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Artykuł przeglądowy *Review*

Impact of stress on the functioning of the immune system, swine health and productivity

IZABELA SIEMIŃSKA, ZYGMUNT PEJSAK

Institute of Veterinary Sciences, University Center of Veterinary Medicine JU-AU, University of Agriculture in Kraków, al. Mickiewicza 24/28, 30-059 Kraków, Poland

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Siemińska K., Pejsak Z.

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Summary

Stress can affect many aspects of the body, including the immune response, and stress factors are an inherent element in the life of animals in intensive production, such as pigs. Major pathways involved in these interactions are associated with the sympathetic nervous system (SNS) axis and the hypothalamic–pituitary–adrenal (HPA) axis. This review is focused on the effects of various stress factors described so far on the swine immune system. The literature data presented here indicate that the effect of stress factors depends not only on the duration and severity of stress, but also on the animal's temper. Stress, through its influence on the immune system, strongly influences the digestive tract of pigs such as response to pathogens, microbiome disturbance and influence on appetite. Thus, long-term stress has negative effects on the animal's development, including a high rate of morbidity and mortality, an increase in the feed conversion rate (FCR), and, important in intensive production, weight differentiation of the same age groups of pigs. Therefore, the role of stress and the immune system itself in the production of pigs should not be underestimated. Any decrease in animal stress is crucial.

Keywords: stress, immune system, swine, production efficiency

Stress is a natural, physiological phenomenon in humans, animals, plants, and microorganisms. Formulating a universal definition of stress remains a challenge even though research on stress began already in the 1930s (62). It seems that the most common definition is that stress is a biological phenomenon consisting in the organism's reaction to excessive physical or mental demands. According to Selye, a living organism is constantly exposed to various unfavorable stimuli that disturb its homeostasis (63). Stress are all stimuli that adversely affect the body. The organism's sensitivity to stress varies and depends on the biological properties of a given species of animals or plant, but mainly on the duration and severity of stress (5, 50). Stress activates the so-called general adaptation syndrome (GAS), characterized by a specific hormonal activity, and hence pathological changes (adrenal enlargement, atrophy of the thymus gland, ulceration in the digestive system). The main sign of a stress reaction is an increase in the output of glycosteroids from the adrenal cortex. The dynamics of the stress syndrome are characterized by three phases: alert, adaptation, and exhaustion (63). According to research on stress conducted by Solely, stress has two aspects: a negative one and a positive one. Negative stress is a chronic distress, which is physically and mentally degrading. Positive stress (eustress) is constructive and motivating – it determines concentration, effort, and achievement (64, 58). Some authors, however, reject the idea that some stress has a positive effect (14).

During stress, we can distinguish two types of reactions, depending on the behavior of the affected individual: an active reaction, which is an attack or flight, and a passive reaction, consisting in immobility and depression during longer-lasting stress (18). The adrenaline and noradrenaline rush is characteristic of an active reaction. During a passive reaction, increased levels of corticosteroids are observed (41). Due to connections between various physiological mechanisms, stress may negatively affect not only immunity and consequently health, but most of all reproduction (12).

The available literature indicates that the greatest stressful impact on farm animals, especially horses and pigs, is due to biological and physical elements of the environment (31). In the case of the widespread intensive production of animals, especially pigs, stress may be caused by quantitative or qualitative disturbances, such as those related to the excessive density of animals, their large number, frequent movement, or long transport, which disturb the balance between the environment (ecosystem) and the animals, necessary for the normal functioning of the organism (49).

The result may be a deterioration in the harmonious functioning of different systems in the body, which in turn disturbs its homeostasis, potentially resulting in decreased production and even disease. It can be concluded that the breeding environment, as well as the physical and biological environment, determines the physical and mental condition of animals, the maintenance of homeostasis, the functioning of the immune system, feed consumption efficiency, and even the use of the genetic potential.

