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Elevation of Pro-inflammatory and Anti-inflammatory Cytokines in Rat Serum after Acute Methamphetamine Treatment and Traumatic Brain Injury

Firas H. Kobeissy[1,2,3] · Zaynab Shakkour[1] · Samer El Hayek[4] · Wael Mohamed[5,6] · Mark S. Gold[7] · Kevin K. W. Wang[2,3]

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Abstract
The use of methamphetamine (METH) is a growing worldwide epidemic that bears grave societal implications. METH is known to exert its neurotoxic effects on the dopaminergic and serotonergic systems of the brain. In addition to this classical studied mechanism of damage, findings from our laboratory and others have shown that acute METH treatment and mechanical injury, i.e. traumatic brain injury (TBI), share common cell injury mechanism(s). Since neuro-inflammation is a signature event in TBI, we hypothesize that certain cytokine levels might also be altered in rat brain exposed to an acute METH insult. In this study, using a cytokine antibody array chip, we evaluated the serum levels of 19 cytokines in rats 24 h after exposure to a 40 mg/kg acute regimen of METH. Data were compared to rats subjected to experimental TBI using the controlled cortical impact (CCI) injury model and saline controls. Sandwich ELISA method was used to further validate some of the findings obtained from the antibody cytokine array. We confirmed that three major inflammatory-linked cytokines (IL-1β, IL-6, and IL-10) were elevated in the METH and TBI groups compared to the saline group. Such finding suggests the involvement of an inflammatory process in these brain insults, indicating that METH use is, in fact, a stressor to the immune system where systemic involvement of an altered cytokine profile may play a major role in mediating chemical brain injury after METH use.

Keywords IL-10 · IL-6 · IL-1β · Methamphetamine · Traumatic brain injury · Drug use

✉ Kevin K. W. Wang
kawangwang17@gmail.com

[1] Department of Biochemistry and Molecular Genetics, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

[2] Program for Neurotrauma, Neuroproteomics, and Biomarkers Research, Gainesville, FL, USA

[3] Department of Emergency Medicine, University of Florida, Gainesville, FL, USA

[4] Department of Psychiatry, American University of Beirut, Beirut, Lebanon

[5] Clinical Pharmacology Department, Menoufia Medical School, Menoufia University, Al Minufya, Egypt

[6] Basic medical science department, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

[7] Washington University School of Medicine, Department of Psychiatry, and National Council, Washington University in St. Louis, Institute for Public Health, St. Louis, MO, USA

Abbreviations

IL	Interleukin
METH	Methamphetamine
DA	Dopamine
TBI	Traumatic brain injury
NK	Natural killers
APC	Antigen-presenting cells

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability across all ages in the United States, affecting over 2 million persons annually (Taylor et al. 2017; Haskins et al. 2005; Farkas et al. 2005; Pineda et al. 2004; Smith et al. 2003). For the past two decades, extensive studies have been dedicated to investigating the mechanisms of action underlying the pathophysiology involved in TBI. It has been shown that TBI results in an imbalance between pro- and antiapoptotic protein machinery, promoting either cell survival or death (Lotocki et al. 2003; Shimamura et al. 2005; Sullivan et al.

2005). Studies reported from our and other laboratories provided evidence for the involvement of activated cysteine proteases as major intracellular effectors of neuronal cell death in TBI, via both the necrotic and apoptotic pathways mediated mainly via the calpain and caspase protease systems, respectively (Czogalla and Sikorski 2005; Pineda et al. 2004). Secondary insults often involve apoptotic cell death orchestrated by caspase-8 and caspase-9 activating caspase-3, leading to cellular injury (Lotocki et al. 2003; Wennersten et al. 2003).

