Applied immunology and the effects of stress on the immune system

Victor S. Cortese, DVM, PhD, Dipl ABVP (Dairy)
Director, Cattle-Equine Immunology, Zoetis, Inc., 746 Veechdale Road, Simpsonville, KY 40067; vetvic@aol.com

Introduction

The immune system is the focus of intense current research in both veterinary and human medicine. This research encompasses such diverse areas as cancer treatments and AIDS vaccines. Many of the advances in future treatments of diseases are already coming from chemicals derived from the immune system. With increased pressure on drug residues, these products will continue to flourish.

There are some important concepts to consider when making these decisions. These concepts often change as we look at the different organisms that can attack the cow. Different diseases are handled differently by the immune system. The life cycle of the organism will also determine what parts of the immune system are important for protection.

What does immunity really mean? For all practical purposes, if a cow is healthy and is exposed to a disease agent, the animal rids the organism with minimal disruption of body functions. The immune system often moderates disease rather than preventing infection.

Factors Affecting the Immune Response

Stress

1. Stress is defined by Webster as a state in which a strong demand is made on the nervous system. It is further clarified as any factor; environmental, physical or psychological event that creates a disharmony in the body.[2] In domestic animals, many different stresses have been identified and they fit into all 3 categories listed above. Common stresses that have been studied include: temperature, overcrowding, transport, surgery, weaning, parturition, noise, social stresses, and poor nutrition.[19,33] Stress effects are seen in all animals, including insects. These stresses can be made more severe by stress modifiers. These modifiers include stress severity, duration, novelty, host genetics, immune status, and nutritional status.[10]

Studies on the effect of stress on the immune system of animals have been most intense in laboratory animals because of the ease of handling and genetics available, and in livestock because they often undergo multiple stresses. Furthermore, a large number of animals can be impacted by stresses, often with severe economic consequences. However, studies on the actual effectors of stress on the immune system have been limited somewhat to laboratory animals. Neuroimmunology focuses on the interaction between the nervous system and the immune system; these links are most noticeable under stress conditions.

Stress and its effects on the immune system are often integrally related in disease conditions. The doctrine of multiple causation is based on the fact that most infectious diseases develop due to an interaction of host, environment, and the microbe.[16] Stress is interrelated to both host factors and the environment.

Stress and Its Impact on the Body

Stress mechanisms were initially thought to be via a single pathway described by Seyle and others as the General Adaptation Syndrome. It is now felt that stress exerts its effects via 4 different and interrelated pathways, although all of the pathways are not yet fully defined. These 4 are:

1. Autonomic nervous system - Stress affects the autonomic nervous system in several different methods and increases the responses of this system to other stress pathways. The autonomic nervous system is primarily mediated through stimulation of the sympathetic nervous system and depression of the parasympathetic nervous system. It is through a system of neural connections in the brain stem that this stimulation .occurs. It is often mediated through the neurotransmitting/neuromodulating effect of corticotropin releasing factor (CRF).[5] The area of the brainstem most sensitive to CRF is the sympathetic region called the locus coerulues, where 50% of the sympathetic brain neurons are located. Norepinephrine is then released by the sympathetic immune system. These sympathetic nervous system responses are due to both chemical stimulation as well as direct innervation. Sympathetic stimulation causes increased heart and respiratory rates, redirection of oxygen and nutrient flow, down regulation of non-essential functions for survival, and direct effects on primary and secondary immune lymphoid tissue.[1] This is the pathway described by the general adaptation syndrome.
2. The hypothalamic-pituitary-adrenal axis (HPA) - A second response to CRF release is the effect on the pituitary gland and subsequent release of adrenocorticotropin hormone (ACTH). ACTH is actually a cleavage product of the polyprotein proopiomelanocortin, which is released from CRF-stimulated basophilic cells of the anterior pituitary. ACTH exerts

its primary effect on the adrenal gland, causing a release of corticosteroids. Corticosteroids regulate metabolism of the various nutrients. In stress situations where they are elevated above normal, their primary function is to mobilize energy stores for use by the muscles. Corticosteroids are also potent immunosupressors, and are often blamed for the suppression of the immune system in stressed animals. They are commonly measured to determine both the stress level and duration of stress on an animal.[32] The HPA can be stimulated by different stresses as well as toxins.[30]