Influence of stress on the immune response

The mechanisms related to stress that determine its impact on the immune system are still not fully understood. However, the mutual influence of the nervous and immune systems is largely known. The major pathways involved in these interactions are the sympathetic nervous system (SNS) axis and the hypothalamic–pituitary–adrenal (HPA) axis. These systems communicate with each other through two axes. The SNS axis is the one between the sympathetic nervous system and the adrenal medulla. The sympathetic nervous system is part of the autonomic nervous system, which activates internal organs and is responsible for the fight-or-flight response (69). First, after a stressor is triggered, the sympathetic system stimulates the adrenal glands to release adrenaline and noradrenaline, which, among others, leads to an acceleration of the heart rate and breathing, and pupil dilation. The activation of the sympathetic system in pigs can be measured by Chromogranin A (CgA), which is an acidic soluble protein belonging to the granins family (13). The other axis, HPA, is activated minutes or hours after stress occurs (33). By releasing corticoliberin, the hypothalamus stimulates the pituitary gland. Under the influence of this hormone (neurotransmitter), the anterior pituitary gland secretes corticotrophin, which, reaching the adrenal cortex, causes the secretion of glucocorticoids, including cortisol, by the cells of this organ. Cortisol reduces the sensitivity of the senses, while increasing the ability to distinguish between separate stimuli. Glucocorticoids inhibit the activity of the pituitary and hypothalamus, thanks to which they regulate the intensity of the stress response (20). Hence, cortisol has been widely used as a marker of stress in swine, also as a noninvasive test from saliva (22, 56, 75).

Glicocorticoids have a negative effect on the immune system. They may have an impact on the innate immune response reducing the number of circulating monocytes and hence also proinflammatory cytokines IL-2, IL-6, TNF-α, and IL-12, which results in reduced Th1 lymphocyte differentiation. Moreover, glucocorticoids decrease the number of T cells and the production of IL-2, which is necessary for T cells. In addition, glucocorticoids inhibit leukocyte traffic and thereby the access of leukocytes to the site of inflammation (67). Moreover, a strong and prolonged stress inhibits the humoral and cellular response of the immune system because of the secretion of excessive amounts of cortisol by the adrenal cortex. This results in „hyperadaptosis", often leading to the manifestation of a disease (17). Glucocorticosteroids also reduce the reactivity of lymphocytes, limit their production, and sometimes activate the process of their apoptosis (21). However, a short psychological stress, such as the social isolation of piglets, induces a state of cortisol resistance in blood immune cells, which may be an adaptation aimed at maintaining cellular immune responses in the short term (71). This is also confirmed by other studies showing an increase in CD8+ lymphocytes and hence a decrease in the CD4+/CD8+ ratio after the social isolation of piglets (26, 73).

Due to the variety of stress factors and the distinction between acute and chronic stress, it is important to approach the effects of a given stress factor individually. After only 20 minutes of transporting swine, we can observe rapid changes in their immune response, such as an increase in some acute phase proteins (APP), haptoglobin, and CRP (15). In addition to APP changes, there is an increase in the neutrophil/lymphocytes ratio, which has long been suggested as a stress marker in pigs (53). Other authors suggest salivary serum amyloid A as a better and longer lasting biomarker for the assessment of complex stress in pigs (65). Another immune marker of stress may be the level of immunoglobulin (Ig) A, since it increases after immobilization (47). Moreover, the IgA level returns to its previous value after the removal of stress faster than that of cortisol, which is related to different regulation of the secretion of these substances by the SNS axis and the HPA axis, respectively (42, 43). SNS stimulation may also be responsible for an increase in IL-18 in saliva during acute immobilization stress, which is another candidate for an immune marker of stress (52).

In summary there are a few immune biomarkers that change immediately after stress, and therefore could be easily used as biomarkers of acute stress. Acute stress is commonly associated with a proinflammatory response, which may be helpful in setting the immune system to fight and heal (11). In piglets, this pro-inflammatory response due to repeated social isolation results in an increase in cytokines, such as IL-1β (27, 72). Stress associated with the isolation of young piglets was also associated with an increased expression of IL-6 mRNA in the hypothalamus (74). Prolonged stress in mice and humans may be associated with a pro-inflammatory response and an increase in cytokines such as IFN-γ, TNF-α, IL-6, IL-1Rα, as well as an increase in anti-inflammatory IL-10 (36, 82). In swine, long transport (more than 6 h) has been related with an increased concentration of pro-inflammatory cytokines (IL-2, IL-6, IL-12, IL-1β, and IFN-γ) and a decreased concentration of anti-inflammatory cytokine IL-4 (8). In general, studies on humans and animals have shown that chronic or repeated stress reduces immune responses, whereas a single exposure to stress enhances immunity (10). This is also supported by studies on innate immunity in pigs. However, the ultimate effect of a stressor also depends on stress factors. For example, chronic social stress had a predominantly immunosuppressive influence on pigs, characterized by a significant down-regulation of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-8, probably due to a robust upregulation of IL-10 expression in the ileum and colon (2).