Along the same line, many studies focused on the activated immune pathways and inflammatory markers involved in TBI (Apuzzo et al. 1979; Czigner et al. 2007; Lotan and Schwartz 1994). These markers contribute to the secondary damage observed after brain injury. Such immunomodulatory events, occurring in a timely fashion, are particularly mediated by exogenous infiltrating effector immune cells and by secreted cytokines, and develop as a result of the breakdown in the blood–brain barrier (BBB) (Liu and Sturner 1988). This is additionally accompanied by an endogenous transcription of different genes involved in the immunoregulatory response (Marciano et al. 2002).

Among the different players mediating the inflammatory response in TBI are the inflammatory-related interleukins (IL) and cytokines IL-1β, IL-6, IL-10, and TNF-α, all of which have been detected in the cerebral spinal fluid (CSF) of TBI patients (Csuka et al. 1999; Stahel et al. 1998). One feature in characterizing these cytokines is their time course of release following brain injury. In one study evaluating the dynamics of appearance of IL-1β and IL-10 after applying a TBI weight-drop model in a rat, IL-1β was upregulated within the first hour following injury, to reach a peak level after 8 h, after which it slightly declined. On the other hand, IL-10 presence showed a delayed increase, with a sustained level after 24 h. (Kamm et al. 2006). Despite this variation, human TBI studies have shown that, overall, different cytokines including IL-10, IL-1β, IL-8, and IL-6 are all co-elevated after TBI, reflecting an immuno-dynamic change (Hayakata et al. 2004; Maier et al. 2001).

Another form of chemical brain injury is induced by methamphetamine (METH) use, a major problem in the United States and worldwide (Lan et al. 1998; NSDUH-Report 2006; Perez et al. 1999). METH use has been on the rise due to several factors such as its ease of use, availability, affordable price, and high potential of addiction (Courtney and Ray 2014; UNODC 2019). In 2017, METH was responsible for approximately 15% of all US drug overdose deaths. Its consumption also increased by 7.5 times over the past 10 years (Hedegaard et al. 2018). METH is a potent psychostimulant drug known to cause brain damage by exerting its destructive effects on dopaminergic and serotoninergic systems in different brain regions, including the striatum, frontal cortex, hippocampus, and cerebellum (Bowyer et al. 2007; Jimenez et al. 2004; Pu et al. 1996; Seiden et al. 1988; Sokolov and Cadet 2006; Warren et al. 2006b). Besides, the general neurotoxic effects observed in METH use are strongly associated with the degeneration of the dopaminergic system, leading to a wide range of neuronal destruction (Cadet et al. 2003, 1997). It is believed that METH redistributes dopamine (DA) from vesicular storage, by acting on the dopamine transporter (DAT) and vesicular monoamine transporter-2 (VMAT-2), to the cytoplasm and extracellular space, where it is auto-oxidized into reactive oxygen species (ROS) and nitric oxide species (Miyazaki et al. 2013). These ROS then trigger a cascade of cellular damage and neuronal injury, thus implicating oxidative stress as a major contributor to METH-induced cellular death (Cadet et al. 2003). In fact, the increased synaptic availability of DA and associated metabolic changes following METH exposure can lead to the destruction of dopaminergic nerve terminals and neurons, eventually resulting in symptoms similar to the ones observed in neurodegenerative disorders such as in Parkinson's disease (Ares-Santos et al. 2013; Suwanjang et al. 2012). Moreover, METH damages phagocytic cells such as microglia and disrupts several molecular and immune cell functions, thereby increasing the vulnerability of users to acquire central nervous system (CNS)-related infectious diseases (Eugenin et al. 2013; Najera et al. 2016; Patel et al. 2013). Lastly, neurological deficits and psychiatric symptoms can occur secondary to the ability of METH to readily cross the BBB and directly damaging neurons and glial cells (Loftis and Janowsky 2014).

