International Journal of Veterinary Health Science & Research (IJVHSR)
ISSN 2332-2748

HDFx: A Novel Immunomodulator and Potential Fighter Against Cytokine Storms in Inflammatory and Septic Conditions in Dogs and Farm Animals

Editorial

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Over the past decade, a disturbing trend in antimicrobial resistance of both gram-negative and gram-positive "superbugs" in addition to fungal "superbugs" has seriously complicated the treatment of not only immune-compromised patients but dogs and farm animals (e.g., cattle, pigs, horses, etc) as well [1-8]. To this, must be added the numerous hospitalizations and veterinary visits caused by contaminated meats, poultry, vegetables, seafoods, and multiple types of animal feeds [9-12]. Government resources, worldwide, are being stretched-thin and often remain powerless to combat these assaults to our patients, dogs and farm animals. By about 2075, the number of people dying from drug-resistant infections and diseases could reach in excess of 35 million while the deaths in the pet and farm animal populations could be expected to far exceed this number. Added to this is the ever-growing and soaring worldwide use of antibiotics in agriculture. How much of this indiscriminate use of antibiotics is contributing to the ever - growing resistance of pathogens to antibiotics noted above?.

A major problem associated with infectious microorganisms and fungi is the underlying production of "cytokine storms (CS)" which often result in very severe illness and death. The major factors producing these CS usually are tissue trauma, burns, and blood loss which cause extensive tissue damage of large numbers of cells of diverse types, particularly those of the innate and adaptive immune systems. But, it should be kept in mind that multiple virus infections, such as dengue, hanta viruses, diverse hemorrhagic fever viruses, and influenza viruses can also trigger massive cell destruction, resulting in extensive cytokine release and death [13, 14].

Septic shock caused by severe bacterial infections accounts for about 10% of all human deaths in the U.S.A., alone, each year, and is a major cause of farm animal deaths each year. These severe bacterial infections in both humans and animals are associated with characteristic signs such as fevers, myalgias, rigor, depression, and nausea, resulting from release of cytokines. Major cytokines involved in these septic-inflammatory states are TNF-alpha, IL-1beta, IFN-gamma, IL-6, and IL-8 among others, as well as several macrophage factors. These cytokines and chemokines when released then go-on to cause increases in nitric oxide synthases, leading to nitric oxide and COX-2 which then result in release of diverse tissue-damaging prostanoids and leukotrienes, production of severe acidosis, fever, tissue lactate release, uncontrollable falls in arterial blood pressure, elevations in plasma histamine, serotonin, kinins and catecholamines, eventuating in multiple organ failure (particularly of the kidneys, lungs, and heart). This sequelae of events prior to death usually causes intravascular coagulation and vast increases in capillary permeability leading to extensive fluid loss [15, 16]. The predilection of various animals to sepsis varies greatly [15]. Those species with pulmonary intravascular macrophages (i.e., cats, horses, sheep, and pigs) are more susceptible than dogs which lack pulmonary intravascular macrophages and are much less susceptible to lung injuries [15].

Our laboratories have been working on a brand-new approach to develop host-defense factors that stimulate various arms of the innate and adaptive immune systems. To this end, we have discovered a new host-defense factor, termed "HDFx", that is a conserved 35-40 kD protein found in mice, rats, gunea-pigs, rabbits, dogs, cats, piglets, and sub-human primates [16-22]. We assume it is also present in humans and farm animals such as sheep, cattle, pigs, and horses, particularly since it is a conserved molecule. More than 135 years ago, Elie Metchnikoff, the great father of immunology, hypothesized that the body, under stressful circumstances, might produce powerful immunostimulants which perforce would act on different arms of the innate immune system and serve to protect

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Received: May 10, 2017
Published: May 18, 2017

Citation: Altura BM, Gebrewold A, Carella A, Altura BT (2017) HDFx: A Novel Immunomodulator and Potential Fighter Against Cytokine Storms in Inflammatory and Septic Conditions in Dogs and Farm Animals. *Int J Vet Health Sci Res.* 5(2e), 1-3. **doi:** http://dx.doi.org/10.19070/2332-2748-170006e

against major insults, inflammatory conditions, and diseases [23]. Metchnikoff's early studies pointed to the important contributions of macrophages and phagocytic leukocytes to natural (innate) resistance against pathogenic bacteria and viruses. Over the past 40 years, considerable evidence has accumulated to support a strong relationship between the functional (physiological) state of the microcirculation, macrophages-phagocytes, natural killer (NK) cells, the reticuloendothelial system, and "pit cells" in the liver to host defense and resistance to pathogens, trauma, sepsis, wounding, circulatory shock, and combined injuries [4, 5, 24-31].