Prolonged stress associated with food intake interruptions was associated with increased APP, especially in males (46). Chronic heat stress had no effect on lymphocyte proliferation (3, 45), whereas a 14 day exposure of pigs to heat and crowding stress was associated with an increased proliferation of T cells and NK cell cytotoxity, without any effect on the total IgG concentration (68). On the other hand, a 4 day cold stress reduced NK activity, T cell proliferation, and the total plasma IgG concentration (57). The effect of stress on the immune response is not only confined to the stressed individual alone, but may also influence individuals in utero. It has been revealed that heat stress causes a greater cytokine response (TNF-α, IL-1β, and IL-6) to lipopolysaccharide (LPS) in fetuses in utero compared with fetuses that are not exposed to heat stress, probably due to an altered metabolic and cortisol response (24). Additionally, maternal stress resulted in a significantly decreased serum IgG level in suckling piglets and immunosuppression of B and T cell proliferation without any change in NK cell cytotoxity. These changes were accompanied by a reduced thymus weight (70).

It seems that the ultimate effect of stress on the immune system depends not only on the duration of stress and stressor factors, but also on the individual exposed to this stress. Social stress appears to suppress the immune response to a viral vaccine and consequently impairs protection against a challenge infection more in dominant than in subordinate individuals subjected to social stress (16).

Generally, socially dominant and submissive pigs showed alterations in the immune function (elevated numbers of neutrophils and decreased antibody production) compared with average pigs. Heat and social stress interact in their effect on the pig's immune system and cause immunosuppression in average animals, although there are also immunological costs to dominant pigs as well (39).

Stress is also connected with stereotypies and even destructive disorders, such as tail biting, which may be counteracted by environmental enrichment (9). What is interesting, environmental enrichment may also affect certain components of the immune system (35, 38, 54, 60, 61). Some data indicate lower N: L ratios and haptoglobin levels in enriched-housed pigs, which suggests that they are less stressed and their immune system is less activated (1). These results confirm the relationship of stress with the immune system, as well as the beneficial effect of enrichment on pig behavior and welfare. At this point, it should be emphasized that a short-term activation of the immune system and pro-inflammatory response may be beneficial, although it has a negative effect in the long term.

Stress-associated immune response changes in the gastrointestinal tract

Above all, it is necessary to maintain the balance between the animal's organism and the surrounding ecosystem. Prevention of chronic inflammatory processes on the enormous surface of the intestinal mucosa (about 300 m^2 in a 100 kg fattener) is particularly important. Gut-associated lymphoid tissue (GALT) is the largest bastion of the immune system (IS) just beneath the epithelium of the gastrointestinal tract. The function of the immune cells that are part of GALT is a quick and strong reaction to invasion by microorganisms or to their toxins. At the same time, GALT limits the scope of reaction against non-pathogenic factors to prevent the excessive activity of the IS and, consequently, excessive damage to the organism by the inflammatory reaction (4).

Among GALT we can distinguish a few pivotal populations such as innate like-lymphocytes (ILL) which combines intraepithelial lymphocytes (IEL), mucosal-associated invariant T (MAIT) cells, and invariant natural killer T (iNKT), and innate lymphoid cells (ILC) (2). Innate-like lymphocytes, which are located in the small intestine and, to a lesser degree, in the large intestine, play an important role as producers of cytokines, cytotoxic molecules, and antimicrobial peptides (78). MAIT recognize a microbial vitamin B metabolite and may have an adaptive capacity with probable participation in host defenses against both infectious and non-infectious diseases (80). Invariant natural killer T cells recognize glycolipids derived from microbes and modulate the immune response to intestinal pathogens via cytokines, such as IL-12, IL-18, IFNγ, IL-17, and GM-CSF (59). The population of ILC with three subpopulations mainly play role in intestinal homeostasis and protection of the gastrointestinal tract (77). These cells play an important role in the cytokine-driven integrity of the intestinal epithelium. ILC3, by producing specific cytokines (IL-17A and IL-22), regulate the level of anti-infective immunity and, consequently, limit the multiplication and spread of pathogenic bacteria in the intestines. They also limit the response of helper lymphocytes (Th CD4+) to commensals that are part of the microbiome (19). In the digestive tract of pigs, there are several hundred species of various bacterial strains, which, in exchange for nutrients and living space, provide the body with benefits resulting, among others, from protection against excessive multiplication of pathogenic bacteria (30).

