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ZEARALENONE AS A POTENTIAL ALLERGEN IN THE ALIMENTARY TRACT – A REVIEW*

Maciej Gajęcki, Magdalena Gajęcka, Łukasz Zielonka, Ewa Jakimiuk, Kazimierz Obremski

Division of Veterinary Prevention and Feed Hygiene, Department of Veterinary Public Health Protection, Faculty of Veterinary Medicine, University of Warmia and Mazury in Olsztyn, Olsztyn

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It is a common opinion that pathologic signs of allergy are connected with the prompt anaphylactic reaction. The knowledge about the so-called late reaction of the response to the allergen is less widespread. In the case of frequent or constant exposure to the allergen of late type, chronic inflammation and irreversible tissue damage appear. It may happen due to the intake of low doses of zearalenone in plant material. Zearalenone in the first period of its activity interferes in the processes of protein synthesis. On the other hand, the presence of environmental estrogens affects feminization of fish, birds and mammals. These xenobiotics, including zearalenone, probably take part in pathological conditions that occur as a result of autoimmunization and allergy. These dysfunctions and pathological conditions are in majority of cases noted more often in females than in males. They are often the primary cause of the induced diseases of the allergic origin like asthma, inflammation of nasal mucosa, skin inflammation and disturbances in the alimentary tract. In addition, environmental estrogens directly influence the immunological system or more probably they indirectly modulate this system through other tissues in order to change the model of cytokines.

This study presents the thoughts over the hazards for human and animal health posed by environmental estrogens (especially zearalenone) even in the allergies. In humans the number of the results that would allow for any conclusion is minimal. In this situation, first their influence on the immunological system in animals should be considered, then the pathological effect of low doses of the xenobiotic on the immunological system should be estimated.

It would be recommended to take longer period into account focusing on the results of the possible autoimmunization or allergy.

INTRODUCTION

In the animal organism there are three systems that determine its homeostasis, namely nervous, endocrine and immunological systems. The smallest disruption in any of them can induce a disease with irreversible changes.

This study shows a preliminary analysis of the influence of zearalenone (environmental modulator of the endocrine system – EDs – endocrine disrupters) that is present in plant materials, on the animal organism and especially on the immune system [Gajęcki, 2002; Sweeney, 2002; Čonková *et al.,* 2003; Zwierzchowski *et al.,* 2004; Laciaková *et al.,* 2005].

IMMUNOLOGICAL HYPERSENSITIVITY OF ANIMALS

Along the evolution, the immunological system created many specific mechanisms that are indispensable to eliminate or neutralise environmental infectious, toxic and other agents potentially harmful to the mammals. It has been noticed that immunological reactions in secondary response are especially effective and dynamic. At the same time, the immunological mechanisms defending the integrity of the organism against internal dangers have been created. The immunological response can become intensive and improper in both forms. The situation when the immunological response is "distorted", which in turn leads to destruction in tissues and diseas, is referred to as "hypersensitivity" [Sicherer, 2002; Sicherer & Leung, 2004].

At the beginning, when the term "allergy" was used it was understood as the change in reactivity of the organism exposed to the antigen for the second time. With time, "hypersensitivity" was used as a synonym of irregularity of the immunological response that comes from the exposure to the external agents [Jackson, 2003].

Current conditions of animal breeding in highly developed countries are totally different from those of phylogenic development of their ancestors [Sweeney, 2002]. The changes concern the prevalence of infectious diseases, therapy, exposure to new microorganisms, diet, environmental pollution and many others. There is no doubt that these changes are the cause of the high prevalence of different atopies, especially in highly productive animals and pets.

Phylogeny development of animals persisted in the conditions of the constant contact with parasites and exposure to viral and bacterial agents. It was the so-called "immunological training". Nowadays, many cases of allergy are noticed in the countries of highly developed animal breeding and farming. The reasons of these allergies cannot be defined, and what is worse, recognised. It results from the improving conditions of farming and the fact that contacts between ani-

Author's address for correspondence: prof. Maciej Gajęcki, Division of Veterinary Prevention and Feed Hygiene, Department of Veterinary Public Health Protection, Faculty of Veterinary Medicine, University of Warmia and Mazury, ul. Oczapowskiego 13, 10-950 Olsztyn; e-mail: gajecki@uwm.edu.pl

mals and microorganisms (not necessarily pathogenic) have become limited. Moreover, the disease does not affect animals which do not develop the natural immunity because of the massive prophylactic vaccinations [Bolhuis *et al.,* 2003]. It results in dysfunction of some immune mechanisms (*e.g.*: predominance of the activity of lymphocytes Th2 in comparison with Th1), which together with unused defence ability against multicellular parasites (based on mast cells, eosinophils and IgE antibodies) leads to the increased incidence of allergies. That way of thinking is in agreement with the hygienic hypothesis that univocally explains the reasons of allergy in young organisms [Jackson, 2003].

