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Microbial Infections, Immunomodulation, and Drugs of Abuse

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INTRODUCTION AND HISTORICAL BACKGROUND

The recreational use of legal and illegal drugs of abuse in this country and abroad has aroused serious concerns about the consequences of these drugs on immunity. Marijuana, cocaine, heroin, and other opiates are widely used illegal drugs. There have been numerous clinical reports on the association between infectious diseases and use of illegal drugs. In addition, legal substances such as alcohol and tobacco have been linked to excessive and addictive use and have been correlated with major health problems. Heavy smokers and/or alcoholics are often hospitalized with infectious diseases. Experimental studies using drugs of abuse support the clinical observations that these substances are associated with immunomodulation.

Studies concerning the effects of addictive drugs on immunity became even more urgent with the onset of the worldwide epidemic of AIDS. AIDS is caused by human immunodeficiency virus (HIV) and results in a collapse of the immune system, making an individual highly susceptible to opportunistic microorganisms (77, 130, 150). Drugs of abuse have been suggested as possible cofactors, resulting in a more rapid progression of disease (58, 63, 69, 212). Approximately one-third of all AIDS patients in the United States are intravenous drug users (IVDUs), and contaminated needles or equipment often spreads HIV (57). AIDS patients also often use other drugs such as marijuana, alcohol, and nicotine, which some investigators think are immunosuppressive (13, 59, 106, 216). Thus, there is concern that abused drugs are serving as cofactors in AIDS progression and in alteration of susceptibility to other infectious diseases (63, 73, 124, 161, 164).

OPIATE EFFECTS ON IMMUNITY AND SUSCEPTIBILITY TO INFECTION

Opiates compose a collection of drugs derived from the poppy *Papaver somniferum* (199) which include opium, morphine, and heroin. An excellent review of the historical use of opiates has been written by Risdahl et al. (190). It is clear from this review that opiates have had a great impact throughout history on mankind both from use and from the wars over the control of opium. Opium was derived from the Greek word meaning "of sap" or "juice", because the drug is obtained from the juice of the poppy plant. Relics from the Stone Age, predating recorded history, show widespread poppy cultivation. Over time, the addictive nature of opium was also recognized. First morphine (in the early 1800s) and then codeine, heroin, and other opium alkaloids (in the late 1800s) were synthesized from opium with claims of being the cure of opium addiction (91).

During the late 1800s and early 1900s, many medical practitioners began to recognize infections as serious complications of opiate addiction (28, 105, 165, 260). The list of infections associated with opiates continued to increase during the 1900s (89, 90). Also, experimental evidence began to accumulate during this time demonstrating the detrimental effects of opiates on immunity in humans and animals (90, 115, 116, 123, 187). For example, Cantacuzene demonstrated in the late 1890s that morphine-treated guinea pigs had altered phagocytosis and leukocyte trafficking (36). Studies of drug addicts in the early 1970s further demonstrated a connection between drug use and infectious diseases (117, 185). It is now recognized that IVDUs face many complications from the use of opiates (243). Pulmonary infections, caused by *Mycobacterium*, *Staphylococcus*, *Streptococcus*, *Haemophilus*, and other bacteria, are among the most common diagnoses of opiate abusers (190). Other serious diseases caused by microbial pathogens in IVDUs are AIDS (HIV), endocarditis (*Staphylococcus*, *Enterococcus*, *Pseudomonas*, *Klebsiella*, *Serratia*, and *Candida*), abscesses and cellulitis (*Staphylococcus*, *Streptococcus*, *Haemophilus*, *Enterobacter*, *Pseudomonas*, *Klebsiella*, *Clostridium*, *Candida*, and others), hepatitis A, B, and C (hepatitis A, B, and C viruses), sexually transmitted diseases, and skeletal infections (*Staphylococcus* and *Pseudomonas*) (77, 188, 190).