Our laboratory and others have recently reported that in vivo acute METH administration induced neurotoxicity in both cortical and hippocampal brain regions (Wallace et al. 2003; Warren et al. 2005, 2006a). Interestingly, it has been shown that METH treatment, similar to TBI, activates two major protease systems, the calpain (a calcium-dependent protease) and caspase systems, leading to neuronal cytoskeletal damage (Wallace et al. 2003; Warren et al. 2005). Along the same lines, studies have provided substantial evidence on immunomodulatory changes following METH administration, with elevation in inflammatory cytokines, such as IL-6, and increased neuronal cell death (Akbari et al. 2019; Asanuma et al. 2004; House et al. 1994; Kuhn et al. 2006; Yu et al. 2002; Ladenheim et al. 2000). Similarly, Yamaguchi et al. reported that the pro-inflammatory cytokine IL-1β was upregulated in the hippocampus following METH treatment (Yamaguchi et al. 1991). Several other recent studies investigated the neurological impairments associated with METH-induced inflammation, demonstrating a significant role of inflammatory mediators in developing and sustaining METH-induced neurotoxic effects (Lwin et al.

2020; Vargas et al. 2020; Yang et al. 2020). This current study aimed at examining the serum profile of inflammation-linked cytokines after the administration of acute METH (4 × 10 mg/kg) in adult rats and comparing it to the findings obtained in a TBI-CCI model.

Material and Methods

Animal Housing Conditions

All procedures involving animal handling and processing were done in compliance with guidelines set forth by the University of Florida Institutional Animal Care and Use Committee and the National Institutes of Health guidelines (IACUC). Animals were housed in groups of two per cage and maintained on a 12 h light/dark cycle (lights on 7 AM to 7 PM). Food and water were available ad libitum. All experiments were carried out on male Sprague Dawley rats, divided into four groups as follows: an experimental METH group ($n = 4$), a saline vehicle control group ($n = 4$), a TBI model group ($n = 7$), and a naïve group ($n = 7$).

Methamphetamine Drug Administration

Pharmacologic agent (+/−) methamphetamine hydrochloride (8.3 mg/ml) (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in 0.9% saline. Rats were intraperitoneally (i.p.) injected with METH in a bolus of 0.3 ccs to achieve a 10 mg/kg dose. This was repeated four times every hour to deliver a final dosage of 40 mg/kg. The saline group received a similar injection of physiological saline. METH and saline animals were euthanized by decapitation 24 h post-injection.

Experimental TBI Animal Model

A controlled cortical impact device was used to model brain injury in the TBI group, as described previously (Pike et al. 1998). Rats were mounted in a stereotactic frame and impacted in the right cortex (ipsilateral) with a 5-mm-diameter aluminum impactor tip, at a velocity of 3.5 m/s and to a depth of 1.6 mm. Naïve control rats were kept under the same environmental conditions but did not receive an impact injury. Naïve and injured animals were euthanized by decapitation 48 h post-injury.

Body Weight Measurement and Serum Collection

For groups receiving an injection, rats were weighed immediately prior to their first injection and after 24 h before euthanasia. In the case of TBI-treated animals, rats were weighed before the TBI procedure and after 48 h before euthanasia. After the desired periods, rats were briefly anesthetized with 3–4% isoflurane and were euthanized by decapitation; blood was collected from the trunk in plain vacutainer tubes. Serum was isolated from collected blood samples by centrifugation (4000 × g) and stored at −80 °C until use.

Measurement of Cytokine Release Using a Cytokine Antibody Kit

METH samples, TBI samples, and control saline samples were evaluated with the RayBio™ Cytokine Array kit 1.1 (RayBiotech Life, Inc., Norcross, GA, USA) according to the manufacturer's instructions. The cytokine membrane consisted of 19 different secreted cytokines spotted in duplicates along with positive and negative controls. This assay can simultaneously measure the relative levels of cytokines with high specificity. Serum obtained from METH-treated animals, TBI animals, and control saline animals were incubated with antibody cytokine membrane to determine the relative concentrations of cytokines. The relative densities of individual spots were measured using ImageJ software for spot analysis. Densitometric readings were analyzed and normalized using the RayBio™ Antibody Array Analysis Tool (RayBiotech Life, Inc., Norcross, GA, USA).

