

HDFX: A Stress-induced Biologic that Inhibits and Reverses Endotoxin-induced Fevers and Depression in Cardiac Hemodynamics in Rabbits, Guinea-pigs and Rats: Potential Relevance to Corona Viral Fevers and Role of NF-Kb

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ABSTRACT

Our laboratories, for almost 55 years, have been working on novel approaches to develop host defense molecules which can stimulate the innate and adaptive immune systems. Over this period of time, to the present, we discovered HDFX.

Keywords: *Endotoxin; Fevers; Depression; Cardiac hemodynamics; Corona viral fever*

DISCOVERY AND UNIQUE PHYSIOLOGICAL PROPERTIES OF HDFX

We have found HDFX to exist not only in rodents, farm animals, and piglets but in cats, dogs, monkeys and baboons as well unpublished findings. Approximately 135 years ago, the Nobelist and father of immunology, Elie hypothesized that the body under stressful circumstances would produce powerful immunological stimulants which could act on different arms of the immune system and serve to protect the host against major, dangerous injurious insults, inflammatory conditions, severe wounding, and various diseases. Earlier studies pointed to the important contributions of macrophages and phagocytic leukocytes to natural, innate resistance against pathological micro-organisms. Over the past 65 years, considerable evidence has been brought forth to substantiate a strong relationship between the functional (physiologic) state of the microcirculation, macrophages, phagocytic leukocytes, Natural Killer (NK) cells, the Reticuloendothelial System (RES) and "pit cells" in the liver to host defense and resistance to hemorrhage, trauma, burns, circulatory shock, combined injuries and pathogenic micro-organisms (i.e., bacteria, fungi, viruses, and rickettsia). Using Oetchniko hypothesis, we posited all of these deadly bodily insults, including endotoxins, should produce protective factors (i.e., host-defense molecules) in all surviving animals. Indeed, as predicted, we found at least one such powerful immunostimulant we termed HDFX. His novel stress protein, HDFX, protects (to different degrees), so far, against experimental lethal hemorrhage, fungal micro-organisms (*Candida*, *Aspergillus*), combined injuries (e.g., hemorrhage

plus trauma), centripetal forces, sublethal body trauma, sublethal burns, NASH, and bacterial endotoxins. A unique attribute of HDFX is the ability to accelerate wound healing. Most importantly, it has been shown to inhibit release of cytokines and chemokines, including tumor necrosis factor (TNF α), IL-1 beta, IL-6, IL-8, IFN-gamma, and numerous macrophage factors unpublished findings. Thus, HDFX has the ability to modulate "cytokine storms" [1,2].

ENDOTOXIN-INDUCED FEVERS, THEIR ATTENUATION WITH HDFX AND ROLES OF MACROPHAGES

Using Wistar strain male rats, male guinea-pigs, and New Zealand male rabbits, we have found that daily systemic injections (seven days, once/day), of crude extracts of purified HDFX, dramatically attenuated the rises in rat colonic temperatures (to 38.4-39.5°C), induced by two different LPS (i.e., *E. Coli*; *S. enteritidis*) towards normality (37.6-37.8°C). In other experiments, three systemic injections (one every eight hours) of HDFX, reduced the high body temperatures (i.e., 39-40°C) induced by two different LPS (i.e., *E. coli*; *S. Enteritidis*). Similar findings were found in the guinea-pig and rabbit. Approximately 10 years ago, we found that when macrophages and NK cells were depleted in rats, using a number of chemical agents, there was a marked reduction in the generation of HDFX produced either by endotoxins or hemorrhage, unpublished findings. Using this macrophage and NK cell depletion technique, in rats, we found that minute injections of LPs pyrogens, which normally did not affect blood pressure, cardiac hemodynamics, or body temperature, would

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now increase the lowering of arterial blood pressure and induce fever, From these experiments, we must conclude that since HDFX prevents/reverses endotoxin-induced rises in body temperature, at least in rodents, probably due to its ability to inhibit release of cytokines from T-lymphocytes (thus inhibiting “cytokine storms), HDFX may be an innate regulator of body temperature. A number of previous investigations have clearly demonstrated that systemic administration of endotoxins to rodents usually results in a number of physiologic alterations within 3-20 hours, depending upon dose of endotoxin and batch, strain of the animal, and its sex. These alterations in cardiac hemodynamics, including reductions in coronary blood flows, reduction in LV pressures, reductions in cardiac contractility, and stroke volume were all either attenuated or abolished by seven days of HDFX pretreatment [3-5].

IMPORTANCE OF NF-KB SIGNALING IN ENDOTOXIN-INDUCED FEVERS AND CARDIAC DYSFUNCTIONS AND THEIR INHIBITION BY HDFX: RELEVANCE TO CORONAVIRAL LUNG PATHOLOGY

SARS-and MERs-induced lung pathologies have been found to depend upon activation of NF-kB signaling. NF-kB signaling is vital for numerous lung responses, including stress, cytokine signaling, responses to bacteria and endotoxins, apoptosis, and tissue and cell responses to viral infections. NF-kB signaling leads to cytokine signaling (i.e., cytokine storms) and inflammatory responses in the lung tissues and cells. Experiments have previously demonstrated that chemical inhibitors of NF-kB signaling reduce lung pathology and inflammatory response induced by SARS and MERS in lab animals. We have found that chemical inhibitors of NF-kB, and extracts of HDFX, reduced lung inflammations, cytokine storms, lung pathology, and cardiac hemodynamic dysfunctions induced by endotoxins. Unique actions of HDFX on NF-kB most likely not only contribute to reduction in endotoxin-induced fevers, but prevention of fibrosis in the lungs. It is thus, probable that lung pathology induced by coronaviruses like COVID-19 would be markedly reduced by use of HDFX.

DISCUSSION AND CONCLUSION

Endotoxins derived from gram-negative bacteria are well-known to induce lung, cardiac, kidney, and liver pathologies, accompanied by high fevers, which eventuate in systemic sepsis followed by death. Coronaviruses, as is seen with numerous infectious viruses, also eventuate in sepsis, often caused by invasion of the lungs, kidneys, and liver) by gram-negative and gram-positive bacteria. All endotoxins raise core body temperature to very high levels. Unless these compounding temperatures can be lowered towards normal, within a reasonable period of time, death will follow. We have discovered a stress, conserved protein, HDFX. In every mammal so far

investigated, including subhuman primates. Using rats, guinea-pigs and rabbits, we have found that HDFX will either lower or ameliorate endotoxins induced elevated core body temperatures. In addition, release of cytokines, major molecules for endotoxin-induced with high temperatures are inhibited with administration of HDFX. Depletion of macrophages and NK cells in rodents causes very tiny doses of endotoxins to lower arterial blood pressures, compromise cardiac hemodynamics and raise body temperatures; these procedures result in marked reductions in generation and release of HDFX. Moreover, HDFX inhibits activation of endotoxin-induced temperature elevation in rats, guinea-pigs, and rabbits, probably by inhibition of macrophage and NK cell activation of NF-kB. We thus believe that HDFX may be a valuable prophylactic and therapeutic agent in the war against coronaviruses such as MERS, SARs and COVID-19.

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