Journal of Neuroimmunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Circulating cytokine levels are associated with symptoms of depression and anxiety among people with alcohol and drug use disorders

Priscilla Martinez[a], Lars Lien[b], Sarah Zemore[a], Jørgen G. Bramness[b], Sudan Prasad Neupane[b,c,*]

[a] Alcohol Research Group, Public Health Institute, 6001 Shellmound St, Suite 450, Emervyville, CA 94608, USA
[b] Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders, Innlandet Hospital Trust, Box 104, 2381 Brumunddal, Norway
[c] Norwegian Center for Addiction Research, University Of Oslo, Box 1171, Blindern, 0318 Oslo, Norway

ARTICLE INFO

Keywords:
Depression
Anxiety
Psychological distress
Alcohol abuse
Drug abuse
Substance abuse treatment
Cytokines

ABSTRACT

Background: Psychological distress is common among people with a substance abuse disorder in treatment. Identifying correlates of psychological distress may serve as points of intervention to improve substance abuse treatment outcomes. Immune function measured as cytokine levels have been associated with psychological distress, but this association remains unexplored among people with a substance abuse disorder in treatment. This study aimed to examine whether cytokine levels in patients treated for a substance use disorder were related to depression, anxiety, and overall psychological distress, and to observe these associations separately among people with a past year alcohol use disorder and those with a past year drug use disorder.

Methods: We collected cross-sectional data from 80 inpatients at five alcohol and substance abuse treatment centers in Norway. We determined alcohol and drug diagnoses, and assessed symptoms of depression, anxiety, and overall psychological distress. We tested blood samples for IL-1, IL-6, TNF-α, INF-γ, and IL-10. We used multivariate linear regressions to examine the associations between cytokine levels and psychological distress measures.

Results: All cytokines were significantly and positively associated with depression score. INF-γ was significantly and negatively associated with anxiety, and IL-6 was significantly and positively associated psychological distress. Among people with only an alcohol use disorder, IL-6 was positively associated with depression and psychological distress scores, and IL-10 was negatively associated with anxiety score. Among people with only a drug use disorder, TNF-α was positively associated with depression score.

Conclusion: The relationship between immune function and psychological distress is robust in the context of substance abuse, and further research is warranted.

1. Introduction

Substance use disorders and psychological distress, encompassing symptoms of depression and anxiety, are among the most common and costly disorders challenging healthcare systems worldwide. Psychological distress is also highly prevalent among people struggling with alcohol and illicit drug use disorders. In a nationally representative study of adults residing in the U.S., the 12-month prevalence of major depression and any anxiety disorder among people with a current substance use disorder was 14.5% and 17.7%, respectively (Grant et al., 2004a). Among people with substance use disorders accessing treatment, comorbid symptoms of depression and anxiety are typically even higher. A multisite study among people admitted to substance abuse treatment facilities in the U.S. observed a past year prevalence of 51.4% for depressive symptoms and 41.6% for anxiety symptoms (Chan et al., 2008). In a study of people with substance use disorders in treatment in Norway, 36% had past-year major depression and 78% had any past-year anxiety disorder (Landheim et al., 2003). The impact of depression and anxiety on treatment outcomes for people with substance use disorders is also well established: those with such comorbidity have a reduced physical and mental health status (Lynskey, 1998), and are more likely to drop out of treatment and experience relapse (Burns et al., 2005; Landheim et al., 2006a). Thus, understanding contributors to psychological distress among people with substance use disorders accessing treatment may help identify targets for interventions to improve treatment outcomes.

* Corresponding author at: Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders, Innlandet Hospital Trust, Box 104, 2381 Brumunddal, Norway.
E-mail addresses: pmartinez@arg.org (P. Martinez), lars.lien@sykehuset-innlandet.no (L. Lien), szemore@arg.org (S. Zemore), j.g.bramness@medisin.uio.no (J.G. Bramness), s.p.neupane@medisin.uio.no (S.P. Neupane).

https://doi.org/10.1016/j.jneuroim.2018.02.011
Received 4 October 2017; Received in revised form 28 January 2018; Accepted 19 February 2018

Immune function, as measured by circulating cytokine levels, has been associated with depression (Felger & Lotrich, 2013) and, at times, anxiety (Salim et al., 2012). Cytokines are a heterogeneous group of signal-transducing proteins secreted by immune cells to regulate immune activity and communicate with the nervous and endocrine systems. Higher circulating and brain inflammatory cytokine levels has been consistently reported in both animal models of depression as well as among depressed human subjects (Dowlati et al., 2010; Schiepers et al., 2005; Liu et al., 2012a). However, debate remains around whether the observed inflammatory augmentation is consequent to or a cause of the depressive state (Stewart et al., 2009; Valkanova et al., 2013), and over which cytokines are potential determinants of depression (Dowlati et al., 2010; Schiepers et al., 2005; Maes et al., 2011). Nonetheless, there is biological plausibility suggesting inflammatory cytokines may be mediators of both environmental and genetic factors that may lead to the onset of depressive disorders (Raison & Miller, 2011). In contrast to depression, there is scant and conflicting data on the correlation between immune function and anxiety disorders. One of the first large studies to investigate anxiety disorders and immune function identified elevated levels of C-reactive protein (CRP) in men with a current anxiety disorder, but not in women, and no association with cytokine levels (Vogelzangs et al., 2013). This is inconsistent with findings from smaller, clinical samples that have identified associations between elevated inflammatory cytokine levels and anxiety disorders (Hoge et al., 2009; Gill et al., 2009). Methodological differences between clinical and general population-based studies notwithstanding, further studies are clearly needed to clarify the relationships between immune function and depression and anxiety.