Densitometry Evaluation

Densitometric quantification of the sample array films was performed using an Epson Expression 8836XL high-resolution flatbed scanner and NIH ImageJ densitometry software (version 1.6, NIH, Bethesda, MD, USA). The densitometry values were evaluated for statistical significance with SigmaStat software (version 2.03, Systat Software Inc.). All data presented are expressed as mean ± SEM. Student's *t*-test was used to draw comparisons between intensities in the METH-treated vs. control (saline) groups and TBI vs. control (saline) group.

IL-6 and IL-10 ELISA Procedure

IL-6 and IL-10 levels were determined by an enzyme-linked immunoassay (ELISA) purchased from Bender MedSystems (Vienna, Austria) which was applied to validate the protein ship data. Serum cytokine levels were measured from 12 rats (TBI, naïve, METH, and control saline) according to the manufacturer's instructions. The cutoff value of serum IL-6 and IL-10 levels were 12 pg/ml and 1.47 pg/ml, respectively. The values given are quoted in pg/ml. All data presented are expressed as mean ± SEM. Student's *t*-test was used to draw comparisons between intensities in the treated group (METH and TBI) vs. control (saline) group. A p-value < 0.05 was used to denote significance.

Results

Changes in Rat Weight After METH Administration and TBI Insult

Changes in rat body weight after METH administration are shown in Fig. 1. Maximum weight loss was achieved 24 h after METH treatment. Following METH treatment, weight loss reached 30 g (12% of the rat body weight). This may be attributed to the METH-induced increased locomotor activity. This significant weight loss was not observed in the post-TBI group. In addition to this significant weight decrease, METH-treated rats exhibited violent behaviors, as shown by increased fighting tendencies. This was also accompanied by teeth loss, eye redness, and severe sweating. These stereotypical behaviors are associated with METH-induced central release of dopamine and norepinephrine (Ginawi et al. 2005, 2004).

Altered Cytokine Levels via Protein Cytokine Array

Serum analysis of the cytokine antibody array revealed a statistically significant increase in the levels of certain cytokines in both METH treatment and TBI groups (Figs. 2 and 3). Our array measured the levels of: CINC-2, CINC-3, fractaline, GM-CSF, IFN- γ, IL-1α, IL-1β, IL-4, IL-6, IL-10, LIX, leptin, MCP-1, MIP-3α, β-NGF, TIMP-1, TNF-α, and VEGF (Fig. 2). Interestingly, TBI and acute METH administration showed similar elevation in the levels of the three cytokines IL-1β, IL-6, and IL-10 (Fig. 3). This cytokine elevation in TBI, which is consistent with human TBI data, is indicative of immunostimulatory activation, reflecting a simultaneous elevation of different pro-inflammatory and anti-inflammatory cytokines after a traumatic brain injury, in both CSF and serum (Maier et al. 2001; Muller et al. 2001). These findings suggest that acute METH administration, similarly to TBI, involves an inflammatory process in addition to the classical METH-mediated neurotoxic events. The biological significance of the altered cytokines will be discussed later.

