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REVIEW

CONSEQUENCES OF ALCOHOL CONSUMPTION ON HOST DEFENCE

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Abstract — This communication reviews recent literature and summarizes current views on the immunomodulatory effects of acute and chronic alcohol consumption. Chronic and even acute, moderate alcohol use can increase host susceptibility to infections caused by bacterial and viral pathogens. Impaired host defence after alcohol exposure appears to be linked to a combination of decreased inflammatory response, altered cytokine production, and abnormal reactive oxygen intermediate generation. Furthermore, cellular immunity, particularly antigen-specific immune response, is impaired by both acute and chronic alcohol use. Although T lymphocyte functions can be directly affected by ethanol, decreased antigen presenting cell function appears to be a key element in the ethanol-induced decrease in cell-mediated immunity. In addition, a preferential induction of Th2 vs Th1 immune response has been suggested, based on the increased immunoglobulin levels seen in chronic alcoholics. The effects of chronic and acute alcohol consumption in humans, animal models and *in vitro* systems on host defence and immunity are discussed in the context of the functional abnormalities of T and B lymphocytes, natural killer cells and monocytes/macrophages resulting in the altered immune response seen after alcohol use.

INTRODUCTION

Healthy individuals protect themselves against microbes by many different mechanisms including innate (non-specific) and acquired (specific) immunity. Elements of innate immunity exist prior to exposure to microbes, and include phagocytes such as neutrophils and macrophages, natural killer (NK) cells, circulating molecules i.e. complement, and macrophage-derived soluble mediators. Acquired immunity is triggered by exposure to foreign substances (antigens) and involves an integrated system of host defence in which numerous cells and molecules function co-operatively. Acquired immunity features humoral and cell-mediated immune responses as a result of complex cross-talk between T and B lymphocytes, antigen presenting cells (monocytes, macrophages, dendritic cells, B lymphocytes), and also utilizes specific antibodies and lymphocyte-derived cytokines. However, this well-orchestrated defence mechanism against pathogens can be impaired by exogenous agents that affect any of these components of the immune system. Alcohol has been shown as one of the modulators of host defence. Impaired immunity in patients with chronic alcohol use has long been described in the medical literature (Kanagasundram and Leevy, 1981; Palmer, 1989; Baker and Jerrels, 1993; Cook, 1995; MacGregor and Louria, 1997). Chronic alcoholics are more prone to infections with a variety of pathogens, have decreased ability to fight against infections, and have an increased risk of developing cancers, particularly those of the head, neck, and upper gastrointestinal system (reviewed in Roselle *et al.*, 1993). While malnutrition, vitamin deficiency, and advanced liver cirrhosis can contribute to some of the immune abnormalities in chronic alcoholics, alcohol itself is a potent modulator of the immune system. Increasing evidence from human and animal studies *in vivo* as well as from experiments *in vitro* suggests that alcohol use can indeed modulate the immune system at various levels. In addition to the immunomodulatory effects of chronic alcohol use, recent evidence also points out the immunoregulatory potential of acute, moderate alcohol consumption. Both acute and chronic alcohol use can affect the immune system at the level of innate or acquired immune responses. Altered inflammatory neutrophil, leukocyte, and

macrophage functions after acute or chronic alcohol use contribute to impaired host defence against microbial infections. In addition, the humoral and cellular components of the specific immune system can be equally damaged by alcohol use. Impaired B lymphocyte functions, and increased levels of certain types of immunoglobulins at the expense of others, contribute to the inappropriate immune defence. Furthermore, the impairment of cellular immune responses is pivotal in increased susceptibility to various infections after either acute or chronic alcohol use.

