Medical Hypotheses

Medical Hypotheses (1991) 36, 60–64

Oxidative Imbalance in HIV Infected Patients

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Abstract — We present an outline of the complex interplay of oxidants and antioxidants in infectious diseases in general, and in particular with reference to the HIV infection, and subsequent opportunistic infections. Viral and opportunistic infections may directly or indirectly cause an imbalance in prooxidant/antioxidant mechanisms and result in generation of increased steady state concentrations of reactive oxidants. In HIV patients a prooxidant state could lead to a self-perpetuation of infection via stimulated expression of genes carrying the virus genome, and subsequently to immunosuppression, and promotion of initiated cells to neoplastic growth.

Introduction

The viral etiology of AIDS is clearly established, however, the mechanisms which contribute to the immunodeficiency state and increased tumor incidence are not known. Toxicity by reactive oxygen species has been suggested as a major determinant of cancer, degenerative disease, and aging. The concept of autotoxicity as a significant factor in clinical pathology of certain viral diseases was recently introduced (1). The mechanism of virus induced autotoxicity resembles the action of endotoxin and involves formation of reactive oxygen species by different mechanisms: 1) formation of reactive oxidants by phagocytes can be triggered by the virus itself, by virus-antibody immune complex, or certain mediators, e.g. complement 5a, tumor necrosis factor, and platelet activating factor; 2) reactive oxidants cause formation of lipid peroxidation products and clastogenic factors. Elevated steady state concentration of hydroperoxides can lead to auto-catalytic stimulation of prostanoid enzyme activity (2), and may self-sustain the inflammatory process; 3) induction of prooxidant enzymes, e.g. xanthine-oxidase, and inhibition of antioxidant systems may contribute to autoxidative tissue injury in viral diseases. On the basis of all the above observations, oxidative imbalance in HIV patients is likely. Oxidation induced by the risk factors of patients was even discussed as the primary cause of HIV infection (3). In the following, the knowledge on specific mechanisms and results concerning the balance of oxidants and antioxidants in infectious diseases, and in particular in HIV patients, are being reviewed.

Oxidative imbalance in infectious diseases

Modulation of phagocyte oxidant production by infectious agents. The phagocyte oxygen burst can be stimulated in viral diseases either directly or indirectly. Direct generation of reactive oxygen species

Date received 30 May 1990
Date accepted 15 August 1990

by paramyxo- and influenza virus in neutrophils (4), stimulation of chemiluminescence, and oxygen burst in human neutrophils by the influenza virus (5, 6) are documented. Influenza and Sendai virus also stimulate chemiluminescence in cultured murine spleen cells. This process occurs within a few seconds after infection with Sendai virus (7). The biochemical reactions resulting in chemiluminescence are triggered by the glycoproteins of the virus envelope (6, 8), and both viruses stimulate light emission in a different fashion (8). In contrast, bovine herpes simplex virus I elicits light emission in bovine neutrophils only in the presence of specific antibodies (9). In addition, herpes simplex I (10) and respiratory syncytial virus stimulate chemiluminescence in rabbit neutrophils and in human neutrophils only in the presence of specific immune factors, indicating that immune complexes trigger the reaction.

Other reports indicate inhibition of phagocyte oxidant production in viral diseases. The production of reactive oxidants is decreased in the neutrophils of patients with viral illnesses (11). T lymphocytes from patients with infectious mononucleosis suppress oxygen radical generation in neutrophils. The monocytes obtained from the same patient population, however, display normal level of reactive oxidant production (12). Measles patients with secondary infections show a significant decrease in the generation of oxygen species. Normal neutrophils incubated with T-lymphocytes from these patients generate also significantly fewer reactive oxygen species. In measles patients without secondary infection no abnormal findings of neutrophil respiratory burst are observed. It is suggested that the secondary bacterial infections sometimes seen in measles patients may result from a decrease in oxygen radical generation, which presumably is induced by suppressor T cells (13).