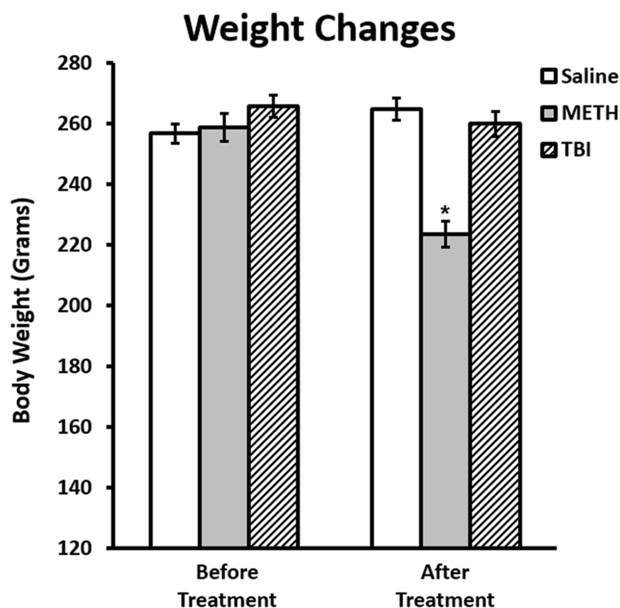


Fig. 1 Changes in rat weight after acute METH administration and TBI insult. For saline treatment (white bars), $n=4$; acute METH treatments (gray bars), $n=4$; and TBI insult (dashed bars), $n=4$. Rat weight decreases significantly following the 24 h drug administration, which reached approximately 12% of the total body weight. This weight loss was not significant in TBI rats. Results are expressed as mean ± SEM (g). Student's *t*-test was used to check for statistical significance ($p<0.05$ for each). *Significant result at the level of $p<0.05$

IL-6 and IL-10 Level Quantitation by ELISA

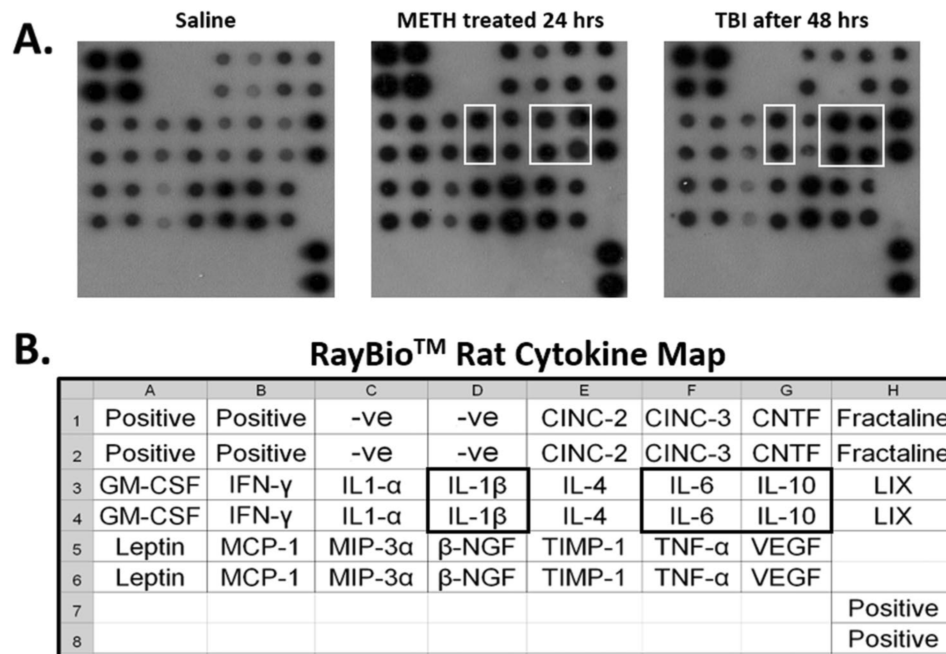
We quantified IL-6 and IL-10 cytokines—two cytokines that showed upregulation in both TBI and acute METH administration—by a conventional ELISA, as described in the Material and Methods section. Consistent with the cytokine antibody array results, ELISA yielded a significant statistical elevation in IL-6 and IL-10 after both acute METH administration (IL-6 = 1633 pg/ml and IL-1 = 944 pg/ml) and TBI insult (IL-6 = 1742 and IL-10 = 759 pg/ml) when compared to saline control (IL-6 = 764 pg/ml and IL-1 = 272 pg/ml) as shown in Fig. 4.