EFFECTS OF CHRONIC ALCOHOL USE ON INFLAMMATION AND HOST DEFENCE

Phagocytic cells and inflammation

During the process of inflammatory response, phagocytic cells, such as neutrophils and macrophages, have a major role in locating, ingesting, and killing microorganisms that invade the body. This complex process involves recruitment of phagocytic cells from the bloodstream to the site of the inflammation by chemotactic agents such as activated complement components (C5a), leukotrienes (LTB_4), or various proteins belonging to the chemokine family. Alcohol use can affect this process at several levels. Migration of neutrophils and monocytes from the bloodstream involves adherence and migration through the vascular endothelium at the site of infection, phagocytosis of the microorganism, and intracellular destruction of the pathogen by proteolytic enzymes in the phagolysosomes or via toxic oxygen-derived radicals (Springer, 1995). In experimental models, chronic alcohol feeding of male Sprague–Dawley rats resulted in increased adhesion molecule (CD18) expression in neutrophils (Bautista, 1997). Furthermore, Kupffer cell (resident macrophages of the liver) supernates from the same chronic alcohol-consumption rat model were shown to increase chemotaxis of normal neutrophils, probably via chemokines such as interleukin-8 (IL-8) and macrophage inflammatory protein-2 (MIP-2) (Bautista, 1995, 1997). These results suggest indirectly that the neutrophil infiltration seen in alcoholic hepatitis might be secondary to increased IL-8, MIP-2, or other chemokines produced in the liver by Kupffer cells (Maher, 1995; French, 1996). Increased systemic IL-8 levels were also reported in the serum of patients with acute alcoholic hepatitis, which appeared to be associated with neutrophil infiltration of the liver (Sheron *et al.*, 1993). Even a bolus injection of ethanol resulted in increased neutrophil chemotaxis to formil-peptide (FMLP) and increased FMLP receptor expression lasting 3–24 h after alcohol treatment in rats. In contrast, Kupffer cells showed decreased chemotactic activity and FMLP receptor expression in the same rat after acute alcohol ingestion (Bautista and Elliot, 1994). These results suggest that acute and chronic ethanol treatment may selectively activate or inhibit various phagocytic cell functions. The above findings in animal models, however, are not in agreement with human studies which show decreased chemotaxis of neutrophil leukocytes from chronic alcoholics *in vitro* (MacGregor *et al.*, 1990; Patel *et al.*, 1996). Impaired neutrophil function is believed to contribute to increased susceptibility to infections in chronic alcoholics. Thus, further studies are needed to evaluate potential selective effects of alcohol on CC- or CXC-chemokines that are involved in site-specific activation of the neutrophils, monocytes, and T and B lymphocytes involved in inflammation (Baggiolini *et al.*, 1997).

In addition to neutrophils, phagocytic monocytes and macrophages are also affected by alcohol use. Defective monocyte phagocytic function was reported in patients with alcoholic cirrhosis (Silvain *et al.*, 1995). In humans, even acute alcohol addition *in vitro* has been shown to inhibit monocyte phagocytic functions, antimicrobial activity, and expression of FcγR-type II, which is involved in phagocytosis of antibody-coated particles (Morland and Morland, 1989; Zuiable *et al.*, 1992). In mice, both short-term and long-term alcohol feeding resulted in decreased phagocytosis by peritoneal macrophages (Castro *et al.*, 1993). In another experimental model of chronic alcoholism, phagocytosis via Fc- and C3b-receptors by rat macrophages was reduced without a decrease in the number of surface receptors expressed (Bagasra *et al.*, 1988). Thus, impaired macrophage phagocytic functions as well as abnormal neutrophil leukocyte adherence and chemotaxis are likely to contribute to impaired local antimicrobial defence after alcohol use.

Reactive oxygen intermediates

Generation of active oxygen radicals, products of the oxidative burst, represents an essential element

of microbial killing. Thus, altered production of the oxygen radicals, superoxide anion and hydrogen peroxide, after alcohol exposure could be a mechanism undermining antibacterial immune defence. Alveolar macrophages from rats fed with ethanol either acutely or chronically have decreased superoxide anion and hydrogen peroxide production (Anthony *et al.*, 1993). Ethanol can also inhibit gene expression for inducible nitric oxide synthase, the enzyme responsible for generation of nitric oxide in alveolar macrophages and neutrophils in response to bacterial stimulation. Both acute and chronic alcohol treatment inhibited alveolar macrophage nitric oxide secretion in a recent study in rats, suggesting that decreased reactive oxygen radical generation by ethanol-exposed macrophages may contribute to the impaired antimicrobial defence after alcohol use (D'Souza *et al.*, 1996). Conversely, overproduction of reactive oxygen radicals has been implicated as a potential pathomechanism for alcohol-induced liver damage. Infusion of ethanol into rats for 1, 3, or 5 h not only stimulated the hepatic output of superoxide anions but also augmented inducible superoxide production (Spitzer and Bautista, 1993). The cellular source of this ethanol-induced superoxide anion was shown to be Kupffer cells, rather than endothelial cells or hepatocytes. These observations imply that the adverse effect of ethanol on reactive oxygen radical production may cause dual damage to the host. First, ethanol may inhibit induction of reactive oxygen radicals and nitric oxide in alveolar macrophages where these mediators play a crucial role in microbial killing. Second, ethanol appears to increase reactive oxygen radical production in the liver where these mediators can mediate or contribute to direct tissue damage.

