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More inflammation but less brain-derived neurotrophic factor in antisocial personality disorder

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ABSTRACT

Antisocial personality disorder (ASPD) is highly comorbid with substance use disorders (SUDs). We hypothesize that chronic neuroinflammation and the loss of neurotrophic factors prompts the pathogenesis of both disorders. We used ELISA to measure plasma levels of proinflammatory (tumor necrosis factor-α [TNF-α], C-reactive protein [CRP]) and anti-inflammatory factors (transforming growth factor-β1 [TGF-β1] and interleukin-10 [IL-10]), and brain-derived neurotrophic factor (BDNF) in male patients with ASPD (n = 74), SUDs (n = 168), ASPD comorbid with SUDs (ASPD + SUDs) (n = 438), and Healthy Controls (HCs) (n = 81). A multivariate analysis of covariance (MANCOVA) controlled for possible confounders was used to compare cytokines and BDNF levels between groups. The results of MANCOVA adjusted for age showed a significant ($p < 0.001$) main effect of diagnosis on inflammatory factors and BDNF expression in these groups. ASPD, SUDs, and ASPD + SUDs patients had significantly ($p < 0.001$) higher TNF-α levels but lower TGF-β1 and BDNF levels. SUDs and ASPD + SUDs patients had higher IL-10 levels than did ASPD patients and HCs. There was no difference in IL-10 levels between HCs and ASPD. Moreover, subgrouping SUDs and ASPD ± SUDs into opioid use disorder (OUD) and other SUDs groups showed that the IL-10 levels were specifically higher in OUD and ASPD ± OUD groups than other SUDs ($P \leq 0.001$). We conclude that uncontrolled inflammation and losing neurotrophic factors, with or without comorbid SUDs, underlies ASPD. IL-10 expression might be more specifically associated with OUD.

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Table 1
Demographic data of ASPD, ASPD + SUDs, SUDs, and Control groups.

	ASPD	ASPD + SUDs	SUDs	Controls	Statistics	P	Post hoc
Number of cases	74	438	168	81			
Age (years) (mean ± SD)	36.8 ± 11.3	36.4 ± 7.7	39.1 ± 8.2	32.5 ± 8.2	F = 11.74	< 0.001*	C > B = A > D
Comorbidities							
Multiple SUD	0	262(59.8%)	92(54.8%)	0	χ^2 = 91.41	< 0.001*	B = C > A
Other Axis I or II comorbidities	6(8.1%)	52(11.9%)	38(22.6%)	0	χ^2 = 14.04	0.001*	C > A = B
Psychotic disorders	1(1.4%)	2(0.5%)	4(2.4%)		χ^2 = 4.50	0.11	
Mood disorders	5(6.8%)	39 (8.9%)	32(19.0%)		χ^2 = 14.22	0.001*	C > A = B
Anxiety disorders	3(4.1%)	20(4.6%)	11(6.5%)		χ^2 = 1.15	0.56	

ASPD, antisocial personality disorder; SUDs, substance use disorders.
A, ASPD; B, ASPD + SUDs; C, SUDs; D, Controls.
* P < 0.05.

1. Introduction

Antisocial personality disorder (ASPD) is a psychological condition in which a person has a long-term pattern of manipulating, exploiting, or violating the rights of others (Gibbon et al., 2010); it is also highly comorbid with substance use disorders (SUDs) (Regier et al., 1990). Epidemiological studies (Coid et al., 2006; Moran, 1999) report that ASPD is more prevalent in incarcerated populations (men: 47%; women: 21%) (Fazel and Danesh, 2002), than in the general population. ASPD challenges our society to adapt as it increases burdens on the criminal justice system and on health and social service agencies (Glenn et al., 2013). The disorder is difficult to treat and its response to psychotherapy or pharmacotherapy is limited (Gibbon et al., 2010; Khalifa et al., 2010), in part because its underlying neurobiological deficits have not been fully explored.