Thus, an immune response is triggered, among others, by the recognition of bacterial, viral, parasitic, and other ligands by IS cells and causes a rapid release of pro-inflammatory cytokines, TGF beta and other mediators into the surrounding tissues and bloodstream. Cytokines point to the effector cells information about the site of infection, where the latter help remove the pathogen through several mechanisms. The bacterial flora of commensals and conditionally pathogenic microorganisms (microbiome) together with the cells of the macroorganism form a comprehensive, interactive ecosystem, determining, among other things, the activity of IS and actively participate in gastrointestinal tract protection.

It has been unequivocally proven that stresses related to the environment in which animals live impairs the intestinal barrier and induces immunosuppression of intestinal immune responses due to the up-regulation of IL-10 (32), which may decrease the efficiency of animal production and increase the incidence of diseases (51). In addition, early stress due, for example, to an early weaning of pigs, is associated with an impaired future response to *E. coli* bacteria (40). Moreover, the activation of intestinal mast cells has been shown in multiple animal models and in humans to be a key immune player in stress-induced gastrointestinal disease (44). This up-regulation of mast cell activity was also confirmed in another study with pigs subjected to chronic social stress (32).

Immune stress and its influence on the body and production

The long-term immunological mobilization of the animal's organism, related to defense against constant pressure from unfavorable environmental conditions, including pathogens, is defined as immunological stress. There is still an incomplete understanding of mechanisms related to long-term immune stress, which determine the negative effects on the animal's development, including a high rate of morbidity and mortality, an increase in the feed conversion rate (FCR) and, important in intensive pig production, weight differentiation of the same age groups of pigs. It is known, however, that the innate immune system is part of the first line of anti-infective defense of the host. These defense mechanisms are innate, and the ability to respond does not change with or adapt to the pathogen. The barriers of the epidermis and mucosa epithelium constitute the first barrier to the pathogenic factor.

When the pathogen is strongly pathogenic or present in large numbers, or when the barriers are damaged (abrasions of the epidermis, disruption of the continuity of the mucous membranes), it is possible to break these barriers and infect the host. Microorganisms that have broken such barriers are recognized by IS cells through pathogen-associated molecular patterns (PAMPs) derived from bacteria, viruses, fungi, and protozoa by Toll-like receptors (TLRs). TLRs, which are expressed on macrophages, dendritic cells, mast cells, and NK cells, as well as on T and B lymphocytes, distinguish pathogens from dead and inactive (debris) elements (37). The activation of TLRs is a pivotal signal for the activation of both innate and acquired immune responses and for combating the pathogen in accompaniment with a massive proliferation of immune cells and production of immunoglobins, cytokines, chemokines, acute phase proteins, and many others. Moreover, the stimulation of individual cells of the immune system, for fear of the threat, is a priority more important than reproduction, weight gain, or FCR. Especially, an enteric infection is one of major stressors causing low productivity in farm animals, including pigs, since it is known to suppress the feed conversion efficiency (29, 81). Survival is always the most important goal of an organism. Thus, it is not surprising that such a state of immunological stress results in a negative energy balance and weight loss (25, 66). During immune stress, the metabolic priority is mainly the production of APP by the liver.

Acute phase proteins include proteins whose concentration in plasma increases by at least 20% after tissue damage. The priority action of APP is to restore the body's homeostasis. Acute phase proteins simultaneously inhibit the synthesis of certain proteins and accelerate the degradation of muscle proteins (20). Similar results were obtained in swine, in which APP levels showed an inverse relationship with weight gain (52). A negative consequence of APP activity is increased catabolism leading to weight loss. According to calculations, about 850 mg APP/BWT is produced in the human body during the activation of IS. The amount of degraded muscle tissue in this period amounts to 1980 mg/BWT.