A large percentage of infections among IVDUs are related to the methods of injection and life-style practices, which increase their exposure to microbial pathogens (57). Recent reports continue to discuss the problem of contaminated heroin or drug paraphernalia and infections (15, 47). Numerous in-

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TABLE 1. Effects of opiates on immune functions in vivo and in vitro

Mode of administration and model	Immune function[a]	Receptor involvement[a]	Reference(s)
In vivo			
Rodents	↓ Phagocytosis	+	168, 191, 240
	↓ Antibody production	+	32, 120, 172, 184
	↓ Mitogen-stimulated proliferation	+	18, 19
	↓ NK/CTL activity	+	18, 27, 207, 258
	↓ Cytokine production	+	27, 125, 194
	↑ Serum IL-6 levels	+	83, 84
	↑ LPS-induced sepsis	NE	195
	↑ IL-12	+	173
	↓ DTH	+	31
Humans	↓ Phagocytosis	NE	239
	↓ NK activity	NE	265
	↓ ADCC	NE	265
Monkeys	↓ Chemotaxis	NE	121
	↓ PMN killing	NE	121
Pigs	↓ DTH	NE	148, 189
In vitro			
Mice	↓ Phagocytosis	+	191, 235
	↓ Cell proliferation	+	18, 19, 203
	↓ Induction of antibody	+	60, 72, 237
	↓ Cytokine production	+	4, 22, 98, 238
Humans	↓ Chemotaxis	+	71
	↓ Superoxide	NE	176
	↓ ↑ Cytokine production	+	38, 39, 179
	↓ ↑ Chemokine production	+	237, 259
	↑ Phagotocytosis	+	178

[a] ↑, increase; ↓, decrease; NE, not examined; CTL, cytotoxic T lymphocyte; LPS, lipopolysaccharide; DTH, delayed-type hypersensitivity; ADCC, antibody-dependent cellular cytotoxicity; PMN, polymorphonuclear leukocyte.

vestigators, however, have proposed that increased exposure is not the only factor that enhances microbial infections. They hypothesize that opiates cause immunosuppression and therefore serve as cofactors for microbial infections. These studies have been previously reviewed (59, 139). They have been expanded on by the advent of the AIDS epidemic in the 1980s (30, 176). AIDS and its corresponding decreased host immunity were, and still are, principal players in opportunistic infectious diseases in IVDUs (63, 76, 124, 150). Several studies support that intravenous use of opiates influences the outcome of HIV infection (16, 58, 63). Heroin addicts have been observed to have an increased risk of acquiring HIV (16, 227), and at one time half of IVDUs from certain areas of the United States were infected with HIV (103). Moreover, mortality rates from infectious diseases among HIV-infected IVDUs decrease when drug use was discontinued, and this abatement correlated with a decrease in the rate of progression to AIDS (256). Therefore, a correlation between the use of opiates, increased susceptibility to infection, and depressed immunity does indeed exist. Whether this correlation is due, however, to increased exposure to infectious pathogens through risky behaviors, to immunosuppressive effects of opiates, or to a combination of these two is uncertain at this time.

Experimental studies to investigate the effect of opioids on immune responses and on microbial pathogens have extended the earlier clinical correlative observations and animal studies (Tables 1 and 2). Several good reviews of these studies have been previously published (59, 139, 188, 190). Several opiate receptors have been identified on cells of the nervous system, with μ-, κ-, and δ-receptors and their subtypes being the most predominant and being referred to as classical receptors (2). The classical receptors are G-protein coupled seven-transmembrane receptors (186). Opiates have been linked to modulations of host resistance to bacterial, protozoan, viral, and fungal infections, using animal models, cell lines, and primary cells. Opiates appear to affect the immune response directly through opioid receptors on immune cells and indirectly via the receptors on neuronal cells. The μ-, κ-, and δ-opioid receptors as well as nonclassical opioid-like receptors have been demonstrated on immune cells, suggesting possible mechanisms for the direct actions of opiates on immune cells (139). In vitro studies of immune cells have demonstrated receptor-mediated reduced phagocytosis (235), chemotaxis (71), and cytokine and chemokine production (4, 22, 39, 179).

While opiates directly modulate host immunity, their effects on physiological function of nonspecific host mechanisms are thought to also alter immune responses and play an important role in increased susceptibility to infection. These effects are proposed to act through the central nervous system (CNS) and the hypothalamus-pituitary-adrenal (HPA) axis. Opiates are known to alter the release of HPA hormones (corticotrophin-releasing hormone and adrenocorticotrophic hormone) (5), which, in turn, alter glucocorticoids (cortisol and corticosterone), the end-effectors of the HPA axis. The glucocorticoids play an important role in decreasing and regulating cellular immune responses (29). Studies have shown that morphine treatments suppress immune parameters in mice through the HPA axis (31, 64, 183, 200, 201). In addition to these corticoids, immunosuppression via the autonomic nervous system has been observed (144, 257). Shavit et al. observed that natural killer (NK) activity in rats was suppressed following morphine injection into the lateral ventricle of the brain via opioid receptors (206, 207). The central opioid pathways were involved in immunosuppression of lymphocyte proliferation (78, 82, 126). Receptor-mediated increase in the production of transforming growth factor β, an immunosuppressive cytokine, is another possible indirect method by which opiates suppress immunity (38). Thus, it appears that immunosuppression occurs through direct and indirect mechanism involving receptors on immune cells and the CNS.