Recent studies from our laboratories have clearly shown that HDFx is protective (to different degrees) against a variety of systemic insults ranging from hemorrhage, trauma, endotoxins, a variety of bacteria (e.g., *E. coli, S. enteriditis, C. wechii, among others*), combined injuries, and centripetal forces to septic shock [16-22]. A unique attribute of HDFx is that it can accelerate wound healing [21]. Most importantly, HDFx has been demonstrated in several animal models to inhibit the release of multiple cytokines and chemokines, including TNF-alpha, IL-6. IL-8, Il-1beta, IFN-gamma, numerous and macrophage factors [18-22]. In other terms, HDFx clearly either prevents or ameliorates the intensity of "cytokine storms" induced by both gram-negative and gram-positive bacteria, toxic fungal microorganisms, trauma, systemic inflammatory conditions, tissue damage, blood loss, and sepsis, among other dangerous insults [[16-22], unpublished findings]. HDFx also has protective qualities even in diseases such as nonalcoholic steatohepatitis (NASH) which often results in liver carcinomas [20]. We have also produced preliminary data to suggest that HDFx might be useful in the treatment and amelioration of hemorrhagic fevers [22].

Gram-negative "superbugs" seem to be the major culprits in many hospitalized patients, very sick dogs, and a variety of sickly farm animals. Gram-negative bacteria appear to be more difficult to kill than gram-positive bacteria because they are protected by "double membranes". So, in order to kill the gram-negative bacteria, most of the approaches have been to design antibiotics to penetrate these membrane barriers. In our opinion, another likely approach would be to engulf the bacteria and digest them within "supercharged" macrophages, Kupffer cells, phagocytic leukocytes, platelets, "pit cells" and NK cells. HDFx appears, at least experimentally, to induce a "supercharged effect" in these various cell types in all animals we have investigated to date. But, for this to occur, in an expeditious manner, we believe the microcirculation to key organs and tissues must perforce produce optimal capillary blood flows and distribution. Therefore, an ideal drug or therapeutic molecule would be one that could stimulate multiple arms of the innate immune system coupled to modulation of microcirculatory blood flows to the aforementioned key organ and tissue systems. So far, of all molecules, we have investigated, HDFx appears to be the only molecule that embodies all these qualities and demonstrates therapeutic attributes against several classes of "superbugs" [16-22].

We, thus, believe that the approaches outlined in the above, using HDFx or its derivatives, could be the ideal drug (s) to pretreat all patients scheduled for major surgeries as well as all cats, dogs and farm animals to prevent a variety of infections and assaults from "superbugs".

A major objective of our group is to secure adequate funding to elucidate the complete, complex molecular structure of HDFX and then via genetic engineering to produce large quantities of HDFx for further testing in human subjects and farm animals under diverse pathophysiological conditions, including infections induced by "superbugs".

Acknowledgements

Some of the original studies and thoughts needed for the discovery of HDFx and reviewed, above, were initiated while the first author was at New York University School of Medicine and The Albert Einstein College of Medicine of Yeshiva University. Some of the original studies reviewed, above, were supported, in part, by unrestricted research grants from several pharmaceutical companies (CIBA-GEIGY Pharmaceuticals, The UpJohn Company, Sandoz Pharmaceuticals, and Bayer Pharmaceuticals) and anonymous donors. The authors are indebted to many colleagues, over many years, who helped to make our studies and background experiments possible: C.Thaw, E.W. Burton, J. Hanley, and C. Parillo. The authors are also grateful to Dr. Solomon G. Hershey (deceased) who suggested several animal models to us.

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