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Pathogenesis of human suppression in hypercatabolic diseases: AIDS, septicaemia, toxic shock syndrome and protein calorie malnutrition

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Summary - The immune system's main function is the constant elimination of endogenous cell debris, and when necessary, the disposal of foreign structures. It seems appropriate, therefore, to complement the existing paradigm of "self and non-self" with the concept of "altered self". The concept of stress comprises a multitude of environmental assaults, all of which result in a displacement towards catabolic metabolism. This is based on the activation of the neuroendocrine stress axis hypothalamus-pituitary-adrenal glands, which results in increased production of catecholamines and glucocorticoids. The latter limit life-threatening acute phase reactions by means of the body's own inflammatory mediators. The purpose of displacing the cytokine profiles of CD4 lymphocytes from Th1 to Th2 is to enable them to take over temporarily the inflammation-inhibiting role of cortisol until normality is re-established. In autoimmune disease a permanent Th2 displacement is a sign of persistent hypercortisolism. Failure by cortisone to arrest inflammation due to severe stress, results in hypercatabolic diseases such as AIDS, septicaemia, toxic shock syndrome and protein calorie malnutrition (NAIDS). Preventing and treating AIDS and NAIDS entails, besides removing the causes of stress, activating mesenchymal production of anabolic matrix components, eg. glycosamineglycanes, and the neutralisation of O and NO radicals, as well as inflammatory mediators from overactivated macrophages, using polyanions and polyphenols as food supplements. Septicaemia and toxic shock syndrome are, in our opinion, best treated with speedy administration of high doses of intravenous gammaglobulins.

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Introduction

The immune system's main function is to maintain the genetically determined individuality of the human body. The body consists of about 1014 cells. Daily turnover of cells through mitosis and apoptosis is around 1012 cells.(1) The immune system has, first to eliminate endogenously arising cell debris, and secondly to eliminate exogenous, foreign matter. According to the current paradigm, the role of the immune system is restricted to eliminating foreign "non-self" structures, and it does not concern itself with the body's own "self-structures". In our opinion, we must enlarge the immune system's role to include the disposal of a constant stream of "altered self-structures." The disposal of exogenous "non-self" structures is to be regarded as a secondary function, called upon only when the need arises. The elimination of exogenous "non-self" structures is in the main the function of B-cells, derived from bone marrow and mucosa-associated Iymph tissue (MALT), which produce humoral antibodies.(2)

Cannon and Selye's concept of stress, which goes back to the 1930s, includes a variety of external assaults, all of which result in displacing cell metabolism towards catabolism. Several causes of stress must be distinguished: they can be psychic, toxic, infectious, traumatic or nutritional in origin, and the extent of metabolic displacement is determined by the sum of the contributing factors. Stress responses of limited duration are necessary, even vital, in special situations such as "fight or flight". Enduring stress responses, however, are destructive.(2)

A stress-induced catabolic displacement in metabolism depends on the activation of the neuroendocrine hypothalamus-pituitary-adrenal axis. The endocrine-induced metabolic displacement is linked to the sympathicotonic displacement of the vegetative nervous system. The heightened production of adrenaline by the adrenal gland, and noradrenaline by sympathicotonic nerve endings, has the effect of concentrating cell metabolism to provide quickly available energy supplies, ie. glucose, to ready muscles to fight or take flight. The function of glucocorticoids produced in the adrenal cortex is to limit the effect of life-threatening overactivation of the neuroendocrine stress axis. The increase in cortisol together with the corresponding decline in dihydroepiandrosterone (DHEA)

has the ongoing effect of suppressing T-cell dependent cellular immune responses. This is due to the counteracting activation of B-cell dependent humoral immune responses.(2)

Accounts by Mosmann and Coffman of the counteracting cytokine profiles of CD4 helper lymphocytes provide strong support for the described counteracting behaviour of the cellular and humoral immune responses.(3) They showed that CD4 helper cells could be differentiated into two groups, which they called Th1 and Th2. Th1 cells secrete mainly IL-2, IL-12 and IFN which stimulate cellular responses; Th-2 cells however, produce mainly IL-4, IL-6 and IL-10 which stimulate humoral immune responses. Research into the numerous functions of CD4 helper cells has expanded considerably in recent years; although their actual functions in anabolic and catabolic metabolic mechanisms remain poorly understood.(4,5) Surgery is an ideal means of studying short-term stress responses regarding the relative immune performance of T and B-cells. In 1953 in his classical work on the course of surgical stress reactions Moore described four phases following major surgery.(6)