TABLE 2. Opiates and microbial pathogens

Pathogen	Host species	Effect[a]	Reference(s)
Salmonella enterica serovar Typhimurium	Mice	↑ Gut colonization	127
Toxoplasma gondii	Mice	↑ Mortality	40
Endogenous[b]	Mice	↑ Sepsis	81
HSV-1	Mice	↑ Infection	169
FLV	Mice	↑ Mortality	224, 242
Candida albicans	Mice	↑ Mortality	240
Swine herpesvirus plus *Pasteurella multocida*	Pigs	↑ Pneumonia	189

[a] ↑, increase; ↓, decrease.
[b] Retrovirus.

TABLE 3. Effects of THC and other cannabinoids on immune functions in vivo and in vitro

Mode of administration and model	Immune function[a]	Reference(s)
In vivo		
Humans	↓ Lymphoproliferation	154
	↓ Antimicrobial activity	14
	↓ Cytokine production	14
Mice	↓ ↑ Serum Ig levels	155
	↓ Cellular immunity	112, 163, 214
	↓ Antimicrobial activity	8, 34, 147, 222
	↓ Humoral immunity	10, 102, 198
	↑ Apoptosis	140
	↓ ↑ Cell signaling	50, 241
In vitro		
Humans	↓ Lymphocyte proliferation	153, 221
	↓ NK cell activity	219, 220
	↓ Neutrophil antifungal activity	55
	↑ ↓ Cytokine production	223, 255
Mice	↓ Lymphocyte proliferation	113, 140, 181, 182
	↓ NK cell activity	104, 110, 133
	↓ Antibody formation	9, 107
	↓ ↑ IL-2 system receptors	46, 79, 270, 271
	↓ ↑ Cytokine production	14, 108, 162
	↑ Apoptosis	140, 269
	↓ ↑ Cell signaling	46, 62, 79

[a] ↑, increase; ↓, decrease; ↑ ↓, both increase and decrease.

MARIJUANA-INDUCED ENHANCEMENT OF SUSCEPTIBILITY TO INFECTION

Marijuana is the common name for *Cannabis sativa*, a plant that has long been known for its "medicinal" and recreational properties and for its fiber (hemp). Chemical extracts of marijuana contain over 400 compounds and more than 60 cannabinoids. Cannabinoids, especially the major psychoactive component Δ^{9-}tetrahydrocannabinol (THC), exert immunomodulatory effects that alter normal functions of T and B lymphocytes, NK cells, and macrophages in human and animals. These modulations have been observed during both in vivo and in vitro cannabinoid treatment (Table 3). The molecular and cellular mechanisms for these effects are not fully defined; however, it appears that receptor as well as nonreceptor mechanisms are involved (106). Like opiate receptors, cannabinoid receptors (CBRs) are G-protein-coupled seven-transmembrane receptors of which two types have been identified, CB_1 and CB_2 (85, 86, 108, 134, 151, 174). CB_1 receptors are associated with the brain and certain peripheral tissues and are responsible for behavioral effect of THC, while CB_2 receptors are located in the periphery, especially on immune cells (86, 108, 174). The discovery of CBR has led to the identification of a class of endogenous compounds that bind to these receptors, called endocannabinoids, although the majority of the compounds are eicosanoids (53, 138, 142, 261). The broad spectrum of action of THC on immune functions is thought to result in decreased host resistance to bacterial and viral infections as observed in various experimental animal models (Table 4).