Modulation of inflammatory cytokine production by alcohol

Induction of inflammatory cytokines by pathogens is a pivotal step in the host's immune defence. The typical inflammatory cytokines, such as TNF-α, IL-1, and IL-6, are primarily produced by inflammatory monocytes, macrophages, whereas other cell types including neutrophils, endothelial cells, lymphocytes, and activated tissue cells can also be a source during overwhelming inflammatory responses. Chronic alcohol use, particularly alcoholic liver disease, was shown to be associated with elevated levels of circulating TNF-α, IL-1, and IL-6 (Deviere *et al.*, 1989; McClain and Cohen, 1989; Khoruts *et al.*, 1991). Increased levels of these inflammatory mediators have been suggested to contribute to most of the pathological changes (hypermetabolism, fever, wasting, elevated acute phase reactants, decreased albumin) in patients with alcoholic hepatitis (McClain and Cohen, 1989). Alcoholic hepatitis patients with highly elevated TNF-α reportedly have a worse outcome (Bird *et al.*, 1990). The cellular source of the elevated inflammatory cytokine levels in chronic alcoholics has not been clearly defined. In one report, monocytes from patients with alcoholic liver disease produced greater levels of TNF-α in response to lipopolysaccharide (LPS) stimulation than normal monocytes (Schafer *et al.*, 1995). In contrast, production of inflammatory cytokines by alveolar macrophages from chronically ethanol-fed mice was reduced, potentially contributing to lung infections (Nelson *et al.*, 1989; Standiford and Danforth, 1997).

Altered response to bacterial pathogens

Chronic alcoholics are thought of as 'immunocompromised hosts', because of the increased incidence and severity of infections seen in this patient population. Infection with intracellular pathogens is prevalent. The effect of chronic ethanol treatment on the susceptibility of mice to the obligate intracellular bacteria *Listeria monocytogenes* infection has been studied. Jerrels found that mice receiving a Lieber–DeCarli diet for 7 days prior to i.v. injection with *L. monocytogenes* at 0.5 median lethal dose had larger liver lesions than the controls (Saad *et al.*, 1993). Additional experiments suggested that ethanol does not impair the influx of inflammatory cells to the liver, but does reduce the ability of the host to inhibit *L. monocytogenes* growth. Anti-*Listeria* defence is largely antigen-specific, T cell-dependent, and requires IFN-γ and IL-12 induction (Hsieh *et al.*, 1993). Ethanol treatment even in mice immunized with *L. monocytogenes* resulted in about a 100-fold greater *Listeria* count in liver homogenates than in the controls, demonstrating a significant defect in antimicrobial defence (Saad *et al.*, 1993). The cellular interactions and the potential role of ethanol-related aberrant antigen presenting cell function, inappropriate IFN-γ and/or IL-12 production under the effect of ethanol are yet to be studied.

