybrid populations (F_2 and back crosses) [3] indicates some genetic association between these traits, but provides no clear-cut information regarding the cause and effect relationship. In order to clarify this issue, the density of α_1-AR in brain structures was studied and compared with the dynamics of AP elevation in NISAG and Wistar rats.

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MATERIALS AND METHODS

Male Wistar and NISAG rats aged 7, 14, 21, 30, 40, 60, and 180 days were decapitated, and the frontal cortex, hypothalamus, and medulla oblongata were isolated on ice. The material was frozen in liquid nitrogen and stored at -40°C prior to use. The binding parameters of α_1-AR were studied by the radioligand method [4] with the use of labeled prazosin (Amersham).

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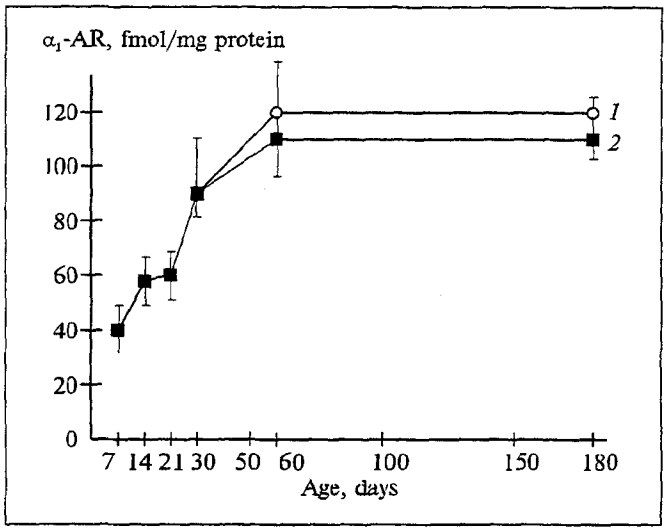

Fig. 1. Age–related changes in the density of α_1–AR in the frontal cortex of Wistar (*1*) and NISAG (*2*) rats.

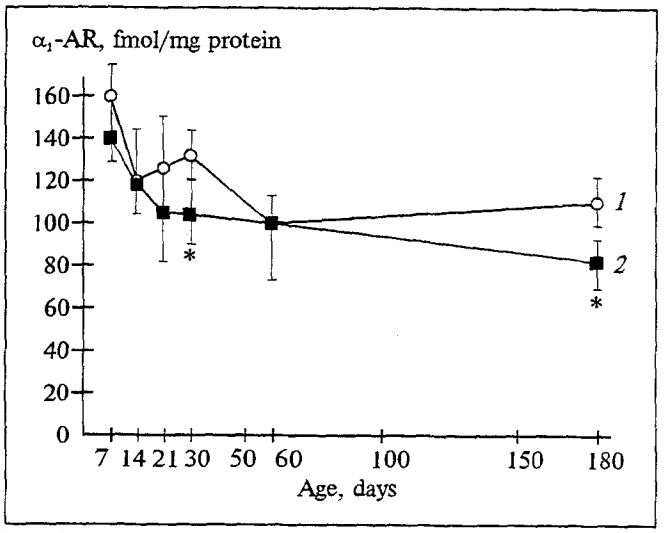

Fig. 2. Age–related changes in the density of α_1–AR in the hypothalamus of Wistar (*1*) and NISAG (*2*) rats. Here and in Fig. 3: an asterisk indicates significant differences compared with Wistar rats of the same age.

RESULTS

In 7-day-old pups of both lineages the density of α_1-AR in the frontal cortex was almost 3-fold lower than in adult rats and reached the adult level only by the 60th day (Fig. 1). In contrast, in the hypothalamus the density of α_1-AR was the highest at 7 days and gradually decreased with age (Fig. 2). In the medulla oblongata, the density of α_1-AR was practically the same in 7-day-old and adult animals (Fig. 3). Similar postnatal changes in the binding pattern of α_1-AR have been reported for Wistar [6] and Sprague-Dawley [12] rats and guinea pigs [7].

There were no differences in the number (Fig. 1) or affinity of α_1-AR in the frontal cortex of Wistar and NISAG rats of all studied ages. However, the numbers of α_1-AR in the hypothalamus (Fig. 2) and medulla oblongata (Fig. 3) were statistically different. In the hypothalami of 30- and 180-day-old NISAG rats the density of α_1-AR was lower than in normotensive Wistar rats of the same age (Fig. 2). The greatest AP rise occurred during the fourth week of life; since changes in the number of α_1-AR were detected later (day 30), it can be assumed that they are secondary to the development of hypertension. A lower density of α_1-AR in the hypothalamus is characteristic of NISAG rats, while in other hypertensive models (spontaneously hypertensive rats) increased expression of α_1-AR in the early days of life has been observed [5,11,13].

In contrast to the hypothalamus, in the medulla oblongata of both NISAG and spontaneously hypertensive rats [8] the density of α_1-AR increased starting from the first week of life (Fig. 3), which may be indicative of a genetic predisposition and a certain universality of this increase for different models of hypertension. Modifications of AR synthesis might be a primary genetic mechanism that is impaired in NISAG rats. The increased rate of synthesis, at least in adult animals, may result from up-regulation, since the noradrenalin concentration in the medulla is lowered [1]. The increased density of α_1-AR in the medulla of NISAG rats may be one of the causes of hypertension. This assumption is supported by the significant positive correlation between the number of α_1-AR in the medulla and AP elevation during stress in the second generation of NISAG-Wistar hybrids [3]. In addition, administration of L-dioxyphenylalanine to NISAG rats in the 4th week of life normalizes their

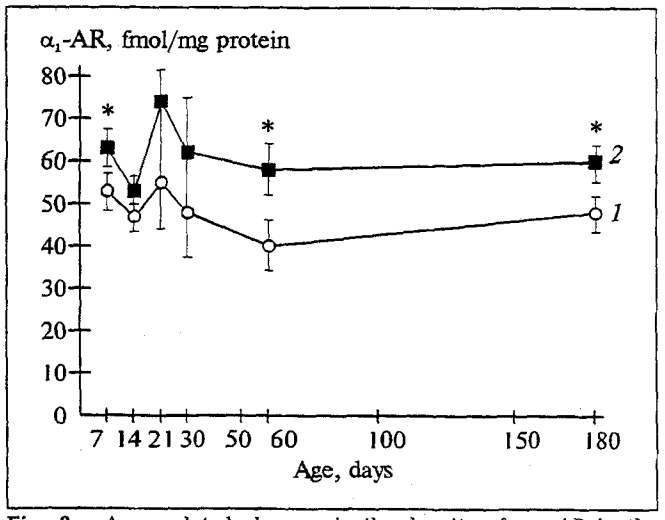

Fig. 3. Age–related changes in the density of α_1–AR in the medulla oblongata of Wistar (*1*) and NISAG (*2*) rats.

AP in adulthood [9], this being accompanied by a decrease in the number of α_1-AR in the medulla [10]. These observations provide additional evidence of a relationship between the number of AR in adult animals and the activity of the noradrenergic system, since after administration of L-dioxyphenylalanine not only is the number of AR in the medulla decreased but the concentration of tyrosine hydroxylase, a key enzyme of noradrenalin biosynthesis, is increased [9].

Thus, hypertensive NISAG rats differ from normotensive Wistar rats in the number of α_1-AR in the hypothalamus and medulla oblongata during postnatal development. Together with other evidence, the increased density of these receptors in the medulla starting from the first week of life indicates that specific genetic characteristics of the brain's noradrenergic system play an important role in the development of arterial hypertension in NISAG rats.

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