It seems that high exposure to allergens especially in youth is a propitious factor of the incidence or development of allergy. However, it cannot be excluded that the frequency of allergy incidence is also caused by factors different than massive exposure to allergen. It can be influenced by the seasonal factors like infections [Kuhn & Ghannoum, 2003], diet, climatic changes and environmental pollution of different origin [Ansar Ahmed *et al.,* 1999].

Allergens are antigens that are able to evoke allergic reaction, which is connected with their ability to induce humoral response with participation of IgE antibodies [Foster *et al.,* 2003]. The majority of naturally occurring allergens (xenobiotics, pollens or other organic compounds) are globular proteins of molecular weight ranging from 10 to 40 kDa. Some allergic proteins contain saccharides or their metabolites, *e.g.*: glucoronic acid that is a product of glucose oxidation. They are usually well soluble in water.

A separate group of allergens are haptens – chemical compounds that evoke allergic reaction after binding to the carrier, *e.g.*: serum protein. It is estimated that 10–20% of allergies are side effects of drugs [Sicherer & Leung, 2004].

There are two major types of the immunological response to allergen. It can be immediate/anaphylactic reaction or late reaction. The first type occurs in several minutes after exposure to allergen and it stops in one hour. Common opinion joins signs of allergy with immediate/anaphylactic reaction, which is connected with degranulation of mast cells and direct influence of mediators. Late response to the allergen, which is clinically very important in veterinary practice, is less known. In the case of often or constant exposure to late allergen, chronic inflammation and irreversible destruction occur in tissues. It is noticed during long-lasting intake of small doses of zearalenone introduced with plant material.

MOULD FUNGI AND THEIR METABOLITES

Mould fungi are eukaryotic organisms that do not have chlorophyll. In majority they are parasites and many of their species are saprophytic organisms. However, their presence on plant or animal material intended for feed or food should be treated as the important risk factor for animals and humans [Čonková *et al.,* 2003]. Undesired health effects in mammals depend on the degree of the pollution by only mould fungi (proteins present on their surface and in spores) and on the number of secondary metabolites (micotoxins) present in the ground [Kuhn & Ghannoum, 2003]. Our knowledge concerning the presence of allergenic proteins in tissues of mould fungi and micotoxins (carried in animal organism by the protein carrier) evoking particular diseases is poor at the moment [Jarvis & Miller, 2005]. We can predict pathological effects regarding the introduction of some mould fungi and several micotoxins introduced separately to the human or animal organism. The recognition of clinical changes in acute intoxication is much more difficult and mixed intoxications have not been recognised so far [Gajęcki *et al.*, 2005].

Micotoxins are a group of secondary mould metabolites, mainly of *Penicillium, Aspergillus* and *Fusarium* genera [Moss, 1991], that can exhibit acute toxic actions [Cetin & Bullerman, 2005]. Acute toxic effects are exceptional but long-lasting exposure to low concentrations of particular micotoxins can induce chronic diseases, liver and kidneys neoplasm and others, including allergies [Jarvis & Miller, 2005]. Some of them display mutagenic (aflatoxins, fumonisins, ochratoxin A, luteoscirin, T-2 toxin), teratogenic (ochratoxin A, patulin, aflatoxin B_1, T-2 toxin) [Smith *et al.,* 1995] and estrogenic (zearalenone) action [Cavaliere *et al.,* 2005; Jarvis & Miller, 2005]. Some micotoxins interfere in the protein synthesis and evoke skin hypersensitivity and necrotic lesions. They (*e.g.* zearalenone) even decrease the level of antibodies [Atroshi *et al.,* 2002; Gajęcka *et al.,* 2004]. Other micotoxins have neurotic effects and their low doses cause convulsions in animals. Slightly increased doses of these micotoxins lead to changes in the brain or even to death [Pitt, 2000].

As the chemical compounds, the micotoxins are enumerated among the aromatic carbohydrates (sometimes to aliphatic carbohydrates) with a low molecular weight. It determines their resistance against environmental agents and a lack or weak immunogenic features [Cavaliere *et al.,* 2005; Speijers & Speijers, 2004] that influence the system in a suppressive way.

Some research [Chełmońska-Soyta *et al.,* 2005] have attempted to identify the site where the micotoxin or a group of micotoxins incorporates in the life functions of a cell as well as to characterise pathological changes in tissues (organs and cells). Some of the micotoxins have a stimulating factor [Cavaliere *et al.,* 2005]. It should also be considered that some micotoxins have a reverse effect, *e.g.*: they evoke negative interaction like patulin that protects fats against oxidation [Riley, 1998; Riley & Norred, 1996]. Multiple research showed the suppressive effects of trichotecens towards the immune system in animals [Pestka *et al.,* 2005; Riley, 1998; Zielonka *et al.,* 2003, 2004]. The examples given in the literature show that kidneys [Braunberg *et al.,* 1994] and liver [Kuhn & Ghannoum, 2003; Obremski *et al.,* 2005] are the most susceptible to the action of the xenobiotics analysed. However, general reactions in the form of oedema or allergy may occur as well [Fischer & Dott, 2003; Jarvis & Miller, 2005].