3. Extradrenal pathways involving neurotransmitters and neuropeptides. There are many other chemicals involved in the stress responses besides chemicals released by the sympathetic nervous system and the HPA. One of these chemicals is the remaining cleavage product of proopiomelanocortin called β endorphin, a potent member of the opiate family. Enkephalins, other members of the opiate family, are released along with the catecholamines (primarily epinephrine) by splanchnic nerve stimulation of the adrenal medulla during stress. Epinephrine works in concert with norepinephrine for effects listed above. Opiates are strong analgesics and are also known to be immunosuppressive. Serotonin and dopamine are also increased during stress. These neurotransmitters increase stimulation of the HPA axis. There are several other chemicals under research. They are elevated during stress, but their exact function and impact on the body are not well defined.
4. Neuroimmunologic mediators (several cytokines) - Many chemicals released by the immune system (both cytokines and lymphokines) are known to have direct effects on the brain and are increasingly important during times of stress. Some of these chemicals mimic other chemicals of the stress response and are responsible for eliciting a stress response during viral infection. These include immunoreactive ACTH, a hormone released by immune cells that can stimulate the same pathways as pituitary-derived ACTH and endorphins. Stimulated immune cells may also secrete small amounts of other neuropeptides and transmitters, as well as CRF. The hypothalamus includes neurons that have receptors for some of the cytokines, including the interleukins 1 and 6 and tumor necrosis factor α. Other lymphokines also have the ability to stimulate the HPA via CRF production. Most of the actions of these cytokines on the brain serve to down regulate the immune system. However, 1 side effect of IL-1 is the increase in body temperature seen in infections. At this elevated temperature the cells of the immune system are more active, and this may be 1 of the few immunoenhancing activities of the cytokine/hypothalamus interaction. Since there are many interactions between the immune system, hypothalamus, and endocrine system, it has been proposed that another axis be defined in infection and stress called the hypothalamic-endocrine-immune-axis.[5]

Stress and Its Impact on Immune Responses

The impact of stress has been studied in most domestic animals as well as laboratory animals, insects, fish, and plants. The general consensus is that stress in all species is immunosuppressive, both in vivo and in vitro. The effects on the immune system have been well documented and may be caused by individual stress outcomes (i.e., corticosteroids) or complex interactions that lead to the immune suppression (sympathetic nervous system up regulation). The following are well documented effects of stress on the immune system:

1. Phagocytic cells.
   a. Neutrophil numbers will initially increase in stress situations due to a decrease in the marginated pool of neutrophils, increased influx from the bone marrow, and less movement of neutrophils from the circulation to tissues.[8] There is no increase in immature (bands) neutrophils, so there is no bone marrow stimulation of increased production by steroids or stress. It is believed that this is primarily a corticosteroid-mediated phenomena. However, this increased number does not increase function. Steers given a dose of ACTH showed increased random migration of neutrophils and decreased iodination, both signs of neutrophil dysfunction. In 1 study, there was no decrease in antibody-dependent, cell-mediated cytotoxicity (ADCC) or *Staph aureus* ingestion.[26] Another study did find depression of most neutrophil functions, including ADCC, bacterial ingestion, oxidative metabolism, and the myeloperoxidase antibacterial system following a single dose of dexamethasone.[25] Stress will also decrease neutrophil attraction to sites of inflammation.
   b. Monocytes have had little study in stress reactions. There is a decreased attraction of monocytes to the site of inflammation. It now appears that the monocyte is responsible for the random migration effect caused by stress on neutrophils. Corticosteroids will cause monocytes to release a neutrophil migration stimulating factor.[28,29] Cytokine production (IL-1 and tumor necrosis factor α) is decreased in stress situations, and monocyte/macrophage phagocytic and bactericidal activity is decreased[11] due to decreased interferon γ production. Expression of class 2 genes of the major histocompatability complex is also inhibited.

