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The Mechanisms of The Toxic Effect of Intrauterine and Early Postnatal Exposure to Pesticides on The Development of The Immune System of Offspring

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Abstract: The aim of the study was to identify the toxic effect of intrauterine and early postnatal exposure to pesticides on the development of the endocrine and immune system of offspring. The experiments were performed on white adult male rats, who respectively received pesticides lambda-cyhalothrin or fipronil during pregnancy and lactation. Progeny from experimental and control animals was studied on the 3rd, 7th, 14th, 21st and 30th days after birth using methods of morphology, electron microscopy, immunohistochemistry and biochemistry. It has been shown that the toxic effect of pesticide exposure during pregnancy and lactation is manifested in the form of growth retardation and formation of the thymus, lymph nodes, spleen and thyroid glands of offspring. In the mechanism of toxic effect of pesticides on the immune-endocrine system, the leading role is played by the imbalance between proliferation and apoptosis of cells, caused both by direct toxic effects of drugs, both developing hypothyroidism and oxidative stress in mother and offspring. This causes the need for early detection of hypothyroidism and oxidative stress in pregnant women and newborns, followed by their pharmacological correction.

Keywords: Pesticides Lambda-Cygalotrin and Fipronil, Hypothyroidism and Oxidative Stress, Postnatal Ontogenesis

Introduction

The immune system, along with the endocrine and nervous systems, is extremely sensitive to the effects of various environmental pollutants. Pesticides are one of the most common pollutants of the environment. Widespread use of pesticides in agriculture, in everyday life and public health causes their entry into the human body and animals. Adverse effects of pesticides on the immune system are defined as immunotoxicity, which implies the violation of certain functions of the immune system under the influence of a toxic substance [1]. However, the immunotoxic effect of pesticides is not limited to the direct exposure of toxic substances to immune cells, causing their death and immunosuppression. In a number of cases, pesticides cause a number of metabolic changes and are inducers of the development of autoimmune reactions and abnormal hypersensitivity of the organism [2]. The mechanism of immunotoxic effects of pesticides is complex and diverse. It is shown that many pyrethroid pesticides lead to a decrease in the concentration of immunoglobulins, interleukins and interferon [3]. Of particular interest is the developmental immunotoxicity, when pesticides or other environmental toxicants have an adverse effect on the developing immune system of the fetus or newborn. It is known that the fetus and newborns are particularly sensitive to the action of various environmental toxicants. In experiments with zebrafish (Danio rerio) embryos, pyrethroid pesticide cypermethrin has been shown to cause immune disorders as a result of the induction of apoptosis of cells [4]. Another pesticide, carbendazim, also induced cell apoptosis and

caused immune and endocrine disorders in zebrafish (Danio rerio) in embryo development stage [5]. Mechanisms of developmental immunotoxicity of pesticides, especially in mammals and humans, are diverse and remain unclear. In our previous studies it has been shown that many modern pesticides in rats through the organism of a pregnant mother can have a negative effect on the development of the fetus and the newborn [6]. A pesticide from the pyrethroid class of lambda-cyhalothrin and an insecticide from the class of benzopyrazoles fipronil had an endocrine-disrupting action in the form of hypothyroidism in the mother and offspring [7]. The same animals showed oxidative stress in the form of an increase in the degree of free radical oxidation, as well as a pronounced induction of apoptosis of cells in the organs of offspring [8]. All this served as the basis for further studies of the mechanisms of immunotoxicity of development in the immune system of offspring.

The aim of the study was to identify the mechanisms of the toxic effect of intrauterine and early postnatal exposure to pesticides on the development of the immune system of offspring.

Material and Methods

Experiments were performed on nulliparous, white adult female rats, which were divided into 3 groups of 30 animals each. Two groups of animals for 30 days daily *per os* obtained respectively pesticides lambda-cyhalothrin (LCT, 8 mg / kg), or fipronil (FPN, 3.6 mg / kg). The third group receiving only the same volume of sterile saline served as a control. The following day, the females were coupled to healthy males for fertilization. Pregnancy was monitored for the presence of sperm in vaginal smears. Exposure of pesticides was continued incessantly during pregnancy and after delivery until the end of lactation. Offspring obtained from the experimental and control females were studied in dynamics on days 7, 14, 21 and 30 after birth. Thymus (Th), spleen (Sp), mesenteric lymph nodes (Mln) and thyroid gland (Tg) were studied by morphometric and electron microscopic techniques. For immunohistochemical studies of proliferation and apoptotic cells paraffin sections of thymus and thyroid gland have been used [9]. Apoptotic cells were detected using a rabbit monoclonal antibody to fragments of caspase-3 proteins and the family of p-53 (manufactured by Thermo Scientific, USA). Proliferation cells have been detected using a rabbit monoclonal antibody to protein Ki-67 (manufactured by Thermo Scientific, USA). Further the numbers of labeled proliferating, and apoptotic cells counted on 1000 – 5000 total cells and calculated an index of proliferation and apoptosis, that is expressed in parts per thousand. Furthermore, in the blood serum of offspring was determined level of thyroxine (T_4), triiodothyronine (T_3), thyroid stimulating hormone (TSH) of pituitary. Besides, biochemical determination of the status of lipid peroxidation and antioxidant enzyme levels in the liver tissue were carried out [10]. All digital data were processed by the method of variation statistics. Statistical significance between control and experimental groups was compared using the Student's test and P values <0.05 were considered significant.