Phase I adrenergic corticoid phase
Phase ll corticoid withdrawal phase
Phase lll spontaneous anabolic phase
Phase IV fat gain phase

The adrenergic-corticoid response

This corresponds to the acute phase response involving a neuroendocrine displacement towards sympathicotony, with production of adrenaline and noradrenaline, followed by hypercortisolism. The catabolic displacement of the metabolism is linked to the activation of proteases of the humoral system: clotting, fibrinolysis, complement and kallikrein/kinin; these in turn are powerful stimulators of the primary inflammatory cells, granulocytes and monocytes/macrophages, which in their turn produce proteases, inflammatory cytokines, O and NO radicals.(7) Lymphocytes, as secondary inflammatory cells migrate in large numbers into non-vascular space, ie. the Iymph nodes, as a result of which, turnover due to mitosis and apoptosis increases greatly. Intra-cellular nucleases and proteases are activated by apoptosis, which decompose the cell contents into fragments of DNA, RNA and proteins, which are expelled from the cell. The activated lymphocytes secrete increased amounts of lymphokines, especially IFN. This activates macrophages to produce increased amounts of O and NO radicals, as well as inflammatory mediators, IL-1 and TNFa. The level of cortisol which increases in this phase, linked with the decrease in DHEA limits the extent of inflammation during this oxidative stress condition. Cortisol has an ongoing inhibitory effect on the inflammatory lymphokines, IL-2 and IFN.(8)

The corticoid withdrawal phase

This is the transition from the catabolic metabolism to catabolic-anabolic equilibrium. While the level of cortisol is declining it is essential for inflammatory inhibition caused by cortisone to be taken over by the inflammatory inhibitor cytokines. This occurs through the temporary switch of the cytokine profile of CD4 Iymphocytes from Thl to Th2 by means of the activation of IL-4 and IL-10. This sets in train a generalised B-cell activation linked to hypergammaglobulinaemia. Cortisol is also responsible for stopping the anabolic formation of extra-cellular matrix components, such as collagen and glycosamineglycanes (GAGs) by fibroblasts. Due to the change in the cytokine profile from Thl to Th2, production of matrix is increased. The increase in production of GAGs is especially significant, because they play an important role as endogenous calcium antagonists, and, as cortisone inhibitors, in maintaining the anabolic-catabolic equilibrium.

The sequence of events in the metabolism during the recovery phase after surgery has recently been confirmed by Decker et al. on the basis of a temporary displacement of the cytokine profile from Thl to Th2 during cholecystectomies.(9)

The effect of persistant displacement of Thl to Th2 of the cytokine profile of the CD4 helper cells

The above describes events during persistent catabolic displacement in metabolism due to hypercortisolism: persistent B-cell activation and hypergammaglobulinaemia, which is characteristic of latent and active autoimmune disease.(10) As already mentioned, the main physiological function of cytotoxic T-cells is to dispose of "altered-self" structures, ie. cell debris left over after apoptosis. This is accompanied by constant scavenging by T-lymphocytes throughout the body. The total number

of specificities of T-cells defined by their surface proteins is of the order of 1O9. This poly-specificity of the lymphocytes prevents a general, inflammatory activation of the immune system when apoptotic cell debris is being removed.(11)

As we have shown in our paper on parenterally transmitted hepatitis viruses, those that have an envelope prevent being eliminated by the host's immune system, because they incorporate some of the body's own structures into their envelopes.(12) As a result the host's immune system becomes unable to eliminate them. Its only response is an autoimmune one. The oligo-specificity of these immune responses to the body's own structures having uniform "altered-self" specificity triggers systemic inflammatory responses.

From the foregoing, we must distinguish between physiological, poly-specific and pathological oligo-specific autoimmune reactions. Prevention and treatment of the latter is limited to disposal of "altered-self" structures, by removing hypercortisolism and by strengthening anabolic metabolism. Using virucidal chemotherapy to treat virus-induced autoimmune diseases is quite inappropriate, because it is not possible to eliminate the pathogen completely from the body. The best that can be achieved is a return to a symptomless carrier state.