As reviewed in Nelson's paper, impaired pulmonary defence mechanisms are also associated with alcohol use (Nelson *et al.*, 1992). In a rat model of pneumococcal pneumonia, a 1-week ethanol treatment prior to infection increased susceptibility to lethal pneumonia. Ethanol feeding of the rats was associated with an increase in the spread of the pneumococci from the lung via the bloodstream and once dissemination occurred, ethanol-fed rats failed to eliminate pneumococci from the bloodstream (Davis *et al.*, 1991; Lister *et al.*, 1993). The other poorly eliminated pathogen in alcoholics is *Klebsiella pneumoniae*. Experimental data suggest that ethanol-related impaired host response to *Klebsiella* can be ameliorated by treatment with granulocyte-colony-stimulating factor (G-CSF) via activation and recruitment of extrapulmonary neutrophils (Nelson *et al.*, 1992). In addition, ethanol-exposed macrophages have been shown as more susceptible to *Legionella pneumophilia* infection, which is a typical intracellular Gram-negative bacillus. Ethanol-exposed macrophages from *Legionella*-susceptible A/J mice showed a rapid increase in pathogen growth by 48 h, implying that physiological ethanol doses may impair macrophage defence against this pathogen (Yamamoto *et al.*, 1993). The other major pulmonary pathogen associated with chronic alcoholism is *Mycobacterium tuberculosis* (Roselle, 1992; Jacobson, 1992). The negative behavioural and social effects of alcohol use in conjunction with its biological, and immuno-inhibitory potential create a host that is increasingly susceptible to *Mycobacterium* infection and has impaired capacity to prevent the activation of the disease (Roselle, 1992). In mycobacterial infectious models, ethanol has been shown to augment intracellular survival of *Mycobacterium* (Bermudez and Young, 1991). A recent review further discussed the adverse effects of alcohol on the interaction of host defence and *M. tuberculosis* (Nelson *et al.*, 1995).

Viral infections

Investigation of the potential relationship between alcohol use and HIV-1-infection is evolving. Although increasing evidence is emerging on the immunological abnormalities due to alcohol use and HIV infection, respectively, our understanding is limited as to the specifics of the combined immunosuppressive effects of alcohol use and HIV-1 infection. It has been proposed that the modulatory effects of alcohol on the immune system may play a role, not only in increased risk of initial infection, but also in the rapid progression of HIV-1 disease (Saravolatz *et al.*, 1990; Kruger and Jerrels, 1992). Bagasra and colleagues reported increased HIV-1 p24 levels *in vitro* in infected peripheral blood mononuclear cells from individuals after a one-dose acute alcohol infusion or binge drinking (Bagasra *et al.*, 1996). A prospective study of 199 HIV-1-positive i.v. drug users found that ethanol use (no alcohol, less than 21 drinks/week or more than 21 drinks/week) did not correlate with changes in the percentage of CD4-positive lymphocytes. However, the percentage of CD8-positive T cells significantly increased among the heaviest drinkers between 2 to 5 years post-seroconversion (Crum *et al.*, 1996). While the clinical significance of this observation needs further investigation, this study suggests a potential for greater immune changes in those HIV-1 positive patients who also consume alcohol. A case report of an HIV-1 infected individual showed rapid progression of HIV-1 infection and development of AIDS upon heavy alcohol use (Fong *et al.*, 1994). In contrast to the human data, mice kept on a liquid chronic alcohol diet (Lieber–DeCarli diet) and infected with the murine model of AIDS (MAIDS) virus showed no increase in MAIDS infectivity, and only a moderate delay in development of MAIDS-related immune changes was seen (Fitzpatrick *et al.*, 1995). Other studies in Watson's laboratory on MAIDS suggest that ethanol may accelerate the development of AIDS by disrupting cytokine production (Wang and Watson, 1994; Wang *et al.*, 1997). Taken together, our current knowledge suggests that alcohol use (potentially both acute and chronic) is likely to increase host susceptibility to HIV-1 infection and to contribute to an accelerated progression of HIV disease. However, further research is needed to understand cellular and intracellular mechanisms by which ethanol consumption may modulate the biology and clinical course of HIV-1 infection.

The other viral disease where alcohol consumption has been shown to adversely affect the natural course of the disease is Hepatitis C infection. Recent reports show evidence that alcohol consumption promotes clinical progression and liver damage in patients with chronic hepatitis C infection (Wiley *et al.*, 1998; Ohta *et al.*, 1998; Ostapowicz *et al.*, 1998). Although the immune mechanisms leading

to chronic hepatitis C infection are yet to be clarified, abnormal levels of monocyte-derived mediators, particularly of IL-12 and inflammatory cytokines, were suggested to contribute to the progression of hepatitis C virus and subsequent liver damage (Llorente *et al.*, 1996; Kakume *et al.*, 1997). The cellular and molecular mechanisms leading to increased disease progression after alcohol use in chronic hepatitis C are yet to be explored.