Studies in the early 1970s using human peripheral blood mononuclear cells (PBMCs) from marijuana smokers showed a tendency for heavy use to result in suppression of lymphocyte proliferation in culture as well as alterations in PBMCs immune cell subsets (154). Serum immunoglobulin (Ig) levels were also modulated by marijuana use, with IgG protein levels decreasing and IgE protein levels increasing. Animal studies started in earnest with the isolation and synthesis of THC by Mechoulam et al. (143), when it became possible to inject THC into animals or treat human and animal cells in vitro. Various groups have observed both in vivo and in vitro that THC suppresses immune functions (Table 3). These functions vary from lymphocyte proliferation and antibody production to cytotoxic activity (Table 3). Other studies have demonstrated that THC enhances certain functions (Table 3). B-cell proliferation increased in the presence of THC at nanomolar concentrations (51), and the production of the chemokines MIP1α and interleukin-8 (IL-8); increased at micromolar concentrations (223). The latter group also observed decreases in the levels of other cytokine after THC treatment (223). Therefore, the data that have accumulated over the past three decades indicate that THC and cannabinoids are immunomodulatory.

One of the important risk factors of marijuana use is its suppression of host resistance to infections (99). This aspect has been studied in both humans and animals, and the results have suggested that cannabinoids have a moderating effect on various infection paradigms and that at least some of the effects involve CBRs (Table 4) (33, 112). A correlation between marijuana smoking and herpesvirus infection was observed to increase the risk of mortality in HIV positive marijuana smokers (211). Furthermore, alveolar macrophages from marijuana smokers were found to be deficient in several functional properties including phagocytosis and bactericidal activity (14). Experimental animal studies have also suggested that THC treatment causes increased susceptibility to various infectious agents (Table 4). Disease progression and mortality in different animal models were increased on infection with herpes simplex virus (HSV) and Friend leukemia virus (FLV) (35, 147, 222) and with bacterial pathogens such as *Listeria*, *Treponema*, and *Staphylococcus* (87, 149, 170).

These studies leave major gaps in our understanding of the cellular and molecular mechanisms mediating these effects on immunity and resistance. Immune cells have been demonstrated to express CBR; therefore, it is likely that at least a portion of the cannabinoid-induced modulations of the immune cells are directly mediated via their own CBRs (79, 119). The host immunity, however, involves many cell types, both

TABLE 4. Effects of cannabinoids on resistance to infections

Infectious agent	Host	Effect[a]	Reference(s)
HSV	Mice	↑ Mortality	147, 149
Listeria	Mice	↑ Mortality	149
HSV	Humans	↑ Recurrence	100
HSV	Guinea pigs	↑ Infection	35
FLV + HSV	Mice	↑ Mortality	222
Staphylococcus	Rats	↓ Lung infection	87
Treponema pallidum	Rabbits	↑ Progression	170
Legionella	Mice	↑ Mortality	111, 163
Staphylococcus	Rats	↓ Macrophage activity	
HIV	Humans	↑ Risk of mortality	211

[a] ↑, increase; ↓, decrease.

TABLE 5. Effects of cocaine on immune functions

Mode of administration	Immune function[a]	Reference(s)
In vivo		
Humans	↓ Antimicrobial activity	14
	↑ ↓ Cytokine production	14
Rodents	↓ Lymphoproliferation	20, 21, 171
	↓ Antibody formation	166, 253
	↓ DTH	253
	↓ ↑ Humoral immunity	11
	↑ ↓ Cytokine production	250
In vitro		
Humans	↑ HIV replication	12, 177
	↓ Lymphocyte proliferation	23, 49, 109
	↓ Cytokine production	131, 132
Rodents	↓ Cytokine production	250, 254, 262
	↓ Lymphocyte proliferation	262
	↓ NK activity	262

[a] ↑, increase; ↓, decrease; ↑ ↓, both increase and decrease; DTH, delayed-type hypersensitivity.

immune and nonimmune, as well as chemical factors such as cytokines and chemokines and hormones of the HPA axis. Thus, there are numerous cellular and molecular mechanisms where THC could be exerting its effects as demonstrated by our *Legionella pneumophila* infection studies. In our studies, THC pretreatment of mice infected with THC affects both innate immunity and the development of the adaptive (cell-mediated) immune response. Initially, we reported that mice receiving a THC injection 1 day before and 1 day after a sublethal *L. pneumophila* infection died of septic shock resulting from a detrimental production of high levels of proinflammatory cytokines (111). Induction of tumor necrosis factor alpha (TNF-α) has since been confirmed, most recently in CB_2-transfected HL60 cells stimulated with the cannabinoid agonist CP55,940 (52). We further observed that a single injection of THC 18 h prior to infection inhibited the development of Th1 immunity in mice (163), which involved both CB_1 and CB_2 receptors and suppression of Th1 development by inhibiting the production of gamma interferon and IL-12 and reducing the amount of IL-12Rβ2 mRNA (112). This THC-induced shift away from a Th1 response has also been observed in other models involving THC treatment and tumor immunity (268), endotoxemic mice (215), and NK cell activity (133). These studies suggest that cannabinoids have the ability to bias the developing immune response from Th1 (cell-mediated) toward Th2 (antibody-mediated) immunity. Interestingly, Th shifts have also been observed toward Th2 following treatment with morphine (193) and toward Th1 following treatment with norepinephrine (229). It is possible, therefore, that drugs used either recreationally or therapeutically might enhance or suppress infections by modulating Th activity in the host. Clearly, the full extent of these findings needs clarification.