Enduring hypercortisolism due to a persistent displacement in the cytokine profile towards Th2 is also associated with a selective decline in CD4 cells, with CD8 cells remaining constant. As Fauci originally showed, if there is a raised cortisol level in the bloodstream, part of the CD4 cells migrate into the bone marrow, where they activate B-cells. Once cortisol levels return to normal, the CD4 cells reappear in the circulation. The later idea that the selective decline in CD4 cells was due to their destruction by HIV proved the be untenable.(14) Another important indication of persistent hypercortisolism is the loss of delayed cutaneous skin reactions, while the Th2 profile is maintained. These reactions correlate closely with the Th1 profile and its inflammatory cytokines.

Hypercatabolic diseases under severe stress due to the failure of cortisol to inhibit inflammation

The Thl/Th2 displacement in cytokine profile of CD4 cells is, according to present understanding, meant to help stress-induced hypercortisolism return to normal. In cases of severe stress the function of cortisol to inhibit inflammation fails, which leads to a state of systemic hypercatabolic stress, because of overactivation of proteases and inflammatory cytokines, as well as to overproduction of O and NO radicals from granulocytes, macrophages and lymphocytes. The increased production of IFN from activated Iymphocytes is primarily responsible.(15,16) The most important examples of hypercatabolic diseases are AIDS, septicaemia, as well as protein calorie malnutrition (NAIDS = Nutritional AIDS, kwashiorkor). The increased production of IFN by activated lymphocytes causes macrophages to produce corresponding amounts of neopterin and ferritin.(l7,l8) The selective reduction of CD4 Iymphocytes, and the increase in neopterin and ferritin levels in the blood are all signs of lymphocyte and macrophage activity. Susceptibility to saprophytes is characteristic of hypercatabolic disease, as is the activation of latent pathogens and opportunists. Pneumocystis carinii pneumonia (PCP) is important in AIDS and protein calorie malnutrition. Contrary to earlier belief, it has now been classified as a ubiquitous fungus and not an opportunistic protozoon.(19)

AIDS and protein calorie malnutrition are diseases in which the sum total of all causes of stress have brought the body to an irreversible hypercatabolic state. In AIDS, a major stress factor is the psychological effect of the medical death sentence pronounced after a diagnosis of "HIV positive"; in addition, there is the stress of chronic hepatitis B and C infection. On top of this comes the toxic stress of drugs (opiates, poppers etc). Central to the deadly endgame is long-term treatment with nucleoside analogues and folic acid inhibitors, which drastically reduce the ability of mitchondria to produce ATP, the primary energy source for all metabolic processes.(20) With children suffering from kwashiorkor, stress is due mainly to malnutrition, and most of them die from PCP and anergic miliary tuberculosis.(21)

Septicaemia and toxic shock syndrome following trauma, burns and major surgery manifest themselves only a few days after the event. Lipopolysaccharide intoxication from gram-negative bacteria is the main problem. In one-quarter of cases intoxication is due to toxins from gram-positive germs, ie. staphylococci. The disease process is dominated by activation of proteases from the humoral system, which in turn produce other proteases, inflammatory cytokines, O and NO radicals from granulocytes and macrophages.(7) Lymphocytes, too, are activated and their mitotic and apoptotic turnover is increased massively. They reinforce the exocytotic activity of macrophages by increasing the output of IFN. It is easy to pass a point of no return in this group of hypercatabolic

conditions, beyond which the outcome is always fatal. Treatment up till now has been aimed at dealing with immunological neutralisation of bacterial toxins and neutralising inflammatory cytokines by monoclonal antibodies and receptor antagonists.(22,23)

Despite intensive efforts along these lines, there has been no breakthrough. The most promising treatment currently is to suppress the generalised protease activation. Early administration of high doses of antithrombin III has produced some initial successes.(7) In our opinion, speedy prophylaxis with high doses of intravenous gammaglobulins is most likely to be suitable in decisively reducing mortality.(24) The use of gammaglobulins in emergency medicine is compelling, which is independent of antibodies, to stop the activation of serine proteases and the production of proteases by phagocytes in cases of septicaemia and toxic shock syndrome.

Prophylaxis and treatment of hypercatabolic disease

Successful prophylaxis of AIDS is indicated in those who manifest a persistent displacement in their CD4 cytokines profile from Th1 to Th2.