EFFECTS OF CHRONIC ALCOHOL USE ON IMMUNE REGULATION

T lymphocyte functions

Studies investigating lymphocytes and lymphocyte subpopulations in chronic alcoholics have consistently shown decreased lymphocytic cell numbers in the circulating blood. Similarly, chronic alcohol feeding of mice resulted in decreased size and cell numbers in the thymus, spleen, and lymph nodes (Jerrels *et al.*, 1990; Ewald and Shao, 1993; Pruett *et al.*, 1994). Although the mechanism for ethanol decreasing lymphoid cell number is yet to be defined, a suggested mechanism is programmed cell death, apoptosis. Acute ethanol treatment results in increased apoptosis of thymocytes (Ewald and Shao, 1993). Increased apoptosis was also seen in human blood mononuclear cells after acute ethanol treatment (Szabo *et al.*, 1995). In addition to the decreased number of lymphoid cells, impaired proliferation response has also been reported, suggesting that ethanol-exposed lymphocytes have a reduced capacity to undergo proliferation and differentiation in response to an antigenic challenge (Roselle, 1992; Jerrels and Sibley, 1996). Isolated peripheral blood T lymphocytes from chronic alcoholics without liver disease showed decreased proliferation in response to stimulation with phytohaemagglutinin mitogen or via CD2, which could not be restored by exogenous IL-2 or IL-1 (Spinozzi *et al.*, 1991). A direct effect of ethanol on protein kinase C (PKC) was suggested as a possible mechanism for these T cell proliferation defects (Spinozzi *et al.*, 1991). Decreased delayed-type hypersensitivity response is associated with the immune abnormalities in chronic alcoholics (Jayasinghe *et al.*, 1992). Impaired antigen-specific T cell proliferation and delayed-type hypersensitivity response were also seen in a chronic ethanol-feeding model in mice (Peterson *et al.*, 1998).

The ways by which alcohol affects T cell proliferation are not well understood. Jerrels has shown in a rat model that T cells from chronic alcohol-treated rats fail to proliferate in response to IL-2 and that this was not due to decreased IL-2 receptor expression (Jerrels *et al.*, 1990). Other studies imply that the decreased T cell proliferation after alcohol use might be due to impaired accessory cell/monocyte function (Szabo *et al.*, 1993; Peterson *et al.*, 1998). Additionally, the T cell proliferation-inhibiting effects of ethanol-induced monocyte-derived cytokines and mediators (TGF-β, IL-10, PGE_2) might be important (Szabo *et al.*, 1993). T lymphocyte activation and proliferation are also dependent on the cell surface signals received during cell–cell interactions. Specific T cell activation requires a complex activation of various surface receptors including major histocompatibility complex Class II (MHC II) antigens, T cell receptors, and co-stimulatory molecules (CD28 and receptors for cell adhesion molecules). There was also reduced expression of MHC II antigens on lymphocytes from chronic alcoholic individuals (Cook *et al.*, 1991), human monocytes exposed to ethanol (Szabo *et al.*, 1993), and Kupffer cells from chronic alcoholic rats (Bautista, 1995). Expression of MHC I molecules, required for recognition of virus-infected cells and tumour cells, is increased on lymphocytes and other cell types (Roselle, 1992). Expression of extracellular matrix proteins, CD29 (β-integrin), VLA-3, VLA-4, VLA-5 has been reported in peripheral T cells of chronic alcoholics, which may also contribute to abnormal T cell functions (Sacanella *et al.*, 1999). The overall immune alterations after both acute and chronic alcohol exposure are consistent with decreased cellular immune responses. One of the recently entertained and debated mechanisms for impaired cellular immune response in various diseases is the decrease in Th1-type immune responses at the expense of Th2-type (humoral) immunity (Mosmann and Coffman, 1989; Romagnani, 1991). The immunological abnormalities after both chronic and acute alcohol consumption appear to be consistent with a decreased Th1-type immune response based on reduced antigen-specific T cell proliferation, and increased antibody and autoantibody levels.