Discussion

Based on the accumulated data, TBI and acute METH use share several biochemical events, such as the dual activation of the caspase and calpain systems (Kobeissy et al. 2006; Pike et al. 2001). Furthermore, the activation of immune response is a signature feature in TBI in response to injury of neuronal cells (Csuka et al. 1999; Stahel et al. 1998). Thus, we hypothesized that an immunomodulatory response may be also involved in acute METH abuse.

We evaluated the differential serum cytokine expression in acute METH treatment (40 mg/ml) compared to that of TBI and control saline serum, using a cytokine antibody array kit that detects 19 different cytokines, as shown in Figs. 2 and 3. Interestingly, our cytokine data revealed an elevation in serum IL-1β, IL-6, and IL-10 in both TBI and acute METH treatment. IL-6 and IL-10 levels, which were quantified by sandwich ELISA, confirmed the cytokine antibody array data, as shown in Fig. 3.

Our TBI data, showing elevated IL-6 and IL-10, are in agreement with other human TBI studies which show



	A	B	C	D	E	F	G	H
1	Positive	Positive	-ve	-ve	CINC-2	CINC-3	CNTF	Fractaline
2	Positive	Positive	-ve	-ve	CINC-2	CINC-3	CNTF	Fractaline
3	GM-CSF	IFN-γ	IL1-α	IL-1β	IL-4	IL-6	IL-10	LIX
4	GM-CSF	IFN-γ	IL1-α	IL-1β	IL-4	IL-6	IL-10	LIX
5	Leptin	MCP-1	MIP-3α	β-NGF	TIMP-1	TNF-α	VEGF	
6	Leptin	MCP-1	MIP-3α	β-NGF	TIMP-1	TNF-α	VEGF	
7								Positive
8								Positive

Fig. 2 Serum analysis via the rat cytokine antibody array. Serum analysis via the rat cytokine antibody array revealed a correlation between increasing levels of certain cytokines with the two brain insults (acute METH administration and TBI). A panel of 19 secreted cytokines was checked for any changes in control saline-treated rats and rats with acute METH administration or TBI insults, by the RayBiotec cytokine array kit. (**A**) A representative cytokine blot is shown from the saline control, METH-treated, and TBI samples. The boxes bordering differential spots on the blots demonstrate the cytokines that are upregulated, which included IL-1β, IL-6, and IL-10, compared with the saline control serum. (**B**) The cytokine array map from RayBio™; it detects CINC-2, CINC-3, fractaline, GM-CSF, IFN- γ, IL-1α, IL-1β, IL-4, IL-6, IL-10, LIX, leptin, MCP-1, MIP-3α, β-NGF, TIMP-1, TNF-α, and VEGF

a marked elevation of both pro-inflammatory and anti-inflammatory cytokines, including IL-1β, IL-6, IL-8, TNF-α, and IL-10, which are also detected at different time points in time course studies (Csuka et al. 1999; Gonçalves et al. 2008; Maier et al. 2001; Muller et al. 2001). This differential expression of cytokines detected in serum or CSF is due to BBB disruption.

IL-6 is a pleiotropic cytokine that regulates immune response mechanisms and is produced not only by the immune cells but also by epithelial cells (Krueger et al. 1991). IL-6 is also important in development as it plays a role in cell growth and acts as a neurotrophic factor (Rothaug et al. 2016). However, despite its valuable roles, the overexpression of IL-6 is associated with several CNS abnormalities such as Alzheimer's disease (Lai et al. 2017), Parkinson's disease, and multiple sclerosis (Rothaug et al. 2016). Indeed, research has shown that acute activation of the inflammatory system is closely associated with neurological malfunctions, with a proven link between the inflammatory response, increased cytokine formation including IL-6, and neurodegeneration (Erta et al. 2012). When it comes to substance use disorders, several studies have provided substantial evidence that immunomodulatory effects follow drug use (Asanuma et al. 2004; House et al. 1994; Kuhn et al. 2006; Yu et al. 2002). These studies were focused on demonstrating how inflammatory cytokines, such as IL-6, are prominent factors that contribute to neuronal cell death following METH use. Along the same lines, it was indirectly shown that METH-induced neurotoxicity is attenuated in mice with IL-6 null mutation (Ladenheim et al. 2000) or mice pretreated with sigma receptor antagonists (Robson et al. 2013).