COCAINE AND INFECTIONS

Cocaine is derived from the coca plant, *Erthroxylon coca.* Being an alkaloid, cocaine is water soluble and readily absorbed through mucous membranes of the body. It appears to function at least partially through the sigma$_1$ (σ_1) receptor, a protein first proposed to be involved with morphine binding (122, 135, 137, 205, 228). The σ_1 receptors are distributed throughout the brain and periphery of the body (137), similar to the classical opiate and cannabinoid receptors.

TABLE 6. Effects of cocaine on resistance to infections

Infectious agent	Host	Effect[a]	Reference
LP-BM5 retrovirus	Mice	↑ Cryptosporidiosis	48
HIV	SCID mice implanted with human PBMCs	↑ HIV-infected PBL	192
		↑ Virus load	192
		↓ CD4/CD8 ratio	192

[a] ↑, increase; ↓, decrease; PBL, peripheral blood leukocytes.

A limited number of in vivo and in vitro studies have been done to examine cocaine-induced modulation of immune responses (Tables 5) and infections (Table 6). Much of the work with cocaine and infections has been centered on HIV and progression to AIDS (13). Epidemiologic studies on IVDUs and AIDS link abuse of cocaine, even more than other drugs, to increased incidence of HIV seroprevalence and progression of AIDS (7, 37, 42, 56). Cocaine increases HIV infection of human PBMCs in vitro (12, 177). Roth et al., using a model of human PBMCs implanted into severe combined immunodeficient (SCID) mice, demonstrated that cocaine treatments resulted in increased numbers of HIV-infected PBMCs and viral load, as well as a decreased CD4/CD8 ratio (192). These immunomodulations may be through receptors located in the periphery, as was demonstrated with cocaine-induced suppression of mitogen-stimulated lymphoproliferation (171). Therefore, while studies of the immunological impact of cocaine have started, there is much more research in this area to be done.

NICOTINE EFFECTS ON RESISTANCE TO INFECTIONS

Cigarette smoking is linked to community-acquired pneumonia and is considered one of the risk factors for respiratory

TABLE 7. Effects of nicotine and cigarette smoke on host resistance mechanisms in vivo and in vitro

Mode of administration	Immune function[a]	Reference(s)
In vivo		
Rats	↓ Antibody-forming cells	66, 67
	↓ Intracellular Ca^{2+} stores	101
	↓ Lymphocyte proliferation	218
	↑ T-cell anergy	67, 218
	↓ Antimicrobial activity	217
In vitro		
Humans	↓ NK activity	156
	↓ Cytokine production	167
Mice	↓ Splenocyte proliferation	74, 75
	↓ ↑ Cytokine production	74, 75, 136
	↓ Antimicrobial activity	136

[a] ↑, increase; ↓, decrease; ↑ ↓, both increase and decrease.

TABLE 8. Effects of alcohol on immune functions

Mode of administration	Immune function[a]	Reference(s)
In vivo		
Mice	↓ ↑ Cytokine production	3, 94, 210, 246, 248, 249, 251
	↓ NK activity	141, 249
	↓ IgA and IgG production	249
	↑ Apoptosis	61
	↓ DTH	245, 246
Rats	↓ TNF-α	114, 158
	↓ Serum chemokines	266
	↓ TNF-α processing	267
	↓ Alveolar nitric oxide	70, 114
	↓ Chemokines production by Kupffer cells	17
Humans	↓ Monocyte stimulated proliferation	232
In vitro		
Mice	↓ Macrophage killing	26
	↑ Bactericidal capacity	263
	↓ Cytokine production	41
Humans	↓ Macrophage killing	26
	↓ ↑ Cytokine production	25, 68, 231, 233, 234, 244
	↓ TNF-α receptor	25
	↓ NF-κB activation	129
	↓ T-cell proliferation	232
Rhesus macaques	↓ TNF-α	226