B lymphocyte functions

One of the characteristics of the immune aberrations in chronic alcoholics is the elevated

levels of serum antibodies (immunoglobulins), particularly those of IgG and IgA classes (Roselle, 1992). Considering that immunoglobulins are produced by cells of B lymphocyte lineage, the elevated immunoglobulin levels in alcoholics indicate B cell dysfunctions. In a murine model of acute alcohol intake *in vivo*, Kawakami *et al.* (1990) showed increased mitogen-induced immunoglobulin production in the alcohol-treated group. While the functions of B lymphocytes appear to be impaired in alcoholics, the absolute number of B cells is no different from that in non-alcoholic individuals (Roselle, 1992). In contrast, splenocytes isolated from mice after a 14-day alcohol feeding showed a fivefold decrease in the IgM^+ splenocytes. Splenic B cells from ethanol-consuming animals showed impaired proliferation in response to a T cell-dependent antigen (sheep red blood cells), but normal proliferation to a T cell-independent antigen (TNP-ficoll), suggesting that B cell functions are intact, despite alcohol use. Intact T cell-independent antibody response was also seen in chronic alcoholics in response to pneumococcal polysaccharide vaccination (Jerrels *et al.*, 1993). Studies *in vitro* attempting to understand the mechanism for the increased immunoglobulin production in alcoholics demonstrated an opposite, inhibitory effect of alcohol on B lymphocyte antigen-induced antibody secretion. Studies *in vitro* with physiologically relevant doses of ethanol resulted in decreased IL-4-induced B cell proliferation and IL-4-induced Ig class switching, while IL-2-induced B cell proliferation was not affected by ethanol (Aldo-Benson, *et al.*, 1992).

Alterations in NK cell activity

Alcohol consumption is associated with increased morbidity and mortality related to malignancy (Roselle *et al.*, 1993; Smith-Warner *et al.*, 1998). The activity of NK cells, which are involved in destruction of virus-infected cells and prevention of tumour development and metastasis, is important in anti-cancer defence. Chronic exposure of rodents to ethanol was shown to reduce the number and activity of large granular lymphocyte/NK (LGL/NK) cells. The activity of NK cells can be suppressed by the presence of ethanol *in vitro*; however, other studies reported no effect of ethanol treatment *in vitro* on NK cell function (Meadows *et al.*, 1992). A recent paper from Taylor's group showed that acute alcohol intoxication can promote NK cell-dependent tumour metastasis in rats. In a 3-week study acute alcohol administration 1 h prior to tumour inoculation resulted in a 10-fold increase in the number of lung metastases of the NK-cell-dependent adenocarcinoma, MADB106. However, the tumour-promoting effect of ethanol was transient, because ethanol administration neither 24 h before nor after tumour inoculation affected the number of metastases (Ben-Eliyahu *et al.*, 1996). In human chronic alcoholics, decreased frequency of activated NK cells (identified as CD56-positive, lineage-negative lymphocytes) was seen in peripheral blood (Cook *et al.*, 1997).

Immunomodulatory cytokines and mediators affected by chronic alcohol treatment

Cytokines, immunoregulatory proteins produced by lymphoid cells, have a capacity to affect the functions of both lymphoid and non-immune cell types (neurons, endocrine organs, etc.). Research on cytokines, including interferons and interleukins, is an area of immunology which is growing rapidly with increasing understanding of the complexity of the cellular sources and interactions of the various members of the cytokine superfamily. Thus, the effect of either chronic or acute alcohol use is only partially understood on cytokine production and functions. IL-2 is one of the most important cytokines promoting T cell growth, survival and proliferation. Studies *in vitro* suggest that alcohol has no effect on the ability of T cells to produce IL-2. Although Jerrels *et al.* (1990) suggested that ethanol probably affects T cell utilization of IL-2, the intracellular mechanisms for this are yet to be understood. In humans, decreased serum IFN-α, IFN-γ, and IL-2 levels were reported after alcohol exposure (Vicente-Gutierrez *et al.*, 1991). Decreased IFN-γ levels in chronic alcoholics might be a key element to many of the immune alterations. IFN-γ, in concert with the macrophage-derived IL-12, is thought to be crucial for induction of Th1-type, cellular immune response (D'Andrea *et al.*, 1992; Trincieri and Gerosa, 1996). In addition to decreased IFN-γ levels in chronic alcoholics, decreased Th1-type immune response after chronic alcohol use is supported by a recent report on IL-12. In mice chronically fed with alcohol, impaired delayed-type hypersensitivity response was restored by exogenous IL-12 administration (Peterson *et al.*, 1998). In contrast, the Th2-type cytokines, IL-4,

IL-10, and IL-13 promote Th2-type immune responses and humoral immunity (Mosmann *et al.*, 1986). Furthermore, Th2 cytokines inhibit the production of Th1 as well as inflammatory cytokines (de Waal Malefyt *et al.*, 1993). Our current understanding of the effect of acute or chronic alcohol use on the production and action of these important cytokines is limited. However, in the absence of appropriate IFN-γ stimulation, as can be predicted in chronic alcoholics with decreased IFN-γ levels, a preferential Th2 induction may occur.

