EFFECT OF CHEMICAL INJURY TO THE ADRENAL CORTEX ON ITS ONTOGENETIC DEVELOPMENT

B. Ya. Ryzhavskii and E. A. Ivashkov

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Oncogenetic development of the adrenal cortex (AC) is characterized by regular changes in the number of adrenocorticocytes (ACC) and in their morphology and metabolism [6, 9]. Meanwhile there is reason to suppose that this process may deviate considerably from the normal course under the influence of various factors [6]. One such factor that is attracting attention is the presence of substances selectively damaging AC in the body. These substances include compounds (elipten/aminoglutethimide, amferon, cholestene, DDD, dioxidine), belonging to different classes of organic substances [4, 10, 11], suggesting that they are widely distributed among anthropogenic factors to which man is currently exposed and that there is a high probability of such exposure being increased in the future.

It is accordingly interesting to study the aftereffects of exposure to these agents at different stages of ontogeny on subsequent development of AC. The aim of the investigation described below was to study morphology of AC in rats of different age groups, intact and exposed to the action of the adrenocorticolytic agent dioxidine [3], a substance used in the treatment of suppurative infections. Immediately after its injection marked changes are observed in AC, and in such cases electron microscopy reveals destruction of mitochondria, multiple autophagosomes, and apoptosis of ACC [3, 7].

EXPERIMENTAL METHOD

Adrenal glands of 69 male rats receiving dioxidine (dispensed in ampules) in a dose of 20 mg/100 g intraperitoneally daily for 1 week at 1 month of age were used. Animals were decapitated 1,6, and 12 days and 1, 3, 5.5, 7, and 13 months after the last injection of dioxidine. Adrenals of 54 rats of the same age as the experimental group, and kept in the same animal house with them, served as the control. Experimental and control animals were sacrificed simultaneously, during the morning. The rats and their adrenals were weighed. The area of section of AC was determined in preparations stained with hematoxylin and eosin by the method in [1]. Succinate dehydrogenase (SDH) activity was determined by the method of Shelton and Schneider, 3β-ol-steroid dehydrogenase (3β-StDH) as in [8]. The intensity of these reactions was estimated cytophotometrically, by the plug method, at a wavelength of 550 nm, on the basis of its measurement in 50 ACC in each zone in every case, and expressed in conventional units. The results were subjected to statistical analysis at a level of significance of $p \leq 0.05$.

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TABLE 1. Morphologic and Cytochemical Parameters of the State of the Rat Adrenal Cortex at Various Times after Last Injection of Dioxidine (in % of control)

Parameters	Time after last injection of dioxidine							
	1 day	6 days	12 days	1 month	3months	5,5 months	7 months	13 months
Mass of adrenal								
absolute	182,4	135,6	95,8*	56,2	84,8*	57,2	63,3*	72,2
relative	208,2	131,0	81,0*	63,6	73,3	86,4	59,7	89,5*
Area of section through AC	164,8	99,4*	94,6*	41,9	70,5	62,3	72,7	80,3
Number of ACC per field of vision								
zona glomerulosa	77,8*	79,7	67,3	63,2	84,3	70,2	80,0	84,0*
zona fasciculata	80,0	72,7	67,0	66,4	82,2	95,2*	87,0*	65,0
zona reticularis	85,2	84,4*	78,3*	50,0	61,2	74,7	80,0	77,9
SDH activity								
zona glomerulosa	56,4	64,7	121,7*	83,0	80,6	79,6	84,7	110,4
zona fasciculata	18,3	13,1	35,9	17,6	150,7	115,3	132,4	120,0
zona reticularis	48,9	21,2	28,2	16,3	105,8*	101,4*	107,6*	98,1*
3β-StDH activity								
zona glomerulosa	67,2	49,6	111,9*	74,1	97,1*	105,3*	114,9*	110,3
zona fasciculata	33,9	10,8	26,4	16,9	114,7*	109,4*	101,6*	93,5*
zona reticularis	28,9	10,9	21,8	16,2	103,5*	103,5*	106,4*	101,8*

*Differences from control not statistically significant.

EXPERIMENTAL RESULTS

A sharp increase in mass of the adrenals and in area of the section through AC were observed 24 h after the last injection of dioxidine (Table 1). This result can be largely explained by an increase in the size of ACC, discovered by the study of preparations stained with hematoxylin and eosin and also by determination of the number of ACC in a standard area of section, which showed that this parameter was significantly reduced. After 6 and 12 days the mass of the gland and the area of section of AC were reduced, with the result that they no longer differed from normal. At these times, just as 24 h after the last injection of dioxidine, marked destructive changes and death of ACC, together with hemorrhages, were detected in the zona fasciculata and zona reticularis of AC. These processes account for the observed reduction in mass of the gland and in the area of section of AC. Destructive changes in ACC in the zona fasciculata and zona reticularis also were found 1 month after the last injection of dioxidine. Many ACC in the zona reticularis and the inner layers of the zona fasciculata had signs of marked fatty degeneration. Values for the mass of the adrenal and the area of section through its cortex were least in this group of experimental rats. These parameters approached the control values more closely 3, 5.5, 7, and 13 months after the end of dioxidine administration, but they did not return completely to normal until 13 months after the last injection of dioxidine. The reduced values for the area of section of AC were combined with a reduced number of ACC per standard area of section in all zones of the cortex, evidence of an increase in size of the parenchymatous cells of AC. On the other hand, the decrease in area of section of AC and in the number of ACC per unit area indicates that for a long time AC of the experimental rats contained significantly fewer ACC.

Activity of the enzymes studied (Table 1), which was sharply reduced in the early stages after the last injection of dioxidine, especially in the zona fasciculata and zona reticularis, subsequently (3 months later) was increased. Activity of 3β-StDH, the key enzyme of steroid formation, located in the smooth endoplasmic reticulum and mitochondria [2, 12], in AC of rats killed 3, 5.5, and 7 months after the last injection of dioxidine, had no significant differences from normal, but after 13 months there was a small increase in its value in ACC in the zona glomerulosa (Table 1). SDH activity, however, in the zona fasciculata, 3, 5.5, 7, and 13 months after the last injection of dioxidine exceeded activity in the control, and in the zona glomerulosa of AC until 7 months there was a small

decrease in its value in the experimental rats, but after 13 months it was a little higher than the control level. The intensity of the reaction for SDH in the zona reticularis 3, 5.5, 7, and 13 months after the last injection did not, however, differ significantly in AC of animals of the groups compared. These results are evidence of different degrees of normalization of activity of the enzyme involved in the specific function of AC (3β-StDH) and in general processes of energy metabolism (SDH), taking place after chemical injury to ACC.

Exposure of the rats to an adrenocorticolytic agent at the age of 1 month, i.e., in the late suckling period [5], thus gave rise to marked differences in important morphological parameters of AC of the experimental animals compared with the control at the ages of 2, 4, 6.5, 8, and 14 months, i.e., in the prepubertal, pubertal, and reproductive periods, and also in periods 1 and 2 of maturity [5], i.e., the results show that chemical injury to the gland in the late suckling period predetermined deviation of the subsequent ontogenic development of AC from the path characteristic of normal.

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