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Growth and Formation of the Adrenal Cortex under the Influence of Pesticides

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Abstract: To date, a large group of chemicals is known that have a toxic effect mainly on the endocrine system, primarily on the hypothalamic-pituitary-thyroid-adrenal axis. These include a number of pesticides, including the latest generations, which in one way or another enter the body and cause a certain hormonal imbalance in it. Clinical and experimental studies have proven the undoubted role of ERCHOS in the pathogenesis of a number of diseases (obesity, atherosclerosis, hypertension and coronary heart disease.

Keywords: Immunotoxicity, endocrine-disrupting, allergic reactions, autoimmune diseases.

The endocrine and immune systems, along with the nervous system, are extremely sensitive to the action of most chemical environmental pollutants [1;2;3]. For more than three decades, the terms " immunotoxicity " (IT, immunotoxicity) and " endocrine -destroying chemicals" (ER, endocrine-disrupting) have been firmly entrenched in the literature. chemicals or endocrine disruptors) [4;5]. Endocrine -destroying chemicals adversely affect various stages of hormone synthesis, transport and function, and can also act as agonists or antagonists of natural hormones and cause a certain hormonal imbalance in the body [15;16]. The term " immunotoxicity " means not only, and not so much the direct toxic effect of various environmental pollutants on immune cells, but also violations of the processes of regulation of immunogenesis and immune responses of the body, including immunosuppression , allergic reactions, autoimmune diseases and other immunopathological conditions. The predominant part of environmental pollutants are pesticides, without which the perspective development of agriculture is impossible [8;9]. It has now been established that a number of pesticides, including the latest generations, have immunotoxic and endocrine -destroying properties [10]. However, the vast majority of studies on the mechanisms of immune and endocrine toxicity of pesticides were carried out in adults and on mature animals, or under conditions of in vitro [9]. Meanwhile, the immune -endocrine system of the fetus and newborns is incomparably more sensitive to the action of various toxic substances compared to adults. In recent years, there is more and more evidence that exposure to pesticides in utero or in early childhood leads to a significant increase in chronic diseases in children, such as asthma, autoimmune, infectious and others, including cancer [1;2]. Unfortunately, the problem of “developmental immunotoxicity” (developmental immunotoxicity), that is, the mechanisms of the adverse effect of pesticides on the developing immune system of offspring, is still far from a final decision [3]. The studies available in this regard are fragmentary and do not give a complete picture of the mechanisms of the toxic effects of pesticides on newborns and children in conditions of their intake through the mother's body [3;4]. Undoubtedly, the identification of the mechanisms of the immunotoxic and endocrine -destroying effects of pesticides will contribute to the development of methods for secondary prevention and pathogenetic therapy of the toxic effects of pesticides on the younger generation under conditions of intoxication through the mother's body.

Goal of the work. Identification of the structural and functional mechanisms of the toxic effect of pesticides on the postnatal development of the immune and endocrine systems of the offspring under conditions of their exposure through the mother's body.

Material and research methods

pyrethroid insecticide lambda-cyhalothrin (LCT) and the benzopyrazole pesticide fipronil (FPN), which are widely used in our country and all over the world, were selected for the experiments . The experiments were carried out on white mature nulliparous female Wistar rats weighing 150-180 g, mature male rats were used only for fertilization. The female rats were divided into three groups of 45 rats each. The first (I experimental) group of rats was administered through the mouth using a probe diluted in a physiological solution of LST at the rate of 8 mg/kg/day. The second (experimental II) group of rats was administered FPN in the same way at the rate of 3.6 mg/kg/day. The dose of both drugs was 1/100 of the LD 50 of the drug. The third group (control) received an equal volume of sterile saline. The introduction of both pesticides to the experimental groups of rats was carried out daily for 75 days until the end of the experiments. On the 31st day of the experiments, females of all groups joined with males for fertilization. Pregnancy was monitored by the presence of spermatozoa in vaginal swabs. After the onset of pregnancy, the females are separated from the males and placed in separate cages for further research. The offspring from all groups of animals were slaughtered on the 7th, 14th, 21st and 30th days after birth, in the morning, on an empty stomach, under light ether anesthesia. Thymus gland (thymus, Tm), mesenteric lymph nodes (Mlu), spleen (Sel) and thyroid gland (TG) were studied using morphometric, ultrastructural and immunohistochemical methods. In addition, the concentration of thyroid and thyroid-stimulating hormones, as well as the main indicators of free radical oxidative stress, were determined in all animals in the blood serum [9;10;11;12]. All digital data were statistically processed using a software package; differences were considered significant if they satisfied $P< 0.05$.