[a] ↑, increase; ↓, decrease; ↑ ↓, both increase and decrease; DTH, delayed-type hypersensitivity.

infections (6, 89, 196). Cigarette smoke is composed of two components, the vapor phase and the particulate phase. The immunosuppressive effects of smoke and nicotine occur in the particulate portion, thus suggesting that the nicotine is at least partially responsible for the inhibitory effects on the immune responses (Table 7) (216, 217). Nicotine is a small organic alkaloid synthesized by tobacco plants and is recognized as the addictive component of cigarettes. While its lipophilic nature allows small amounts to cross directly through cell membranes, the primary biological effects are proving to be receptor mediated. Nicotine is an agonist for nicotinic acetylcholine receptors (nAChRs), which are present on cells of the CNS as well as other cells throughout the body including immune cells (80, 118). The neural nAChRs are upregulated in smokers (118, 264). Rapid progression of nicotine from cigarette smoke in the lungs to the brain increases dopamine transmission within the brain in the shell of the nucleus accumbens, a region essential for reward processing that has been associated with addictive properties of other drugs including opiates, alcohol, and THC (180, 236).

Nicotine appears to affect the immune system through nAChRs on cells in CNS and on immune cells similar to opiates and cannabinoids. Nicotine induces glucocorticoids, through the HPA axis, that modify the immune system (29, 80, 216) as well as directly affecting immune cells (74, 75, 136, 167, 217). Nicotine was demonstrated to enhance the growth of *L. pneumophila* and cause a corresponding inhibition of IL-6, TNF-α, and IL-12 in a murine alveolar macrophage cell line through nAChRs (136). The substance also affects murine splenocyte production of Th1- and Th2-associated cytokines in a differential manner (74, 75). Chronic nicotine treatment of rats induces T-cell anergy, depletes intracellular IP3-sensitive Ca^{2+} stores, and inhibits the antibody-forming cell response and lymphocyte proliferation, which may prevent the animals from developing a protective immune response to microbial pathogens (66, 67, 101). In vitro treatments of PBMCs by nicotine and other extracts from cigarette were observed to inhibit cytokine production (167). Rodents exposed to cigarette smoke in inhalation chambers have increased susceptibilities to infections when challenge with aerosolized bacteria or viruses (217). Smoking among HIV-positive individuals has also been linked to increased numbers of infections (164, 213).

Thus, it is important to determine how nicotine, a legal addictive drug, increases or alters susceptibility to infectious diseases. Studies of this nature have begun with the apparent linking of the effects to nAChRs. However, much more information is needed to ascertain the nature and mechanism whereby nicotine influences the immune response and thus affects host resistance to infectious diseases.

ALCOHOL MODULATION OF RESISTANCE TO INFECTION

Alcohol abuse causes widespread health problems including decreased liver functions and increased incidences of infectious diseases (45). Alcoholics have long been recognized to be particularly susceptible to infections and to be at a greater risk of community-acquired pneumonias (1, 43, 88, 128, 157, 160, 196, 225). Moderate alcohol use (one beer, or one glass of wine, or one mixed drink per day), which may be beneficial to the immune system (159, 230), is not covered here.

Alcohol, unlike the previous drugs of abuse discussed, does not appear to involve receptor mediation. Studies during the last decade have demonstrated that alcohol has multiple effects on the host immune responsiveness to microbial pathogens (Tables 8 and 9). These effects are characterized by depletion of circulating lymphocyte populations and altered lymphoid organ architecture and immune functions (95, 152, 209, 230). In addition, alcohol suppresses the production of cytokines important in antimicrobial immunity, such as TNF-α secreted by mononuclear cells in vitro and/or in vivo, including alveolar macrophages from rats (114, 160) and rhesus macaques (226). The suppression of TNF-α is posttranscriptional and involves

TABLE 9. Effects of alcohol on resistance to infections

Infectious agent	Host	Effect[a]	Reference(s)
Listeria	Mice	↓ Infection	4, 95, 197
Salmonella	Mice	↓ Infection	95, 208
Streptococcus	Mice	↓ Infection	204
Mycobacterium	Mice	↑ Disease	24, 26
Mycobacterium-BCG	Rats	↓ Bactericidal	145
LP-BM5 retrovirus	Mice	↑ Disease	248, 251
LP-BM5 retrovirus	Mice	↑ *Cryptosporidium parvum* infection	3
LP-BM5 retrovirus	Mice	↑ Coxsackievirus-induced myocarditis	202

[a] ↑, increase; ↓, decrease.