Emerging evidence shows that inflammation might be a hidden component in the pathophysiological pathway of ASPD. A genome-wide association study (Salvatore et al., 2015) suggests that immune-related gene sets might be involved in adult antisocial behavior. Studies on cytokines (Coccaro et al., 2014a, 2015; Graham et al., 2006; Ranjit et al., 2007; Suarez et al., 2002) have also reported that elevated levels of C-reactive protein (CRP) and tumor necrosis factor (TNF)-α, both pro-inflammatory cytokines, are associated with hostility, anger, impulsivity, and aggressive antisocial behavior. Cytokines are key signaling molecules regulate innate and adaptive immunological responses, and they have widespread effects on the neuroendocrine system, neurogenesis, neurocircuitry, and neurotransmitter metabolism (Haroon et al., 2012). TNF-α and CRP are important to trigger inflammation pathways (Agrawal et al., 2009; Mosmann and Sad, 1996); interleukin (IL)-10 and transforming growth factor (TGF)-β1 are important anti-inflammatory cytokines that counteract damage caused by excessive inflammation (Li et al., 2006; Lobo-Silva et al., 2016). Based on the above evidence, we hypothesized that the expression of TNF-α, CRP, IL-10 and TGF-β1 may be altered in ASPD.

Brain-derived neurotrophic factor (BDNF), which is substantially involved in a range of intracellular signaling processes, neuron protection, axon and dendrite morphology, and synapse plasticity, is widely expressed in the brain (Numakawa et al., 2010). BDNF-deficient mice show phenotypes with elevated aggression and hyperactivity (Chan et al., 2006; Ilchibaeva et al., 2015). Koenigsberg et al. (Koenigsberg et al., 2012) reported lower BDNF levels in patients with borderline personality disorder, which shares with ASPD some common characteristics of impulsivity and reactive aggression. Therefore, studies on BDNF levels in ASPD might provide a new perspective into the etiology of ASPD and its associated externalized behavioral phenotypes.

About 80–85% of people with ASPD also have comorbid SUDs (Regier et al., 1990), which implies that shared pathogenic changes underlie both disorders (Krueger and South, 2009). Dysregulated neuroinflammation is also involved in the development of addiction (Coller and Hutchinson, 2012). Larger doses and long-term substance use are associated with dysregulation of the immune system which damages neurons and triggers additional glial cells to upregulate the pro-inflammatory cytokines, TNF-α and CRP (Dyuizen and Lamash, 2009; Kapasi et al., 2000; Laso et al., 2007; Loftis et al., 2011; Pacifici et al., 2000; Reece, 2012), and to downregulate the anti-inflammatory cytokines, IL-10 and TGF-β1 (Buchanan et al., 2010; Nabati et al., 2013; Pacifici et al., 2000). This drug-induced activation of central immune signaling contributes substantially to increasing the engagement of classical mesolimbic dopamine reward pathways and withdrawal centers (Coller and Hutchinson, 2012; Narita et al., 2006), and associated with developing an addiction. Conversely, lower BDNF expression levels have been detected in chronic heroin users (Angelucci et al., 2007). Furthermore, postmortem data indicate that progressive neuron loss occurs in the brains of long-term heroin users (Li et al., 2005). Taking all of these findings together, we hypothesized that common event in chronic inflammation and the loss of neurotrophic factors are involved in the development of SUDs and of ASPD, and that patients with ASPD or SUDs will have higher inflammatory cytokine and lower BDNF levels.

It is important to exclude individuals with ASPD who are also substance-dependent when testing our hypothesis. Because comorbid substance dependency will affect cytokine and BDNF levels (Angelucci et al., 2007; Wang et al., 2012), and yield different results for individuals with ASPD and with or without SUDs. In Western populations, ASPD is often comorbid with alcohol use disorder (van den Bree et al., 1998), and it is difficult to recruit Western patients with ASPD but without substance use comorbidites. Approximately 50% of the Han Chinese population carry the ALDH2*1/*2 or 2*2/*2 genotypes, which protect against alcohol use disorder (Chen et al., 1999; Thomasson et al., 1991). Thus, it was possible to recruit a large sample of Han Chinese with ASPD but without alcohol use disorder or other SUDs (Lu et al., 2005; Lu et al., 2003), and to minimize the confounding variables.

The aim of this study was to determine the inflammatory and neurotrophic factors for ASPD. To evaluate the effect of comorbid substance use on the presentation of biomarkers, we investigated the cytokine and BDNF levels in the plasma of patients with ASPD, ASPD + SUDs, and SUDs, and of Controls. The results might increase our understanding in the biological differences between the clusters of externalizing disorders and provide more specific data on ASPD.

2. Methods

2.1. Participants

The research protocol was approved by the Institutional Review Board for the Protection of Human Subjects at National Cheng Kung University Hospital and by the Taiwan Ministry of Justice. Because the prevalence of ASPD for Han Chinese is only 0.1% (Hwu et al., 1988), much lower than the reported prevalence rate of 2–3% in Westerners