AGE DIFFERENCES IN THE EFFECT OF α- AND β-ADRENOMIMETICS ON ADRENAL GLUCOCORTICOID FUNCTION

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An important role in age-related changes in the adaptive powers of the body is played by adjustment of mechanisms regulating the steroid producing function of the adrenal cortex (AC) [4, 7]. As well as by other mechanisms, the steroid producing function of AC is modulated by adrenergic mechanisms of regulation, realized at both peripheral target gland (AC) and hypothalamo-hypophyseal levels [1].

Adrenergic agonists are involved in regulation of adrenocortical function. Adrenomimetics have been shown to exert an activating effect on the mineralocorticoid function of AC, by acting through β_1-adrenoreceptors of the plasma membranes (PM) of adrenocorticocytes (ACC) [8].

Data on the character of the influence of adrenergic agonists on the glucocorticoid function of AC are contradictory. On the one hand, in experiments in vivo with perfusion of the canine [7] and human [13] adrenals, and also on isolated calf adrenals [12], it has been shown that catecholamines cause no significant changes in the glucocorticoid function of AC. The authors cited interpret this fact as proof that elevation of the plasma glucocorticoid level after injection of catecholamines is not the result of the direct effect of catecholamines on the glucocorticoid function of AC. On the other hand, investigations have demonstrated the direct stimulating effect of adrenergic agonists on glucocorticoid production [9, 10]. Evidence has been obtained to show that the stimulating effects of adrenomimetics on steroid production in the zona fasciculata of AC are realized through β-adrenoreceptors of PM of ACC [8], and their inhibitory effects through α-adrenergic structures of PM of ACC [3].

Age-related changes in the mechanisms of adrenergic regulation of the steroid-producing function of AC have not been studied.

The aim of this investigation was to study age-related changes in adrenergic regulation of the glucocorticoid function of the rat AC.

EXPERIMENTAL METHOD

Experiments were carried out on isolated adrenal glands of adult (6 months) and old (28 months) male Wistar rats. The effect of the selective α-adrenoreceptor agonist naphazoline and the unselective β-adrenoreceptor agonist isoproterenol on basal and ACTH-stimulated steroid production in the isolated adrenal gland.

After excision of the adrenals and removal of all adipose tissue from them, each of the pair of glands from the same animal were cut into halves, and the two halves of one adrenal were fixed on a plastic support and placed in a glass vessel containing 5.0 ml of Krebs–Henseleit solution, balanced for incubating adrenal glands [11]. Each of the two adrenals from the same animal were incubated separately. Incubation continued for 3 h at 37°C. The medium was aerated with a mixture of 5% CO_2 and 95% O_2. The incubation medium was changed every 20 min, and thereafter the concentration of 11-oxosteroids (11-OXS) was determined in each portion of medium by a fluorometric method, using corticosterone as the standard [5].

Basal (i.e., unstimulated) and ACTH-stimulated steroid production were investigated in one of a pair of adrenals which acted as the control. The effect of the α- or β-adrenoreceptor agonist on basal and ACTH-stimulated steroid production was studied on the other adrenal. For this purpose, during the first hour of the experiment the control gland was incubated in Krebs–Henseleit solution not containing the trophic hormone, for the second hour in a solution containing ACTH (10 U/liter),

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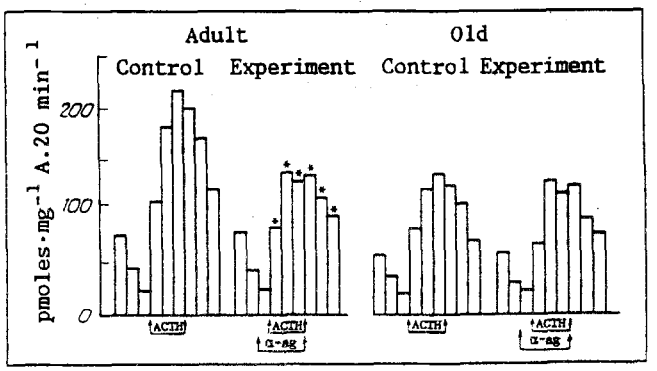

Fig. 1 Dynamics of 11-OXS production by isolated adrenals (A) of adult and old male rats during 20-min time intervals for 3 h of incubation in control and with unselective α-adrenoreceptor agonist naphazoline. Arrows by ACTH indicate period of incubation with ACTH (10 U/liter), arrows by α-ag indicate period of incubation with α-agonist naphazoline (10^{-4} M). Asterisks indicate significant differences from control.

