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Potential therapeutic strategy to treat substance abuse related disorders

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Potential therapeutic strategy to treat substance abuse related disorders

*Sulie L. Chang**

Institute of NeuroImmune Pharmacology and Department of Biological Sciences, Seton Hall University, South Orange, NJ 07079, USA

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ABSTRACT

The "Potential therapeutic strategy to treat substance-abuse-related disorders" session was chaired by Dr. Sulie L. Chang, director of NeuroImmune Phamacology at Seton Hall University. The four presenters were: Dr Wenzhe Ho (Miniway to stop HIV/HCV), Dr Ru-Band Lu (Low dose of memantine in the treatment of opioid dependence in human), Dr Ping Zhang (Treatment of alcohol-related disorders: Learning from stem/progenitor cells), and Dr Yun-Hsiang Chen (Treatment of methamphetamine abuse: An antibody-based immunotherapy approach).

1. Introduction

Speakers at the symposium delineated the multidirectional interaction between the central nervous system (CNS), the immune system, and substances of abuse in the presence of human immunodeficiency virus (HIV) infection, both *in vivo* and *in vitro*. They also discussed the translation of findings from animal behavioral studies into the clinical setting in relation to the potential for developing new therapeutic strategies for HIV-1-infected patients who use addictive substances.

2. Presentations

Since the early 1990s, the link between the CNS and the immune system has been demonstrated through the converging actions of substances of abuse such as alcohol and opiates, cytokines such as interleukin-1 (IL-1), and the brain [1]. Substances of abuse can alter neuronal and immune pathways via modulation of the hypothalamic–pituitary–adrenal (HPA) axis [2], and high concentrations of ethanol (> 32%) can activate the vasopression neurons responsible for osmoregulation in the hypothalamic supraoptic nucleus [3]. Chronic exposure to opiates such as morphine potentiates immune responses to an exogenous challenge with IL-1 by desensitizing the HPA response [2] and accelerates the progression of sepsis caused by the bacterial endotoxin lipopolysaccharide (LPS) to septic shock [4]. In the HIV-1Tg rat, a non-infectious rodent model for patients on highly active antiretroviral therapy (HAART), exposure to LPS increases cytokine levels in the brain. Furthermore, HIV-1Tg rats are more responsive to addictive drugs, including morphine, methamphetamine, and alcohol, compared to control rats [1]. Investigation of the mechanisms behind the heightened response to morphine revealed that LPS increases expression of the mu opioid receptor (MOR), the receptor for morphine, to a greater extent in HIV-1Tg rats than in control rats, indicating that there may be

* *Corresponding author*. Institute of NeuroImmune Pharmacology, Seton Hall University, 400 South Orange Avenue, South Orange, NJ 07079, USA.
E-mail address: sulie.chang@shu.edu.
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a synergistic effect between HIV-1 infection and bacterial infections that renders HIV-1-infected individuals more susceptible to morphine dependence [1,5].

Various mechanisms have been proposed regarding the interaction of substance abuse and the immune system. While investigating the negative impact of viral infection and opioids on the innate defense mechanism of host cells, Dr Wenzhe Ho and his team found that activation of Toll-like receptor 3 (TLR3) in macrophages results in induction of multiple anti-HIV cellular factors (CC-chemokines, tetherin, interferon-stimulated genes, and miRNAs) and suppression of HIV infection/replication. Furthermore, they found that TLR3 activation in hepatocytes by poly I:C could inhibit hepatitis C virus (HCV) replication. These *in vitro* observations clearly indicate the importance of TLR3 signaling in protecting host cells from HIV or HCV infection. Thus, future investigations are necessary to determine whether *in vivo* activation of TLR3 has a protective effect on HIV and/or HCV infection in the context of opioid use.

Interestingly, it has been reported that the Alzheimer's disease medication memantine decreases LPS-induced microglial activation at low doses, possibly by reducing the production of inflammatory cytokines, and decreases morphine-induced conditioned place preference (CPP) partly via its anti-inflammatory effects. In terms of clinical applications, anti-inflammatory benefits of low-dose memantine, as discussed by Dr Ru-Band Lu in his presentation, have been demonstrated in patients receiving methadone maintenance therapy (MMT). Patients receiving methadone treatment tend to become tolerant and dependent on the substance. To test the efficacy of low-dose memantine as an adjuvant therapeutic intervention for opioid-dependent patients during long-term MMT, Dr Lu and his team treated patients with low-dose memantine prior to MMT. Patients pretreated with memantine showed attenuated methadone tolerance, lower plasma IL-8, and increased transforming growth factor (TGF)-β1 and BDNF expression. Dr Lu proposed that the anti-addictive mechanism of low-dose memantine may be attributed, at least in part, to its anti-inflammatory and neuroprotective effects, as well as its ability to upregulate BDNF production.

Alcohol impairs a critical step of the granulopoietic response, which is associated with emergency expansion of LKS cell populations and thus with reprogramming of primitive precursors to enhance their commitment to granulocyte lineage development. However, the mechanisms underlying this association are not yet understood. Dr Ping Zhang and his group investigated the mechanisms by which alcohol damages immune defense function to identify therapeutic targets for effective treatment of alcoholic patients with severe bacterial infection. They found that alcohol-induced disruption of leukemia stem/progenitor cell (LSPC) function may serve as a target for future development of effective therapy to treat alcoholic liver disease. This is based on the findings that incorporation of bromodeoxyuridine (BrdU) into proliferating LSPCs is dose-dependently inhibited by ethanol. Cyclin D1 mRNA expression by LSPCs is suppressed by exposure to 50 mM or 100 mM ethanol, and phase imaging has revealed that alcohol exposure induces a morphological change in LSPC differentiation towards a myofibroblast-like phenotype. Dr Zhang reported that expression of E-cadherin by LSPCs cultured in differentiation medium was downregulated by ethanol, which was accompanied by significant upregulation of Snail repressor gene expression. Finally, alcohol inhibited LSPC self-renewal and promoted epithelial-to-mesenchymal transition during differentiation. Dr Zhang's findings implicate several possible mechanisms by which alcohol may impair cell immune functions. This research has important implications for immunocompromised patients such as those with HIV or leukemia.

Taken together, these studies suggest that targeting of systemic inflammation using anti-inflammatory agents may be beneficial for protection against HIV infection and behavioral disorders related to substance abuse. In addition to pharmacological therapeutic techniques, antibody-based immunotherapies, such as those discussed by Dr Yun-Hsiang Chen, have provided information regarding the mechanisms by which dependence on substances of abuse may be mediated. Dr Chen and colleagues generated a recombinant adeno-associated virus vector encoding heavy and light chains of a characterized anti-methamphetamine monoclonal antibody and found expression of full-length and functional monoclonal antibodies both *in vitro* and *in vivo*. This team also found evidence of virus-induced attenuation of locomotor activity induced by methamphetamine (1 mg/kg, intraperitoneal injection). This novel therapeutic strategy could assist in better treatment of dependence on methamphetamine and other substances of abuse.

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