Changes in immune function are also associated with alcohol and illicit drug use. Alcohol and illicit drugs are well-known immune modulators, and heavy use of both results in increased inflammatory cytokine levels and vulnerability to infections (Crews et al., 2006; Crews & Nixon, 2009; Friedman et al., 2003). Chronic heavy alcohol use has been shown to increase production of systemic and brain pro-inflammatory cytokines, such as tumor necrosis factors-α (TNF-α), interleukin (IL)-6, and IL-1, and to reduce anti-inflammatory cytokines, such IL-10 (Szabo et al., 2001). Similar to alcohol abuse, abuse of illicit drugs such as opiates, cannabis, and cocaine is associated with the induction of pro-inflammatory cytokines. Unlike alcohol, however, illicit drugs are understood to exert their immunomodulatory effects via pathways mediated by receptors bound to immune cells (Ninkovic & Roy, 2013), which may then result in the production of inflammatory cytokines. Given the associations between immune function and depression and anxiety, changes in immune function due to alcohol or illicit drug abuse may be a biological link between substance abuse and psychological distress, and might help explain the increased prevalence of psychological distress among people with a substance use disorder. Moreover, immunological mechanisms may pose new targets for substance use disorder treatment (Loftis & Huckans, 2013). However, to warrant advanced investigations into the validity of this causal model and the biological mechanisms that may underlie such a causal pathway, we need to build associational evidence for the relationships between psychological distress and circulating cytokine levels in the context of substance abuse. For both alcohol and drug studies examining the effects of these substances on immune function, experimental animal models and observational human studies have focused on ex-vivo immune cell activity; far fewer studies have examined circulating cytokine profiles among people with alcohol and drug use disorders that would permit observation of associations between substance abuse and circulating cytokines levels.

With the paucity of studies investigating circulating cytokine profiles among people with a substance use disorder, it remains unknown if circulating cytokine profiles could be correlates of psychological distress in this population. Given the associations between both psychological distress and alcohol/drugs with circulating cytokine levels, it is not clear that associations between cytokine levels and psychological distress would be observed among people in treatment for a substance use disorder. Our previous work among adults with alcohol use disorders accessing treatment in Nepal has shown elevated levels of the inflammatory cytokines IL-6, TNF-α, and INF-γ among those with co-morbid depression compared to those without (Neupane et al., 2014). Other studies have shown associations between elevated levels of circulating inflammatory cytokines and depressive symptoms among people with alcohol use disorders (Irwin et al., 1990). However, these studies are limited in their applicability to people with a drug use disorder seeking treatment. Moreover, studies that have included alcohol measures when investigating the association between immune function and psychological distress typically examine the effect of alcohol only and exclude people with drug use and drug use disorders. Epidemiological studies consistently show that alcohol and drug use disorders frequently co-occur (Stinson et al., 2005), particularly in treatment seeking populations (Grant et al., 2004b). Identifying an association between circulating cytokine profiles and psychological distress in a group comprised of people with an alcohol and/or drug use disorder in treatment would suggest the association between cytokine levels and psychological distress is robust in this context. Furthermore, given that there are different pathways for the immunomodulatory effects of alcohol and illicit drugs, it would be useful to have information about the association between cytokine levels and psychological distress by alcohol use disorder and drug use disorder separately to observe potential differences in the association across disorders. Therefore, our primary aim was to examine whether cytokine levels in patients treated for a substance use disorder were related to psychological distress, including symptoms of depression and anxiety. Our secondary aim was to observe and describe associations between cytokine levels and psychological distress separately among people with only an alcohol use disorder and those with only a drug use disorder. We hypothesized that higher circulating levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines would be associated with greater symptoms of depression, anxiety, and overall psychological distress among people in treatment for a substance use disorder. We also hypothesize that the profile of cytokines associated with psychological measures would be different when examined separately among people with only an alcohol use disorder and those with only a drug use disorder due to the different pathways by which alcohol and drugs affect immune function.

2. Material and methods

2.1. Material

We collected cross-sectional data from convenience samples of inpatients at five alcohol and substance abuse treatment centers that are part of the Innland Hospital Trust in Southeastern Norway. We chose these treatment centers based on geographic proximity to the University of Oslo, and facilities for blood draws and storage of biological specimens. We identified and approached these five sites and all agreed to participate. Three of the five sites specialized in the inpatient treatment of drug- and alcohol-dependent persons using a variety of cognitive therapies. One site specialized in the inpatient assessment of co-morbid psychiatric disorders among drug-dependent persons (hereafter referred to as “the Assessment Unit”). The final study site specialized in the treatment of persons with depression. Data were collected from the Assessment Unit between 2003 and 2010. Data from all other sites were collected between 2010 and 2011. All patients are adults (aged 18 or older) and referred to these sites by a medical doctor for the assessment or treatment of a diagnosed substance use disorder or depressive disorder. We approached 148 people, 85 (57%) of whom agreed to participate and provided written informed consent. We were unable to collect blood samples from 5 people. The final analytic sample was thus comprised of 80 people. Thirty-eight participants were from the Assessment Unit and 42 were from the other study sites.