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Strengthening the Impact of Immune Regulation in Domestic Animals

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Abstract

Animal farming has been affected by a number of factors including national and international restrictions based on their guidelines and regulations, disease outbreak, welfare issues, balance between demand and supply of the meats and animals together with their by-products or processed-products, and economic and cultural demand. The global population increases coincident with an enhancement of living standards in developing countries, which is likely to create a high demand for animal-derived proteins over time. With that in mind, we are under great pressure and constantly facing a challenge in relation with the issues including climate change (i.e., global warming), banning on the use of antibiotics as a feed additive concordant with disease outbreak for both domestic animals (African swine fever, avian influenza, foot-and-mouse disease) and humans (corona pandemic for instance). Yet, high productivity together with high quality meat from the animal would be the most desirable for producers and animal farming industry. Thus, it is fair to say that current animal farming is under various psychological and physical stressful conditions, which can be categorized into nutritional factors, environmental factors, biological factors and physical factors. Basic, however essential, components of immune system include the recognition of self and non-self, and its remarkable specificity for subtle chemical differences that distinguish one foreign pathogen from another. Domestic animal immunology is seemingly important as we could find answers to the convoluted questions such as finding suitable antibiotic replacements, immunomodulants and vaccines with appropriate adjuvants. In this mini-review, we attempt to categorize aforementioned questions and to provide a direction towards our future of the animal science and biotechnology.

Introduction

Factory livestock systems require not only fast-growing bit also high-yielding animals. Factory farming achieved this with the use of high concentrated feed. This often puts animals at risk of developing painful physiologic problems. Lameness, bone weakness or fractures, infections, and organ failure are common health problems observed in factory livestock. By taking the action against aforementioned problematic factory farming, we are in need of a food and farming revolution, and at the same time we should support to stop an inhumane way of producing food that leads to the cruel abuse of animals.

Behavioral and physiological stresses can prevent animals from achieving normal reproductive success. Stressors associated with intensive livestock management may be responsible for reduced reproductive efficiency. It has been reported that several physiological and biochemical changes that accompany or follow stress in animals, but the obtained responses are various. Parameters used to evaluate stress or welfare are commonly based on sympatho-adrenal measures such as heart rate (Cook and Jacobson, 1996), plasma hormones and metabolites (Bobek *et al.*, 1986) and immune indicators (Agnes *et al.*, 1990). Moreover, factors directly or indirectly affect such action include national and international restrictions based on their guidelines and regulations, disease outbreak, welfare issues, balance between demand and supply of the meats and animals together with their by-products or processed-products, and economic and cultural demand. As

aforementioned, it would be ideal and more ethical to remove or modify the stressors to minimize their outcome rather than to employ drugs to reduce physiological and biochemical aspects of various types of stress in animals (Narayan and Parisella, 2017). The present article attempts to introduce the current and future prospects of the strategies against various stressful stimuli, mainly in domestic animals with recent development.

Challenges in domestic animal industry

Demand for meat is expected to be increased over time together with expanding population, and yet it will be extremely difficult to meet the demand of meat consumption with current platforms and technology. Thus, one of the main goals shall be minimizing stressful conditions together with preventing disease outbreak in animal farming industry.

Environmental factors

The livestock sector is socially, culturally and politically very relevant and signified. It accounts for 40% of the world's agriculture Gross Domestic Product (GDP). It employs 1.3 billion people, and creates livelihoods for one billion of the world's population living in poverty. Climate change including global warming and rearing conditions is seen as a major threat to the survival of many species, and to ecosystems and the financial sustainability of livestock production systems in many parts of the world (Sejian *et al.*, 2018; Summer *et al.*, 2019; Lee *et al.*, 2020). Obviously, the potential problems are even greater in developing countries. Economic studies suggest severe losses if current management systems are not modified to reflect the shift in climate. In short, farmers/ managers need to adapt to the changes accordingly in a short period of time (Moeser *et al.*, 2017; Wickramasuriya *et al.*, 2020). There has been considerable interest in gaining an understanding how domestic livestock respond to climatic stressors. It is somewhat unfortunate that studies have for the most part been undertaken in developed countries. Many studies have provided a wealth of knowledge on the effects of the impact of climatic stress on animal production, reproduction and health.

Antibiotics

We should properly understand the precise role and mechanism of antibiotics and how they were acting as an animal growth promoter (AGP) at the first place. The evidence available in the literature speaks volumes on the beneficial effects obtained from antibiotics used as a feed additive. Antibiotics have beneficial effects on promoting growth of the animals and preventing the disease. With the development of the intensive animal husbandry and formula-based feed industry, antibiotics were widely used around the world. However, instead of being assimilated by animal guts, a high percentage of antibiotics were excreted out as prototypes or metabolites with urine and feces. The volume of antibiotics used for growth promotion in livestock outstrips that used for disease treatment in humans and creates a significant selection pressure for the evolution of antibiotic resistance; a challenge for global health and resource conservation.