This is related, among others, to the persistently high level of cytokines secreted by stimulated leukocytes. The problem of weight loss is exacerbated by the overproduction of cytokines, especially IL-6, IL-1β, and TNF-α, which are a significant cause of changes in mood and behavior leading to weakness and sometimes even a lack of appetite (7, 28, 39, 48). Even an increase in cytokines such as IL-1 observed during a virus infection was associated with a lack of appetite and weight loss in pigs (34). The lack of appetite due to the chronic stimulation of IS can also be observed in pigs kept in overcrowded pens, exposed to many conditionally pathogenic microorganisms, frequently moved or rearranged, or in piglets weaned too early (before the 28^{th} day of life).

It should be emphasized that any disturbance of homeostasis due to the impact of long-lasting stress on the organism weakens its immune defense and increases its sensitivity to pathogenic microorganisms present in the environment. Although a piglet or weaner with an efficient immune system can cope with conditionally pathogenic or pathogenic microorganisms present in its environment, an animal that finds itself in conditions of biological and/or physical environmental imbalance may undergo subclinical infection with its economic consequences, or even become sick. As already mentioned, environmental stress factors, such as overcrowding or heat/cold stress, often combine in their unfavorable effects to overcome the barriers of innate and acquired immunity. However, improper feeding of animals may also worsen the effects of the above-mentioned imbalance. Especially in young animals, a diet that does not contain nutrients essential for strengthening the anti-infectious resistance may make the animals more vulnerable to infection by pathogenic microorganisms. It has been shown that an appropriate diet can support the pig's immune system, and if that pig is a sow, such a diet can even have a positive effect on the immune system of its piglets (55, 76). On the other hand, mycotoxins naturally present in corn may result in an altered immune response with systemic inflammation and partial liver damage, causing a reduction in the growth of pigs (6).

For this reason, improper feed may be a secondary factor causing dysfunctions of the physiological systems of the organism, including a dysfunction of IS.

The fact that the organism's immunity has been broken down by pathogens living in the environment is usually noticed only when the clinical form of the disease becomes evident. We are not aware of the fact that pigs exposed to stress, e.g. related to a large daily temperature amplitude in the room or drafts have a reduced appetite and reduced weight gains, even when there is no clinical disease in the herd. The correlation between the microbiological contamination of pigs' habitat and the consequent decrease in production, even in the case of taking the same amount of feed by animals, is well documented and known to most pig producers and veterinarians.

A typical observation is that the first groups of animals reared in a new facility, usually have better weight gains and FCR than subsequent groups, even when all biosecurity rules, including the All-In-All-Out (AIAO) principle, are continuously followed. Potentially pathogenic microorganisms found in the environment increasingly infect subsequent technological groups of animals, thus supporting and sometimes even increasing chronic immune stress.

Mainly because of the labor-intensive and time-consuming nature of cleaning and disinfecting, but also because of the insufficient awareness of the impact of the environment on animals' IS and, consequently, on their health and production effects, pig producers often prefer to use "strategic medication" (which is in principle already banned by the EU), instead of taking care of hygiene on their premises.

An excessive, long-lasting immune alert leads to inflammatory changes in the intestines, and a high level of pro-inflammatory cytokines may lead to intestinal dysbacteriosis, or dysbiosis (a microbiological imbalance in the intestines). This may cause undesirable consequences affecting the entire body, which was also confirmed in swine exposed to heat stress (79). Changes in the composition of the microbiome can be qualitative, such as a decrease in the diversity of the intestinal flora, and/or quantitative, such as changes in the number of individual bacteria.

An additional cost of a long-term alert may be the aforementioned periodical deterioration of appetite and, consequently, a prolonged fattening period. A deterioration in FCR is often observed. Since the pressure from environmental stressors affects individual animals differently, there will be a differentiation in the weight of weaners or fattening pigs of the same age. Weight differentiation among animals of the same age may have serious economic consequences, contributing to problems related to the rhythmic production of numerically appropriate groups of weaners or finishers.