Results and discussions

The impact of pesticides on offspring through the mother's body led to an immunotoxic effect, which manifested itself as a violation of postnatal growth and the formation of immune system organs. The formation of structurally -functional T- and B-dependent zones Mly and Sel in experimental rat pups was significantly behind, being carried out 7-10 days later than in the control. Moreover, the slowdown in the formation of MDR zones was more pronounced with FPI intoxication compared with the effect of LST. Electron microscopic studies revealed a high functional activity of macrophages and destructive changes in subcellular organelles of lymphoid cells. These changes were predominantly observed in T-dependent zones (the paracortical zone Mlu and the periarteriolar zone of the white pulp Cel) of the organs and occurred much more often when exposed to FPI. Morphometric studies also showed a significant decrease in the growth rate and formation of lymphoid tissue of organs in offspring obtained under conditions of exposure to pesticides through the mother's body. Immunohistochemical studies have shown that exposure to pesticides leads to inhibition of the proliferative activity of lymphoid cells Mlu and Cel, especially in T-dependent zones of organs. When exposed to LST, the proliferative index of cells in these areas was 10-15% lower, and when exposed to FPI - by 15-30%, it was lower than the control values. At the same time, intrauterine and early postnatal exposure to pesticides led to a significant increase in the degree of cell apoptosis. Apoptotic cells were most common in T-dependent zones compared to lymphatic follicles (B-dependent zones). The greatest increase in the apoptosis index was observed on days 14–21 after birth, when the indices of experimental animals were 3.2–4.3 times higher than the control indices. At the same time, the induction of cell apoptosis was manifested to a significantly higher degree under the influence of FPI than under LST intoxication. The immunotoxic effect of pesticides was most pronounced in the thymus gland. The growth rate of the average area of the thymus lobule under the influence of LST by 10-15%, and with the use of FPN by 15-30% lagged behind the control parameters. The area occupied by the cortical zone of the thymus decreased by 15–25% and 20–40%, respectively. Along with this, certain disturbances in the postnatal growth and development of Tm microenvironment cells in offspring were identified . Starting from the moment of birth, in the Tm of experimental animals, there was a tendency to a decrease in the number of epithelial -reticular

cells (ERCs) per unit area of the lobule. Moreover, the average number of ERCs more clearly decreased in the cortical zone of the thymus. Electron microscopy in the ERC of experimental animals revealed hypoplasia of the endoplasmic reticulum and the Golgi complex, as well as heterogeneity of secretory vacuoles, indicating a violation of the secretory activity of cells. Their cytoplasm contained a large number of heterophagosomes with thymocyte remnants. Exposure to pesticides led to inhibition of the proliferative activity of thymus lymphoid cells (thymocytes), especially in the cortical zone of the organ. When exposed to LST, the proliferative index of cells in these areas was 35-40% lower, and when exposed to FPI - by 45-55%, it was lower than the control values. At the same time, the immunotoxic effect of pesticides contributed to a significant increase in thymocyte apoptosis. Cells subjected to apoptosis were most often found in the cortical zone of the thymus. Quantitative calculation showed that under the influence of LST, the index of apoptosis of thymocytes in this zone was on average 40-45% higher, and under the influence of FPI - by 50-55% higher than in the control group.

The results showed that the immune toxicity of the pesticides used is closely related to their endocrine -destroying (ER) effect, both on the maternal organism and on the offspring. The ER effect of pesticides was manifested mainly as a violation of thyroid function in female rats and their offspring. Despite the high level of thyroid-stimulating hormone (TSH), the concentration of free thyroxine (T 4), triiodothyronine (T 3) remained significantly lower compared to the control. Morphometric studies have shown that the growth rate of the total area of the epithelium of the follicles under the influence of LST by 10-17%, and under the influence of FPN - by 15-30% lags behind the control parameters. However, the negative effect of pesticides was not limited to inhibiting the formation of new follicles. It has been found that exposure to pesticides leads to a decrease in the area of the follicle as a whole, by reducing the areas of the epithelium of the follicle and thyrocyte. The growth rate of the average thyrocyte area under the influence of LST by 10-20%, and under the influence of FPI - by 15-30% lagged behind the control indicators. Growth retardation and formation of the thyroid gland was accompanied by a significant decrease in the functional activity of the organ. The most pronounced hypothyroidism was observed in offspring under the influence of FPI compared with LST. Electron microscopy revealed a decrease in size mitochondria, as well as components of the endoplasmic reticulum and the Golgi complex of thyrocytes, which indicated a decrease in the secretory activity of cells. Exposure to pesticides resulted in inhibition of the proliferative activity of thyroid cells. At the same time, intrauterine and early postnatal exposure to pesticides led to a significant increase in the degree of apoptosis of thyroid cells. In the thyroid gland of offspring under the influence of LST, the apoptosis index was 3.5-4 times higher, and under the influence of FPI - 4.5-5 times higher than the control values.

The data obtained show that the toxic effect of pesticides on the development of the endocrine and immune systems of offspring is due to a number of metabolic changes in organs and tissues. Our studies have shown the endocrine -destroying, more precisely, thyroid- destroying effect of pesticides, which led to the development of hypothyroidism in the mother and offspring [13; 14]. In addition, we found an important role of oxidative stress as the main inducer of cell apoptosis [11;12]. Hence, it can be concluded that the induction of apoptosis in offspring is due not only and not so much to the direct toxic effect of pesticides. The induction of apoptosis is largely mediated by a weakening of the regulatory role of thyroid hormones on the processes of cell proliferation and apoptosis due to hypothyroidism, as well as an increase in the number of free radicals as a result of oxidative stress.

Conclusions

Exposure to even relatively low doses of pesticides during pregnancy and breastfeeding leads to the development of immunotoxic and endocrine -destroying effects in offspring; at the same time, the FPN pesticide has a more pronounced toxic effect compared to LST.

The immunotoxic effect of pesticides manifests itself in the form of a slowdown in postnatal growth and the formation of peripheral immune organs, a violation of the secretory function of the thymus and the formation of thymus-dependent zones Mlu and Sel.

endocrine -destroying effect is due to a predominant violation of the structure and function of the thyroid gland, leading to the development of hypothyroidism in both the mother and offspring.

In the pathogenesis of immunotoxic and endocrine -destroying effects, hypothyroidism and oxidative stress play a leading role, contributing to the induction of apoptosis while suppressing the processes of cell proliferation of the immune -endocrine system.

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