TNF-α-converting enzyme-mediated processing of TNF-α (114, 267). Furthermore, in human monocytes, alcohol inhibits lipopolysaccharide LPS-induced activation of NF-κB, a transcription factor for inflammatory cytokines (129). Of particular interest is the observation that alcohol use also decreases Th1 cytokine levels and responses (68, 230, 232, 246, 247) and increases Th2 cytokine levels (68, 248, 251), similar to the effect observed with THC (112, 163, 268) and morphine (193). Indeed, Peterson et al. reported that IL-12 therapy could attenuate the suppressed cell-mediated immunity in ethanol-consuming mice (175).

Rodents given alcohol orally show modulation in immune cell functions (Table 8) and infections (Table 9). Bermudez and Young showed that ethanol augments the intracellular survival of *Mycobacterium avium* complex and impairs macrophage responses to cytokines (26). Ethanol treatment increases the growth of *L. pneumophila* in nonpermissive macrophage cultures (263). Furthermore, studies by Jerrells and colleagues showed that immune cells from mice given alcohol and infected with intracellular bacteria (*Salmonella* or *Listeria*) had increased susceptibility to the bacteria (94–97, 197, 208).

Alcohol has also been connected to viral infections. The HSV-2 incidence is increased in women who abuse alcohol (44). Experimental studies indicate that alcohol inhibits Th1 responses generated to LP-BM5, a retrovirus that causes a murine AIDS-like syndrome (3, 248, 251, 252). Whether alcohol serves as a cofactor in AIDS is uncertain (54, 146). However, alcohol does exacerbate opportunistic infections in murine AIDS-like syndrome (3, 202) and opportunistic infections are correlated with the progression of AIDS. Hepatitis C virus infection has also been linked to chronic liver disease in alcoholics (92). Animal studies indicate that alcohol enhances liver damage by activating CD8 cells (93) and increasing apoptosis (65). Thus, the animal models and clinical studies imply that alcohol abuse is detrimental to the host and causes increase susceptibility to disease from microbial pathogens.

DISCUSSION

In recent years there have been more studies concerning the relationship between the use of addictive drugs of abuse and the increased incidence of susceptibility to infectious diseases, including AIDS. These studies have shown that drugs of abuse, including marijuana, cocaine, opiates, alcohol, and nicotine, alter not only neuropsychological and pathophysiological responses of individuals but also immune functions. Such studies support the earlier correlative observations that the use of these drugs is associated with enhanced susceptibility to infectious diseases.

The mechanisms by which abused drugs increase susceptibility to infections in humans as well as experimental animals have begun to be delineated. From the studies reviewed here, it appears that all five classes of drugs affect the immune system through both indirect and direct mechanisms. One indirect method is drug-induced stimulation of the HPA axis, which results in glucocorticoid production and regulation of the immune system. In addition, these abused substances have direct actions on immune cells that seem to be receptor mediated for all of the drugs except alcohol. Studies of receptor-mediated effects on immunity and infection have been performed in detail with opiates and to a lesser degree with cannabinoids and have just been started with nicotine. Another common mechanism of action among the five classes of these abused drugs is their effect on Th1/Th2 responses, either by inhibition of Th1- or elevation of Th2-associated cytokines.

The correlation between IVDUs and HIV infections has led many investigators to propose that the immunomodulation mediated by drugs is a major factor contributing to the progression of AIDS in IVDUs. While it is impossible to determine the cause-and-effect relationships from epidemiological studies, there is growing consensus among investigators of drugs of abuse that drug-induced immunomodulation is involved. Studies of immunosuppression by drugs of abuse are supporting increased susceptibility to opportunistic infectious pathogens by alteration of the immune response. However, there is still convincing evidence that the social practices connected with drug abuse also contribute to increase exposure to infectious pathogens. In the end, it logically seems that it will be a combination of increased exposure and drug-induced immunomodulation that contributes to increase susceptibility to infectious pathogens. A concerted enterprise, however, is essential to determine the mechanisms by which drugs compromise immune responses in general and in concert with immunosuppressive viruses.

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