It is essential to counteract catabolic activation of the immune system with anabolic treatment. This can be done directly and successfully by increased production of extra-cellular matrix by fibroblasts. It is most important to activate the synthesis of glycosamineglycanes (heparin, heparinoids) by augmenting available GAG precursors. It has been shown that extra-cellular sulphated hetero-polysaccharides greatly enhance the synthesis of GAGs.(25) GAGs are incorporated into the glycocalyx of the cell surfaces and reduce the flow of calcium into the cell, and inhibit binding of cortisone to its intra-cellular receptors.(26,27) In practice, this means taking cartilage extracts such as chondroitin sulphate and/or agar from algae as food supplements.

It is also essential to counteract the raised exocytosis of O and NO radicals and inflammatory mediators from activated macrophages, for which plant antioxidants ie. flavonoids and tannins, are appropriate. These polyphenols bind to excess radicals, sequester excess iron and reduce the increased activation of proteases in catabolic conditions.(28) It is most important to note that the numerous plant antioxidants contained in, for example, the Tibetan herbal product Padma 28, far exceeds that in vitamins C and E and in beta-carotene.(28)

In preventing AIDS it is highly desirable to remove the causes of stress as far as possible, and it should be noted that in those at risk who are frequently infected with hepatitis, treatment with antioxidants such as Padma 28 is so effective as to make the patients survive as symptomless carriers.(28)

In cases of septicaemia and toxic shock syndrome following trauma, burns and major surgery emphasis must be laid on prevention rather than treatment. It is our considered opinion that rapid administration of high doses of intravenous gammaglobulin is essential. *

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Glossary

adrenal – gland secreting the hormone adrenaline and three classes of steroid hormones including the glucocorticoids.

adrenaline – also called epinephrine; hormone secreted by the adrenal glands and having the effect of increasing blood pressure and level of blood glucose. Its release is triggered by stress and it prepares the body for 'fight or flight' response.

anergic miliary tuberculosis – disseminated tuberculosis accompanied by diminished response of the immune system to antigen.

autoimmune – against the body's own tissue.

adrenergic – activated by, secreting or characteristic of adrenaline.

anabolism – the construction of body tissues from simpler molecules –- opposite to catabolism.

antagonist – a substance that blocks the action of another substance by binding to the same receptor site.

antithrombin III – a blood protein that inactivates the blood clotting agent, thrombin.

antibody – also known as immunoglobulin – a protein produced in the blood by B lymphocytes in response to and then counteracting antigen.

antigen – any exogenous substance capable of provoking a specific immune response.

apoptosis – programmed cell death.

ATP – adenosine triphosphate, a nucleotide and principal carrier of chemical energy in cells.

catabolism – the chemical reactions within cells by which complex molecules break down to simpler molecules and energy is released.

catecholamines – a group of adrenergic amines that mimic the actions of the sympathetic nervous system.

cholecystectomy – removal of the gallbladder.

collagens – a family of fibrous proteins secreted by connective tissue cells (fibroblasts) that constitute the major proteins of extracellular matrix particularly in skin and bone.

corticoid – corticosteroid; steroid hormones secreted by the adrenal glands.

cortisol – the most important glucocorticoid hormone secreted by the adrenal gland ; its primary effect is on metabolism.

complement – a system of blood proteins which can be activated by the immune system; involved in control of inflammation and activation of phagocytes.

cytokine – proteins released by cells when in contact with antigen, acting as intercellular mediators/messengers in the generation of an immune response.

cutaneous – of the skin.

DHEA – dihydroepiandosterone.

endogenous – originating from within the body.

envelope – the lipid or glycoprotein membrane that forms the outer shell of some viruses.

exogenous – originating externally to the body.

exocytosis – the process of discharge from a cell of particles too large to be secreted via cell-wall diffusion.

ferritin – molecular complex which is the main form of storage of iron in the body.

fibroblast – connective tissue cell which secretes collagen and other substances.

folic acid – a vitamin of the B6 group concerned with the formation of blood cells and protein synthesis.

fibrinolysis – the action of the enzyme fibrinolysin in the dissolution of blood clots (thrombi).

gammaglobulin – a class of blood proteins of which most are immunglobulins.

granulocyte – category of white blood cell containing granules, including neutrophils, basophils and eosinophils.

glucocorticoid – category of steroid hormone secreted by the adrenal glands affecting carbohydrate metabolism and including cortisone, prednisolone and dexamethasone.

glucosamineglycanes (GAGs) – group of polysaccharides including heparin.

glycocalyx – cell coat.