ENVIRONMENTAL ESTROGENS

According to Anser Ahmed [2000], there are two, among many others, terms valid in endocrinology. The first assumes that sex hormones cannot be treated as "reproduction hormones". They influence non-reproductive functions of many tissues and especially of the immunological system. The second assumes that estrogens are present in the organism not only as natural or synthetic compounds but they have also environmental origin. These substances (not necessarily pol-

lution) are referred to as "environmental estrogens". Majority of them is enumerated in the group the so-called "endocrine disrupters" (EDs). They are commonly found in the environment, *i.e.* in soil, air, water and in food [Yurino *et al.,* 2004]. The examples of pollution (xenoestrogens) are: plastic (bisphenol-A), detergents and surface-active substances (nonylphenol), pesticides (DDT, dieldrin), chemical compounds of industrial origin (polychlorinated biphenyls) [Malinowska, 2001; Brevini *et al.*, 2005]. Natural EDs that occur in the environment are: phytoestrogens (genistein, coumestrol) [Chełmońska-Soyta *et al.,* 2005] and micoestrogens – products of mould fungi of *Fusarium sp.* genera (zearalenone) [Gajęcki, 2002].

Ubiquitous presence of environmental estrogens should make us consider that they can affect wild organisms, farm animals, pets and humans in an uncontrolled way. According to Polischuk *et al*. [1995], global access to these substances is evident. It is proved by the presence of DDT (xenoestrogen) in blood and fat of wild animals and humans in the region of Arctic, which is free from industry. Some of these compounds occur also in other groups of wild animals. Feminisation of fish, birds and mammals is the effect of their presence. It causes decreased hatching in birds, fish, turtles and pathological lesions in the reproductive tract of alligators [Fry & Tone, 1981; Chapin *et al.,* 1997]. Our previous research [Gajęcki, 2002] and that carried our by others on different estrogenic compounds [de Jager *et al.,* 1999] showed that these compounds cause increased uterus mass, decreased efficacy of mating, and decreased number of litters. They also negatively affect development of the reproductive tract and sexual behaviour. Numerous environmental estrogens become the cause of the decreased efficacy of the action of natural endogenic estrogens, *e.g.* 17β-estradiol. Many of them are chemically stable and accumulate in the organism (in fat). They can reach high concentrations. These compounds are released while losing weight; in addition they can reach foetus organism during pregnancy and colostrums or milk. They bind to (block) estrogen receptors and they, probably, cause the transfer of a receptor-ligand complex from cytoplasm to the nucleus and provoke synthesis of particular proteins. The phenomenon of binding (blocking) of these environmental chemical compounds to new estrogen receptors is possible [Arcaro *et al.,* 1999]. Environmental estrogens that simulate natural hormones (mimicry) block and change the effect of binding of the hormone to receptor. They can also change the metabolism of natural estrogens [Soto *et al.,* 1995; Withanage *et al.,* 2001].

The correlation between the presence of environmental estrogens capable of modulating the endocrine system (endocrine disrupters – EDs) [Sweeney, 2002; Teilamann *et al.,* 2002] and their potential negative effect on human and animal organism is not univocal. However, the results of the analysis carried out on wild and farm animals and pets prompt to consider development of the methods used to determine the harmfulness of substances modulating the endocrine system [Ansar Ahmed, 2000]. The division of EDs on those inducing reversible and irreversible pathological changes in mammals should be considered as well.

The aim of this review is to show the problem of a double action of EDs on the immunological system, which is often noticed [Yurino *et al.,* 2004]. Ample studies have shown that hormones of the reproductive system influence the morphology of thymus and other parts of the lymphatic system. Administration of estrogens causes thymus involution [Ansar Ahmed *et al.,* 1999; Walker *et al.,* 1999]. On the other hand, the involution of thymus, especially in the postnatal period, causes changes in the endocrine tissues of the ovary, testis and thyroid gland. Estrogens regulate the synthesis of serum and uterus immunoglobulins – IgM, IgA and IgG [Wira & Sandoe, 1987; Makkonen *et al.,* 2001; Gajęcka *et al.,* 2004]. They also evoke an increase in the production of specific and non-specific antibodies [Kurup *et al.,* 2000]. From the biochemical point of view and taking interactions into account it can be concluded that both those forms are not clear. It is likely that hormones and cytokines serve a very important function in the transmission of information between the two systems: the reproductive and the immune one [Krakowski *et al.,* 2004]. This, probably, strict co-operation assumes that the influence of the environmental estrogens on the tissues in the reproductive system can also affect the immunological system. It is still controversial, however, if this result is produced by the direct or indirect action of the environmental estrogens. It should also be considered if the immunological system is a real aim for all EDs or environmental estrogens in particular.