2. Lymphocytes are also dramatically affected by stress. Animal species are often determined to be relatively glucocorticoid sensitive or resistant on the basis of effects of steroids on lymphocyte counts. In glucocorticoid-resistant animals (man, cattle, monkey, guinea pig), either no or transient mild lymphopenia is seen after steroid administration. In corticosteroid-sensitive animals (hamster, mouse, rat, rabbit), there is a marked lymphopenia due to cell death after steroid administration.[23] Function as well as numbers of lymphocytes are impacted by stress. As shown above, the HPA axis is only 1 of 4 pathways that stress utilizes so function decreases are seen in all species, although it is more pronouced in steroid-sensitive species. It is now generally believed that stress will cause decreased lymphocyte blastogenesis responses, both to PMA and ConA (T cell specific), as well as PWM (T and B cells).[3,8] Both decreased interleukin 2 secretion and increased serotonin are involved in the depressed blastogenesis. ACTH has been shown to decrease antibody responses to both T cell-dependent and independent antigen.[13] It is not clear whether this is due to decreased B cell blastogenesis or actual depression of antibody production, it is probably a suppression of both.
3. Complement levels and activation are inhibited by stress and/or elevated glucocorticosteroids both in vivo[24] and in vitro,[22] particularly in corticosteroid-sensitive species.

Stress and Disease

Even though there are dramatic differences in species sensitivity to glucocorticosteroids, stress still causes depression of the major components of the immune system. It is no surprise that stress is associated with both increased incidence and severity of disease.[9] One of the best examples of stress-associated diseases is the "shipping fever complex" in cattle.[12] Although the causative agents of the pneumonia may be different there is usually an underlying stress,[15] and a stress-induced immunosupression was proposed in 1957. Since then, stress and/or steroid administration has been shown to be detrimental to host defenses against many infectious and non-infectious diseases. In cattle for example, studies have been done showing that many different infectious agents including viruses, bacteria, protozoa, and coccidia. Herpesvirus recrudescence in latently infected animals and increased in vitro replication is seen in many species following stress.[4,27] *Anaplasma* and *babesia parasitemias* are more severe during stress.[7,17] Subclinical coccidia infections are exacerbated and acute disease is seen with steroid treatment.[19] Stress has also been associated with a myriad of diseases in humans including inflammatory bowel disease,[31] ulcers, diabetes,[18] cancer,[14] and depression.[2] This is but a small sample of the many diseases either associated with or exacerbated by stress. It is obvious from the multitude of studies that stress-induced immunosuppression is clinically important.

Nutritional Stress

An area getting a lot of research now is the effect of microminerals on the immune system. Deficiencies in microminerals not only affect the immune system by not allowing it to respond properly to a challenge of vaccination,[6,20,21] but also may increase the likelihood of reactions to vaccines. The primary microminerals involved are copper, iron, zinc, and selenium. We also see vitamin E involved in this scenario. Vitamin A deficiencies will also be found, particularly in herds with high corn silage diets.

- **Copper** is involved in correct function of the phagocytic cells and in vitro decreased lymphocyte proliferation and cytotoxic T cell activity. It is also involved in protecting cells from super oxide radicals.
- **Iron** is required for the normal development of lymphoid tissue and for phagocytosis to occur.
- **Zinc** deficiencies will impair all components of the immune system, particularly CMI.
- **Selenium** is involved in nonspecific and humoral immune responses, and is also involved in protecting cells from oxidative damage.
- **Vitamin A** affects all components of the immune system, including the innate system.
- **Vitamin E** is important in all components of the immune system, and in protecting animals from oxidative damage. Leukocytes contain 10 to 35 times more alpha-tocopherol than do red blood cells or platelets.

The impact of stress on the body involves many systems. This paper focused on the pathways and effects of stress on the immune system. There are also dramatic effects on other body systems and functions as well. Impacts on nutrition, metabolism, cardiovascular, and nervous system functions are all affected by stress.

As we learn more about the pathways and interactions of stress on immunity and disease, the possibility of intervention takes on new meaning. In livestock medicine, many principles of stress reduction and awareness of stressful activity are already utilized. For example, vaccination programs are often planned to avoid stress periods in the management practices of the facility.

The possibilities of both chemical intervention as well as stress evaluation and management in both humans and animals gives another avenue for disease interaction/causation studies, disease treatment, and prevention in the future.

Conclusions

The immune system is a complex and interrelated system. Vaccination does nothing more than trying to trick

the immune system into responding as if that disease had attacked it. The closer a vaccine is to the natural wild virus, the stronger the immune response will be, but also there is greater chance of causing disease. Vaccines that completely stimulate all aspects of the immune system should be selected.

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