Gram negative – result of a test in which organisms are stained; those remaining unstained are termed negative and this includes a major category of bacteria with complex cell walls.

Gram positive – the other possible result of the Gram test indicates a class of bacteria that have simple cell-walls.

heparin – a potent anticoagulant secreted by many tissues.

heparinoid – resembling or similar inaction to heparin.

humoral – pertaining to the extracellular fluids, including the blood serum and lymph.

hypercatabolic – a high level of catabolism.

hypothalamus – part of the brain coordinating functions of the autonomic nervous system and regulating body temperature. Releases neurohormones affecting, in particular, the pituitary gland.

hypergammaglobulinaemia – increased level of gammaglobulins in the blood.

IFNs – Interferons – a group of mediators which increase the resistance of cells to viral infections and act as cytokines. the three different IFNs are labelled alpha, beta and gamma, depending on from which cell type they originate. All cells produce one form of IFN.

immunoglobulin – an antibody molecule.

interleukin (IL) – secreted peptide or protein that mediates interactions between white blood cells; a type of cytokine.

inflammatory – response of a tissue to injury or infection.

intercellular – between cells.

intracellular – within the cell or cells.

lipopolysaccharides – a type of molecule which is a major component of the cell wall of Gram negative bacteria; an important antigen.

MALT (mucosa-associated lymphoid tissue) – lymphoid tissue associated with the GI tract, bronchial tree and other mucosa.

macrophages – large cells that ingest (engulf) microorganisms, foreign particles and other cells. Occur in the walls of blood vessels and in other connective tissue and are immobile, becoming actively mobile when stimulated by inflammation.

matrix – the intercellular substance of a tissue.

mesenchymal – pertaining to embryonic connective tissue.

metabolism – the chemical processes that maintain living organisms. Sub-categorised as anabolism and catabolism.

mitosis – cellular division/proliferation.

mitochondrion (pl. mitochondria) – a specialised membrane-bounded structure within each cell in which ATP is synthesised. Mitochondria contain their own nucleic acids and replicate independently.

monoclonal antibodies – antibodies produced by a single clone and which are homogeneous (identical in form).

mucosa – mucous membranes.

neopterin – a substance excreted in increased levels in certain types of disease including viral infection and graft tissue rejection.

neuroendocrine – pertaining particularly to interaction between neural (nerve) and endocrine (hormone) systems.

NO – Nitric Oxide

non-vascular – not in vascular space; not carried in a (blood or lymph) vessel.

noradrenaline – (also called norepinephrine) a catecholamine hormone with a strongly vasopressive action (constrictive of blood vessels).

nuclease – enzymes that split nucleic acids into nucleotides and other substances.

nucleotide – a molecular compound forming nucleic acid; the basic building blocks of RNA and DNA.

nucleoside analogues – molecules/drugs which in certain key ways mimic a nucleoside, a compound into which a nucleotide can be subdivided

O – oxygen radical.

oligo-specificity – specificity for few antigens.

parenterally – not through the alimentary canal (through some other route – intravenous injection etc.).

pathogen – an agent causing disease.

pathogenesis – the development of disease.

pituitary – gland at the base of the brain that regulates the level of neurohormones produced in the hypothalamus

poly-specificity – specificity for many antigens.

proteases – enzymes capable of splitting proteins into smaller molecules (polypeptides).

protozoa – a subkingdom comprising the simplest of animal life.

radical – any group of atoms that goes in and out of chemical combination together without change.

saprophyte – any organism living on dead or decaying organic matter.

septicaemia – the presence of bacteria or bacterial toxins in the blood (blood poisoning).

serine protease – a protease involved in the degradation of extracellular matrix macromolecules, including collagens.

sympathicotony – a stimulated condition of the sympathetic nervous system marked by vascular spasm and raised blood pressure.

systemic – pertaining to or affecting the body as a whole.

TNF – Tumour Necrosis Factor

vegetative – (of nervous system) functioning involuntarily or unconsciously.

virucidal – causing the inactivation or destruction of a virus

Glossary by Chris Baker

VIRUSMYTH HOMEPAGE