There is also convincing evidence that autotoxicity mediated by reactive oxidants is a significant factor in the pathogenesis of gram negative infections and in certain parasitic diseases (14). Endotoxin stimulates in vivo a massive oxygen burst by complement activation (15), and the generation of reactive oxygen species is increased in the neutrophils from patients with bacterial diseases (11). In candidiasis and sporotrichosis tissue infiltration with neutrophils occurs at an early stage, and the reactive oxygen species produced by the inflammatory cells supposedly play an important role in the pathology of the infections (16).

Modulation of prooxidant enzymes and antioxidants by infectious agents. Viruses can induce prooxidant enzymes and cause inhibition of tissue antioxidants. Viral infections, such as lethal parainfluenza infection of mice, can cause a decrease of antioxidants in e.g. the liver, an organ which is primarily not affected by the virus (17). Interferon and interferon–inducing agents (New Castle disease virus and chemicals) induce the prooxidant enxyme xanthine oxidase in various mouse organs (18, 19). Interferon induced induction of xanthine oxidase in the liver is associated with decreased activity of cytochrome P450, and it is suggested that decreased liver enzyme activity is a consequence of increased formation of reactive oxidants (18–21). Influenza virus infected mice have elevated serum and lung xanthine oxidase activity, and lethal influenza virus infection in mice is prevented by systemic administration of superoxide dismutase (SOD) (22). The antioxidant butyl-hydroxytoluene (BHT) protects chickens from the lethal New Castle disease virus at a serum concentration level sufficient for antioxidant activity (23). Simian virus (SV) 40 transformed human embryonic lung fibroblasts have reduced Mn-SOD enzyme activity as well as reduced Mn-SOD immunoreactivity (24). The amount of Mn-SOD is decreased significantly due to a decreased level of translatable messenger RNA for Mn-SOD (25). SV 40 transformed human fibroblasts also have a 80% decrease in catalase activity as compared to controls (26), and transformed mouse embryo cells have 2–5 fold less glutathione peroxidase, catalase, and SOD activity than control cells (27). There is a statistically significant increase in dehydroascorbate and a diminution in ascorbate values in blood of patients suffering from various infectious diseases (meningococcal meningitis, tetanus, typhoid fever, tubercular meningitis) (28).

Infectious agents can also induce an increase in antioxidant activity. In rats endotoxin induces lung SOD, catalase and glutathione peroxidase activity and protects the animals against hyperoxic toxicity (29, 30). Endotoxin, however, does not induce antioxidant enzymes in the lungs of mice (31), indicating that SOD is more easily induced in rats than in other animals. SOD activity in peripheral human lymphocytes is increased 2–5 fold during upper respiratory viral infections (32). Pulmonary indolamine 2,3 dioxygenase, which uses superoxide anion radical and tryptophan as substrate (33, 34), is markedly induced in mice by viral infections or bacterial endotoxin. Interferon produced during the inflammatory reaction presumably mediates indolamine 2,3 dioxygenase induction in lung tissue (35). Influenza virus causes a 95-fold increase in mouse lung indolamine-2,3-dioxygenase, and a 50% decrease in reduced glutathione content of

the lung. Ascorbate, dehydroascorbate and tocopherol tissue concentrations are unchanged.

Clastogenic factors. Clastogenic factors are heat labile, small molecular weight compounds and are considered reaction products of activated oxygen species. They consist of lipid peroxidation products, thiobarbituric acid reactive material and conjugated dienes (36, 37). Clastogenic products or chromosomal breakage factors were first described in plasma from patients irradiated with ionizing radiation (38). These factors are also found in plasma of patients with spontaneous chromosomal instability. The diseases comprise congenital breakage syndromes associated with a high incidence of malignancies, such as Bloom's syndrome, ataxia teleangiectasia, as well as chronic inflammatory and autoimmune diseases (39, 40, 41). The biological significance of clastogenic factor-mediated chromosomal breakage in carcinogenesis is however unknown. Chromosomal breakage may also be caused by tumor and non-tumor associated viruses. In serum of patients with acute hepatitis B a clastogenic factor was detected (42).