The cause of this problem is not just the use of antibiotics to treat the disease. Livestock farmers mix antibiotics into feed to encourage livestock growth and to prevent (although this may not what is happening truly) illness in packed barns and farms. Three-quarters of all antibiotics produced in the world could be used for this purpose (Sejian *et al*., 2018). The use of those antibiotics is very different from that for humans. In humans, the purpose of medication is to treat infections, not preventive ones. This indiscriminate use of antibiotics has been around since the early days of antibiotics and has often been criticized since then. Every time an antibiotic is given, the microbial community is modified as microbiota mutates for self-defense against it (Cromwell, 2002; Hughes and Heritage, 2002). To make matters worse, some of the bacteria in animals are the same as those that cause human pathogenesis, such as Salmonella, Campylobacter, and *Escherichia coli*. Drugs that have become ineffective on the farm often cannot be used to treat humans once the resistance of the particular antibiotics are developed. However, proponents of using antibiotics in animal feed as growth promoters are unsure about the potential to exacerbate antibiotic resistance problems (Wallinga and Burch, 2013; Chattopadhyay, 2014). The adverse effects of inflammation and pro-inflammatory mediators in animals (e.g., reduction in growth, feed intake, reproduction, milk production, and metabolic side effects) are well-known. The anti-inflammatory potential of antibiotics (particularly macrolides) provides a rational basis of their beneficial effects which is independent of their antimicrobial effect (Chattopadhyay, 2014). Hence, there is no doubt about the important role of antibiotics in profitable and efficient production of livestock. AGPs also act directly on host cells and exert anti-inflammatory effects on host physiology including intestinal epithelial cell and gut immune cells. Thinner gut wall and increase of digestive enzyme activities are seen in animals treated with AGPs. The action mode of mechanism of AGP is (1) attenuating the virulence properties of bacteria, (2) beneficial effects to host metabolism, and (3) induction of an anti-inflammatory response in the host.

Disease outbreak

Pigs provide an important source of high-quality protein and production is predicted to increase in future to meet growing global demands for its consumption. However, the supply of pork is threatened by infectious diseases, and amongst African swine fever (ASF) is currently causing greatest concern (Alexander, 2007; Ramos *et al.*, 2017; Dixon *et al.*, 2019; Yun, 2020). ASF has already spread to Southeast Asia and European countries, and cases have been reported in Vietnam, Cambodia, Laos, South Korea, Japan, Myanmar, the Philippines, Poland, Belgium and Bulgaria. In China, which consumes by far the most pork in the world, the impact of such disease is devastating. China lost up to 55% of the pigs it raised during the year 2019. The reality is that pork-producing countries can lose billions of dollars if the disease spreads domestically. The infection destroys the life of livestock farmers and closes the export market. Although ASF is not a threat to humans, there are no vaccines or cures for the disease. Up-to-date information on ASF outbreaks in domestic pigs and cases in wild boar is available on the OIE World Animal Health Information System. This includes daily information on new disease outbreaks, follow-up reports and interactive disease distribution maps for specified time periods are also available.

Immunomodulators

Immunomodulators are medications used to help regulate or normalize the immune system in animals and humans. Lactobacilli, in addition to their role in the development and regulation of immune responses, can effectively enhance antiviral functions in macrophages against avian influenza virus (Shojadoost *et al.*, 2019). The mechanisms of these interactions include enhancement of nitric oxide production, up-regulation of cytokines and immunostimulatory factors, and increased surface expression of co-stimulatory molecules for T cell activation. In-feed *Enterococcus faecium* NCIMB 10415 probiotic increased the production of Salmonella-specific mucosal IgA following immunization with an attenuated *Salmonella enteritidis* vaccine (Beirao *et al.*, 2018). Modulation of the intestinal microbiome is one of the major immune effects; the overall changes in the profile of the microbiome in the "Vaccine+probiotic" group are compatible with reported improvements in live vaccine immunogenicity.

Probiotics have a great potential in effective management for health of ruminant as well. Although feed with probiotics does not affect the growth and meat production directly, it is effective in reducing stress. Several studies have shown that the microbial community in ruminant gastro-intestinal tract (GIT) can be changed by a variety of factors such as diet, probiotics, age, and stress. *In vivo* and *in vitro* studies of the dynamic and functional effects initiated by probiotic therapy can greatly enrich our understanding on when and how these treatments can benefit ruminants. Key areas of future research are to describe the structure and interactions of the intestinal microbiota, and the functional relationship between the microbial community of the intestinal mucosa and host cells. The "metaomics" approach has been used to investigate the dynamic relationship between the GIT microbial community and host metabolism. Such strategy would further identify a key set of to-be-well-defined microbial species for improving health during especially the early development in ruminants.

The GIT microbial diversity and community together with the epithelium is related with the host mucosal innate immune function (Li *et al.*, 2020). A study that focuses on the interaction between mucosal microbial communities and host ruminal epitheliums in particular will facilitate identification of key genes that are important for host immune homeostasis. Ideally, target gene editing technology can be applied to manipulate the genetic composition of entire microbial populations to potentially enable optimal host health and productivity.

Conclusion

Applying the strategy using probiotics and immunomodulators in the host in association with microbial community in domestic animals, often complicated balance is observed between the host immune response and the early colonization of potentially feeding. In addition, considering innate and trained immunity we might be able to find a way to design a set of core microbes with accelerated colonization during the early and crucial time of the animals' life.

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