IMMUNOMODULATION BY ACUTE, MODERATE ALCOHOL USE

The general health impact of acute, moderate alcohol use is yet to be determined. In contrast to chronic, heavy alcohol use, consumption of one drink every other day or up to two drinks per day was associated with decreased mortality and cardiovascular morbidity (Goldberg *et al.*, 1995; Wilt *et al.*, 1996; Kannel and Ellison 1996; Thakker, 1998). Emerging data suggest a beneficial effect of acute, moderate alcohol consumption on cardiovascular morbidity probably due to a protective effect of alcohol on development of atherosclerosis (Wilt *et al.*, 1996). Alcohol-induced elevation in HDL, (the cardioprotective cholesterol, in humans) is one potential component; however increasing evidence suggests that the inflammatory process participating in endothelial damage is key to atherosclerotic plaque formation and, indeed, it may be a target for ethanol's effect (Laman *et al.*, 1997). Induction of inflammatory mediators and chemokines, particularly MCP-1, as a result of endothelial cell and monocyte activation, has been identified as a key element in initiation and progression of atherosclerotic plaque formation (Gu *et al.*, 1998). Thus, decreased MCP-1 and inflammatory cytokine, IL-1 and TNF-α production seen after acute alcohol treatment of human monocytes and after binge drinking in mice has beneficial effects on the inflammatory component of atherosclerotic plaque formation (Nelson *et al.*, 1989; Verma *et al.*, 1993; Szabo *et al.*, 1996*a*, 1999).

In contrast to chronic alcoholics, acute, moderate alcohol exposure downregulates inflammatory cytokine induction in response to various pathogens. Several laboratories have shown, both in murine and human systems, that *in vitro* or *in vivo* acute administration of alcohol blunts inflammatory cytokine responses to subsequent bacterial stimulation (Nelson *et al.*, 1989; Bermudez *et al.*, 1991; Verma *et al.*, 1993; Nair *et al.*, 1994; Szabo *et al.*, 1996*a*). Human monocyte production of TNF-α, IL-1, and IL-6 are reportedly decreased in the presence of ethanol at the protein as well as at the mRNA levels, whether induced by Gram-negative (lipopolysaccharide) or Gram-positive (Staphylococcal enterotoxin A or B) bacterial stimulation (Szabo *et al.*, 1996*a*). Further, decreased TNF-α production by mouse and rat alveolar macrophages has been shown to result in increasing susceptibility to pneumonia (Nelson *et al.*, 1989, 1992). Considering the pivotal role of TNF-α in antimicrobial defence, impaired inflammatory cytokine production after acute ethanol exposure is a major factor in defective host defence (Nacy *et al.*, 1991).

The initial inflammatory response to pathogens in a normal host is downregulated by immunoinhibitory cytokines, which are typically induced in a later phase of the infection. The most studied immunomodulatory cytokines are TGF-β and IL-10, which are produced by macrophages and T lymphocytes. IL-10 is a typical Th2-type cytokine which promotes humoral immune responses and inhibits cellular immune responses by downregulating the production of Th1 cytokines, antigen-specific T cell proliferation, and inflammatory cytokine levels (de Waal Malefyt *et al.*, 1993). Acute alcohol treatment increases human monocyte IL-10 production *in vitro* and augments bacterial stimulation-induced monocyte IL-10 levels (Mandrekar *et al.*, 1996; Szabo *et al.*, 1996*a*). Thus, one of the mechanisms by which ethanol use may disturb cellular immune responses is via elevated IL-10 levels. The other anti-inflammatory cytokine which can control inflammation and also inhibit antigen-specific T cell proliferation is TGF-β. Alcohol at physiologically relevant concentrations can induce TGF-β production in monocytes and augment TGF-β production in response to a bacterial challenge *in vitro* (Szabo *et al.*, 1992). Ethanol-induced elevation in TGF-β may have multiple implications for the immune system, including inhibition of inflammatory cytokine production by monocytes and other cells, inhibition of T cell proliferation, and augmentation of Th2-type immune response. The promoting effect of

TGF-β on collagen production is of additional potential importance. Indeed, Kupffer cell-derived TGF-β has been proposed as a potential mediator for increased collagen production and deposition in alcoholic liver fibrosis (Matsuoka and Tsukamoto, 1990).