Viral expression and tumor promotion. Reactive oxidants may promote expression of dormant viral genes in a host and may modify regulation of genes controlling tumor protection. Hydrogen peroxide induces expression of viral antigen in different cell lines, that harbor the Epstein-Barr virus. The mechanism of action is indirect and mediated by singlet oxygen and hydroxyl radicals (43). Vice versa, chemically induced expression of HTLV 1 virus genes is inhibited by the antioxidant vitamins E and C, and by retinoids (44). Vitamin A supplementation during retrovirus infection causing murine AIDS enhances survival of infected mice and increases the numbers of activated macrophages (45). Cellular proxidant states, e.g increased tissue concentrations of hydroperoxides, reactive oxygen species, and other types of free radicals can promote initiated cells to neoplastic growth (46, 47).

Oxidative imbalance in HIV infected patients

Antioxidants. Studies with HIV patients clearly indicate alterations in their antioxidant/prooxidant balance. AIDS patients have a deficiency of the blood antioxidant ubiquinone-10, which increases with increasing severity of the disease (48). The concentration of acid soluble thiol in the plasma of AIDS patients is about 50%, neutrophil glutathionie about 80%, and monocyte glutathione about 75% of that in healthy blood donors (49, 50, 51). The glutathione concentration in the plasma of HIV infected subjects is about 30% of that in the normal individual (52). The cellular thiol/disulfide redox status is an important control mechanism of cellular functions (53). Lipoxygenase activity in human neutrophils is regulated by the glutathione status (54), and in immunosuppressed mice the antibody response is augmented by lipoic acid, a glutathione regenerating compound (55, 56). The disturbed thiol/disulfide status in HIV infected individuals may thus have important biomedical implications for lymphocyte dysfunction.

Oxidants. Serum ferritin, which is increased in several chronic diseases, is also elevated in AIDS patients. A significant role of ferritin in suppression of the immune function is discussed (57). Elevated serum ferritin may contribute substantially to the formation of reactive oxidants by providing increased serum concentrations of the redox-active transition metal iron. Iron can be released from ferritin by various mechanisms and subsequently initiation of oxidative injury may follow (58). Superoxide itself can release iron from ferritin in vitro (59), and in vivo (60). Superoxide radicals derived from activated neutrophils may potentiate the formation of reactive oxygen species via iron release from ferritin (61). However, reactive oxidant production in neutrophils may be impaired in HIV infected patients.

Neutrophil function. The chemiluminescent activity of neutrophils, as stimulated by opsonized zymosan, is markedly reduced in AIDS patients. In contrast, only part of the patients suffering from LAS show a reduced chemiluminescent activity of zymosan stimulated neutrophils (62). Interestingly, neutrophils from HIV infected chimpanzees have suppressed secretory function similar to those observed in other non-primate viral and retroviral infections (63).

Tumor necrosis factor. Blood monocytes from HIV infected patients spontaneously produce high levels of tumor necrosis factor TNF-alpha (64) and are hypersensitive to endotoxin stimulation, resulting in enhanced synthesis of TNF (65). Monocyte-derived TNF is a glycoprotein that is cytotoxic to tumor cells. Reactive oxygen species were suggested as the mediators in the immunological killing by TNF (66). TNF induces an oxygen burst in neutrophils. N-acetylcysteine, a glutathione regenerating substance, blocks TNF action in HIV infected cells and it was postu-

lated that stimulation of HIV production is mediatetd by reactive oxygen species (67).

Conclusion

Evidence is accumulating that indicates the presence of an antioxidant/prooxidant imbalance in an infected host, and in particular in AIDS patients. This pathomechanism could contribute to the steady decrease of immune function and increasing rate of malignancies in AIDS patients. The analysis of the antioxidant/prooxidant status in HIV patients could indicate increased oxidant generation and antioxidant consumption. If oxidative injury plays a major role in the pathogenesis of the disease, antioxidant supplementation therapy, which bears a low risk of negative side-effects, may be useful in stabilizing the clinical course of the patients. Work is in progress in Europe and in the USA to assess the extent of prooxidant/antioxidant dysregulation in HIV infected patients in different stages of the disease.

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