Results and Discussion

Morphometric studies have shown that exposure to pesticides through the maternal organism significantly slows the rate of postnatal growth and the formation of the immune system of offspring. Thus, the growth rate of the thymus lobule area under the influence of LCT by 10-15%, and when FPN is applied, it is 15-30% lagging behind the control parameters (P_1, P_2 <0.05). The area occupied by the cortical zone of the thymus decreased by 15-25% and 20-40%, accordingly. In the lymph nodes and spleen, a marked lag in the formation of thymus-dependent zones (T-zones) of organs was noted. Electron microscopy in the thymus showed a marked decrease in the secretory activity of epithelio-reticular cells. And, on the contrary, especially in the cortical zone of the thymus, high functional activity of macrophages was noted. In their cytoplasm, numerous heterophagosomes with remnants of destroyed thymocytes were found. All this indicated that exposure to pesticides in the embryonic and early postembryonic periods had an immunotoxic effect on the development of the immune system of the offspring. The toxic effect is manifested in the slowing of the growth and formation of the thymus, a decrease in the secretory activity of the epithelio-reticular cells, and the intensification of destruction and death of thymocytes within the thymus. As a result of violation of the regulatory function of the thymus, in the peripheral organs of the immune system (Sp, Mln), the formation of T-zones of these organs is slowed down.[11]

Our morphometric studies have shown various disturbances in the dynamics of growth and formation of the thyroid gland of offspring under the influence of pesticides. The growth rate of the total area of the

epithelium of the follicles under the influence of LCT by 10-17%, and with the action of FPN, 15-30% lag behind the control parameters (P_1, P_2 <0.05). Accordingly, the area occupied by the colloid decreased by 15-25% and 20-40%. The slowing down of the growth rate and the formation of the structural and functional unit of the thyroid gland - follicle, is most pronounced when exposed to FPN, compared with the action of LCT. However, the negative effect of pesticides was not limited only to inhibition of follicle formation. It was found that the effect of pesticides leads to a decrease in the area of the follicle as a whole due to a decrease in the areas of the epithelium of the follicle and thyrocyte. The growth rate of the height and the average area of the thyrocyte when exposed to LCT by 10-20%, and when exposed to FPN - by 15-30% lagged behind the control parameters (P_1, P_2 <0.05). The slowing of growth and formation of the thyroid gland was accompanied by a significant decrease in the functional activity of the organ. Despite the high levels of thyroid-stimulating hormone (TSH), the concentration of thyroxine (T_4), triiodothyronine (T_3) remained significantly lower compared to the control. Moreover, the most pronounced hypothyroidism was observed in offspring under the influence of FPN in comparison with LCT.[12]

The effect of pesticides led to inhibition of the proliferative activity of cells of both thymus and thyroid gland. On the 7th day after birth, the index of thymus cells proliferation under the action of LCT in 1.5 times, and when exposed to FPN 1.8 times decreased in comparison with the control (P <0.05). A similar decrease in the proliferation index was found in the thyroid gland. A significant decrease in the cell proliferation index in both organs persisted up to 21 days after birth. Thus, exposure to pesticides led to inhibition of proliferative activity of cells in both the immune and endocrine organs of the offspring. In this case, the negative effect of FPN was more pronounced in comparison with LCT. Data of a different nature were obtained when calculating the apoptosis index of cells in the thymus and thyroid gland. Intrauterine and early postnatal exposure to pesticides led to a significant increase in the degree of apoptosis of cells of the thyroid gland and thymus. In the thyroid gland of the offspring, under the influence of LCT, the apoptosis index was 3.5-4 times, and when FPN was 4.5-5 times higher than the control group in all periods of the study (P <0.05). A similar significant increase in the apoptosis index at all times of the study was observed in the thymus of the experimental animals. Thus, exposure to pesticides led to a significant increase in the degree of apoptosis of cells of both the thyroid gland and thymus.

The obtained data show that the toxic effect of pesticides on the development of the immune system of the offspring (the developmental immunotoxicity) is due to a number of metabolic changes in organs and tissues. First of all, it is endocrine-disrupting, more precisely, thyroid- disrupting effect of pesticides, which leads to hypothyroidism in the mother and offspring [13]. Further, it is necessary to emphasize the role of oxidative stress, as the main inducer of apoptosis of cells [14]. Recent data show that thyroid hormones also have a high anti-apoptotic effect, which opens great prospects for the regulation of apoptosis in various diseases [15]. All this makes it possible to consider that the intensity of induction of apoptosis in our experiments is to a certain extent determined by the degree of thyroid dysfunction and the weakening of the proliferation-stimulating and anti-apoptotic effects of its hormones. Consequently, the induction of apoptosis in the experimental progeny is caused not only by the direct toxic effect of pesticides, but also largely mediated by the weakening of the anti-apoptotic function of thyroid hormones due to hypothyroidism and the resulting oxidative stress in the form of an increase in the number of free radicals.

Conclusions

1. The toxic effect of pesticide exposure through the maternal organism during pregnancy and lactation is manifested in the form of a violation of the growth and formation of the thymus, as well as thymus-dependent zones of the peripheral organs of the immune system.
2. In the mechanism of immunotoxic effect of pesticides plays a leading role the imbalance between proliferation and cells apoptosis of the thymus, caused both by direct toxic effects of drugs, and by the development of hypothyroidism and oxidative stress.

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