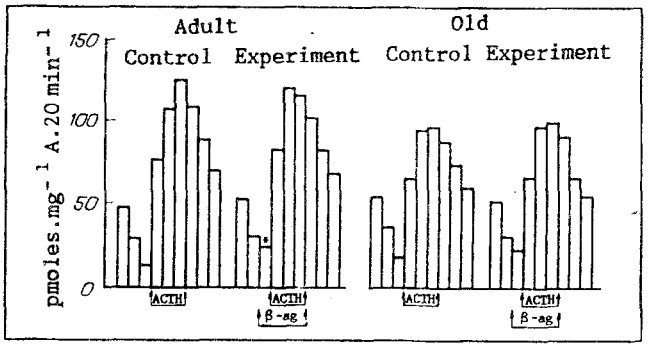

Fig 2. Dynamics of 11-OXS production by isolated adrenals (A) of adult and old male rats during 20-min intervals for 3 h of incubation in control and with unselective β-adrenoreceptor agonist isoproterenol. Arrows by β-ag denote period of incubation with β-agonist isoproterenol (10^{-5} M), remainder of legend as to Fig. 1.

and for the third hour in Krebs–Henseleit solution without ACTH again. The second adrenal was incubated for the first 40 min in Krebs–Henseleit solution not containing ACTH, for the 40th to the 60th minute of the first hour of incubation naphazoline 0.1 mmole/liter or isoproterenol 10.0 μmole/liter was added to the incubation medium, for the second hour of the experiment the gland was incubated in solution containing ACTH and one of the adrenoreceptor agonists in the above-mentioned concentrations, and for the third hour the gland was incubated in Krebs–Henseleit solution not containing any additives. To stabilize the solutions of the adrenoreceptor agonists ascorbic acid (50 mg to 100 ml) was added to the incubation medium.

EXPERIMENTAL RESULTS

In the experiments of series I the effect of naphazoline, an unselective α-adrenoreceptor agonist, was studied on basal and ACTH-stimulated steroid production in isolated adrenal glands of adult and old rats. The results are given in Fig. 1.

The results show that during the first 20-min periods of incubation of the adrenals with naphazoline, i.e., before addition of ACTH to the incubation medium, no significant changes were observed in the basal 11-OXS secretion by the isolated adrenals of animals of the two age groups compared with that in the control for the same incubation period. Addition of the α-adrenergic agonist to the incubation medium of glands from adult animals depressed the reaction of the adrenals to ACTH, whereas in experiments on isolated adrenals from old animals this was not observed.

It can be concluded from the results that in intact adult animals the tonic inhibitory effects of adrenomimetic agents on the ability of the adrenals to respond to the trophic hormone are realized in intact adult animals through the α-adrenergic structures of PM of ACC in the zona fasciculata of AC. The results are also evidence that tonic inhibitory influences exerted on ACTH-stimulated steroid production by α-adrenergic structures of PM of ACC of the zona fasciculata weaken with age.

The results confirm our previous conclusion, based on experiments in which rats received the α-adrenoblocker dibenamine, that the α-adrenergic mechanisms of regulation of the glucocorticoid function of the adrenal cortex weakened with age [2].

In the experiments of series II the effect of the unselective β-adrenoreceptor agonist isoproterenol on basal and ACTH-stimulated secretion of 11-OXS by the isolated adrenals of adult and old rats was investigated. The results are given in Fig. 2.

They show that during the first 20 min of incubation of the adrenals with isoproterenol, i.e., before addition of the trophic hormone to the medium, a significant increase in basal steroid production by the isolated adrenals of the adult animals was observed compared with the control, during the same period of incubation, whereas no changes were observed in basal steroid production by the isolated adrenals of old animals under the influence of isoproterenol. Addition of isoproterenol to the incubation medium had no significant effect on the response of the adrenals of the animals of the two age groups to the action of ACTH, compared with the control.

The absence of an additive effect in the maximal stimulating action of ACTH and isoproterenol on the glucocorticoid function of AC of the adult rats, against the background of significant activation of basal steroid production during the action of isoproterenol alone, is probably evidence that the steroidogenic effects of β-adrenomimetics and ACTH on the postmembrane stages of their activating effect on glucocorticoid production by ACC of the zona fasciculata share a common pathway of realization.

Thus in adult animals the inhibitory influences of adrenomimetics on the secretory response of AC, induced by the action of ACTH, are realized through α-adrenergic structures of PM of ACC. During aging the mechanisms of α-adrenergic correction of the response of AC to the action of ACTH are weakened.

Activating influences of adrenergic agonists on basal steroid production by isolated adrenals of adult animals are realized through β-adrenergic structures of PM of ACC in the zona fasciculata. During aging, these influences are weakened.

No additive effect of activation of the β-adrenoreceptors of PM of ACC on ACTH-stimulated secretion of glucocorticoids by the isolated adrenals of animals of the two age groups could be detected.

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