In addition to cytokines, ethanol has been shown to affect the production of non-protein inflammatory mediators, particularly the cyclo-oxygenase products. Acute alcohol stimulation was shown to increase arachidonic acid metabolite levels. Elevated monocyte prostaglandin E_2 (PGE_2), was also seen in acute ethanol-stimulated human monocytes. The biological relevance of increased (PGE_2) after alcohol exposure is complex: it can inhibit monocyte antigen presentation capacity, inflammatory cytokine production, as well as T cell proliferation. The importance of ethanol-induced TGF-β, IL-10, and PGE_2 is at least twofold. First, increased levels of these mediators after acute ethanol exposure can contribute to the inhibition of inflammatory cytokine production and, therefore, further impair antimicrobial defence. Second, elevated levels of immuno-inhibitory cytokines can inhibit T cell proliferation, particularly antigen-specific T cell proliferation, in alcohol-exposed hosts.

Ethanol *in vitro* was found to inhibit T cell proliferation in a dose-dependent manner in response to phytohaemagglutinin, but not to ionomycin stimulation, and this was associated with inhibition of early signalling events such as *c-fos* induction and Ca^{2+} mobilization (Brodie *et al.*, 1994). Other *in vitro* studies with physiologically relevant concentrations of alcohol showed that acute alcohol exposure can inhibit antigen-specific and superantigen-induced T cell proliferation (Szabo *et al.*, 1993; Waltenbaugh *et al.*, 1994). One of the mechanisms for decreased antigen-specific T cell proliferation is the impaired antigen presentation capacity of ethanol-exposed peripheral blood monocytes (Szabo *et al.*, 1993). Recent data suggest that acute ethanol does not induce IL-12 in human monocytes or mononuclear cells, but it augments monocyte IL-12 production in the presence of IFN-γ (Szabo *et al.*, 1996*b*). This suggests that decreased IFN-γ levels are likely to contribute to additional cytokine abnormalities and impaired cellular immune responses after alcohol use.

Additional clinical evidence for immunosuppression by acute alcohol use is provided by animal models of burn injury where a more severe decrease in T cell proliferation response was seen in mice exposed to ethanol prior to thermal injury (Kawakami *et al.*, 1991; Faunce *et al.*, 1998). These results suggest that even acute alcohol consumption may significantly modulate responses to subsequent challenges to the immune system, whether it is a bacterial, viral pathogen or trauma injury. Consistent with this, in human trauma patients, the production of TNF-α, the major mediator of post-trauma immunosuppression, was shown to be significantly altered in those patients who had detectable alcohol levels in the blood at the time of major trauma injury (Szabo *et al.*, 1995).

SUMMARY AND COMMENTS

Recent research by an increasing number of scientists interested in the immunomodulatory effects of alcohol further confirmed that both acute and chronic alcohol use have profound modulatory effects on the immune system. Studies from animal and human models of acute, moderate alcohol use *in vivo* have shown that alcohol can impair host defence to subsequent bacterial and viral challenges. Results also suggest that the effects of acute alcohol consumption are transient. The clinical implications of such a transient immunodepression after acute, moderate alcohol use need further studies. Failure of an appropriate initial immune response to pathogens probably has a profound and potentially prolonged effect on the immune system in certain types of infections. The effect of acute alcohol use on the immune system is of particular interest with regard to potentially increased susceptibility to HIV, mycobacterial, and other infections.

Our understanding of the complex picture of immunosuppression in chronic alcoholics is also increasing. Further studies are needed to dissect the immunomodulation due to chronic alcohol use itself from that due to other immunomodulatory conditions, e.g. malnutrition, vitamin deficiencies, and liver disease, in the advanced chronic alcoholic population. Understanding the specifics of immune alterations caused by chronic alcohol use will be necessary for designing more specific therapeutic approaches to ameliorate immunosuppression in chronic alcoholics.

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