Various issues related to the impact of stress on the immune response and health in swine are presented in Figure 1.

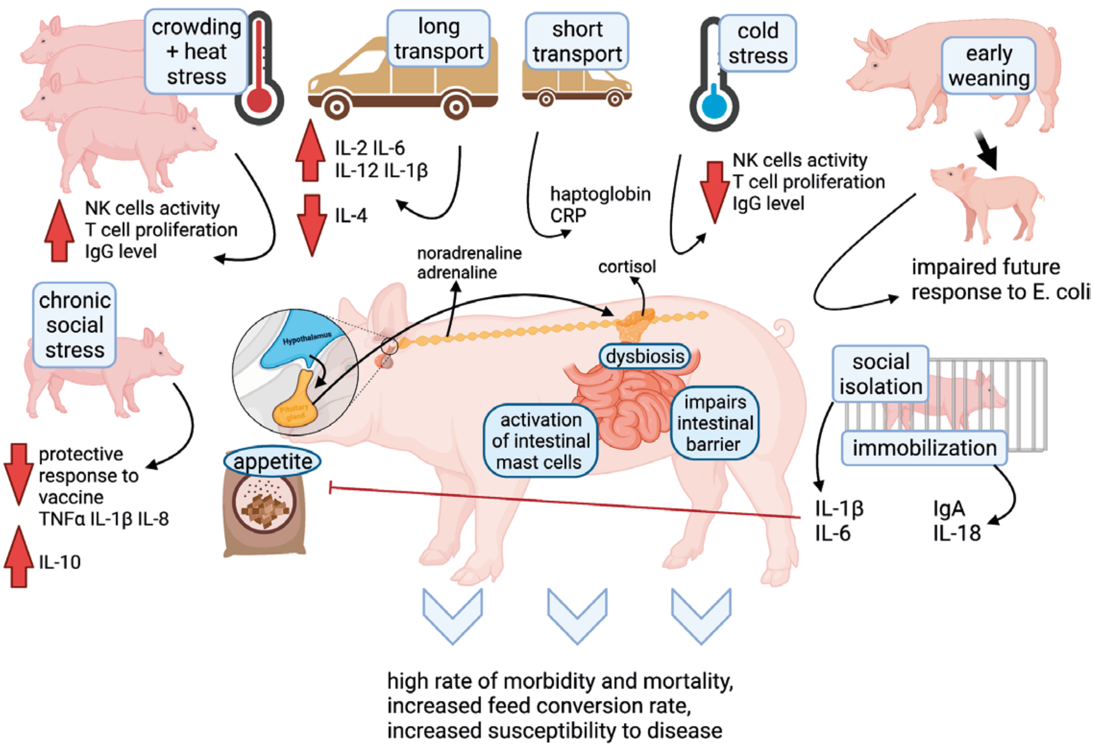

Fig. 1. Impact of stress on swine immune response and health

In addition to influencing the functioning of IS, mediators of immune response also affect several other important functions of the body. They change the way nutrients are used and increase the synthesis of proteins involved in immunological processes. This comes at the expense of using nutrients for several other important bodily functions, and cause change of nutrients use from anabolic to catabolic. It can be argued that cytokines antagonize production processes. This happens, among others, by changing the animal's metabolic priorities towards supporting IS efficiency at the expense of other vital functions.

In conclusion, it can be said that all actions aimed at minimizing the exposure of pigs to stress, limiting the survival and multiplication of pathogenic and conditionally pathogenic microorganisms, as well as improved management, can significantly enhance the functioning of IS and, consequently, reduce the costs of pig production by improving the feed conversion of animals and reducing treatment costs.

There is no doubt that long-term stress, including that related to management errors, has a negative impact on the functioning of the IS of animals. It thus increases the likelihood of symptomatic and asymptomatic infections with microorganisms living in the environment, which have a negative impact on production.

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Corresponding author: Siemińska Izabela DVM, MSc, Institute of Veterinary Sciences, University Center of Veterinary Medicine JU-UA, University of Agriculture in Kraków, 30-059 Kraków, Poland; e-mail: izabela.sieminska@urk.edu.pl