Estrogens are also likely to take part in pathological conditions that occur as a result of autoimmunization or allergy. Commonly, the majority of these indispositions or pathological conditions are noticed more often in female than in male [Chełmońska-Soyta *et al.,* 2005]. Hormones of the reproductive system are often one of the primary causative agents of the allergic conditions like asthma, inflammations of nose mucosa, and skin inflammations in humans and animals [Stubner *et al.,* 1999].

It is very likely that the environmental estrogens trigger particular changes in the immunological system directly or indirectly regarding non-lymphatic tissue. They act through non-estrogenic receptors that fulfil the role of mediators. In addition, they modulate the immunological system in order to change the model of cytokines through influencing this system directly or – what is more probable – indirectly, by other tissues [Ansar Ahmed *et al.,* 1999; Krakowski *et al.,* 2004].

The aim of this review was not to outline the results of ample research proving these suggestions but to present some thoughts over the dangers posed by environmental estrogens (including zearalenone) to human and animal health, even in the part of clinical immunology – allergies.

CLOSING REMARKS

Apart from the results obtained in wild, farm animals and pets there is still a question regarding the safety of the presence or the impact of the environmental estrogens on the immunological system of humans. In humans, the number of the results that would allow for any conclusion is minimal. Therefore, firstly research should be undertaken to determine the impact of non-environmental steroids on the immunological system in animals. Next, it would be very important to estimate the pathological effect of low doses of hormones on the immunological system. Yet, they should be applied for a longer period and attention should be paid to the results of potential autoimmunization or allergy.

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ZEARALENON JAKO POTENCJALNY CZYNNIK ALERGIZUJĄCY W PRZEWODZIE POKARMOWYM – ARTYKUŁ PRZEGLĄDOWY

Maciej Gajęcki, Magdalena Gajęcka, Łukasz Zielonka, Ewa Jakimiuk, Kazimierz Obremski

Zespół Profilaktyki Weterynaryjnej i Higieny Pasz, Katedra Weterynaryjnej Ochrony Zdrowia Publicznego, Wydział Medycyny Weterynaryjnej, Uniwersytet Warmińsko-Mazurski w Olsztynie, Olsztyn

W powszechnej opinii objawy chorobowe alergii kojarzą się z reakcją natychmiastową, anafilaktyczną. O wiele słabsza jest znajomość, tzw. reakcji późnej odpowiedzi na alergen. W razie częstego lub ciągłego narażenia na alergen typu późnego dochodzi do przewlekłego stanu zapalnego i nieodwracalnego uszkodzenia tkanek, co może mieć miejsce w wyniku długotrwałego pobierania np. małych dawek zearalenonu z materiałem roślinnym. Zearalenon w początkowym okresie swej aktywności ingeruje w procesy syntezy białek. Efektem działania estrogenów środowiskowych jest feminizacja ryb, ptaków i ssaków. Te ksenobiotyki, a w tym prawdopodobnie i zearalenon, mają również swój udział w stanach patologicznych powstałych w wyniku stanów autoimmunizacyjnych i alergicznych. W większości przypadków te niedyspozycje czy stany patologiczne spotyka się częściej u samic niż u samców. Są często jedną z pierwotnych przyczyn wywoływania stanów chorobowych na tle alergicznym jak astma, stany zapalne śluzówki nosa czy stany zapalne skóry oraz niedyspozycje przewodu pokarmowego. W dodatku, estrogeny środowiskowe wpływając na układ immunologiczny w sposób bezpośredni, albo co jest bardziej prawdopodobne, w sposób pośredni przez inne tkanki, modulują układ immunologiczny tak, by zmienić model cytokin.

W pracy przedstawiono przemyślenia na temat zagrożeń jakie mogą nieść estrogeny środowiskowe (w tym szczególnie zearalenon) dla zdrowia ludzi i zwierząt z punktu widzenia reakcji alergicznych. W odniesieniu do ludzi liczba wyników z których można byłoby jednoznacznie cokolwiek wnioskować, jest znikoma. W związku z tym w pierwszej kolejności należałoby zająć się ich wpływem, na układ immunologiczny u zwierząt. W dalszej kolejności dobrze byłoby określić efekty patologiczne małych dawek ksenobiotyku na układ immunologiczny, ale przez dłuższy czas, koncentrując uwagę na wynikach ewentualnej autoimmunizacji czy alergii.