Alternatively, IL-1β is a pro-inflammatory cytokine produced by macrophages and dendritic cells (Connor 2004); it acts as an amplifier of immune reactions (Dinarello 2014). Serum elevation of IL-1β, along with IL-6, may be indicative of the pro-inflammatory environment at the injured area, which is infiltrated by peripheral immune cells due to BBB leakage (Liu and Sturner 1988). Following METH treatment, IL-1β was shown to be significantly upregulated in animal models (Du et al. 2017; Yamaguchi et al. 1991) and human cells (Liu et al. 2012; Tipton et al. 2010). Interestingly, a clinical study by Chiaretti et al. investigated the correlation between the expression of IL-1β, IL-6, and neurotrophic factors including NGF and BDNF in TBI (Chiaretti et al. 2008). The authors reported that early NGF and IL-1β levels were strongly related to the severity of the injury, and at 48 h post-TBI, higher expression of NGF and IL-6 with

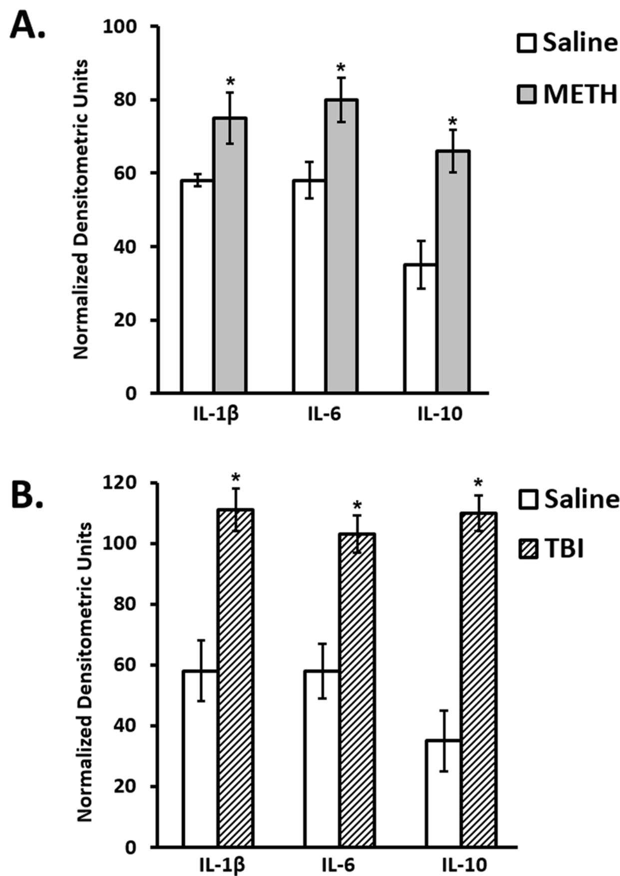


Fig. 3 Altered cytokine analysis in the rat serum after acute METH administration and TBI insult. (**A**) Graphical representation of the upregulated cytokines following acute METH treatment (gray bars) is shown compared to saline control (white bars); significant changes were observed (IL-1β, IL-6, and IL-10 cytokines). (**B**) Graphical representation of the upregulated cytokines following the TBI insult (dashed bars) is shown compared to saline control; significant changes were observed (IL-1β, IL-6, and IL-10 cytokines). Results are expressed as mean ± SEM (arbitrary densitometric units). Student's *t*-test was used to check for statistical significance ($p < 0.05$ for each). *Significant result at the level of $p < 0.05$

lower expression of IL-1β correlated with better neurological outcomes. Several studies have suggested that the neuroprotective effects associated with elevated expression of IL-6, IL-8, and IL-10 may be due to their ability to regulate the biosynthesis on NGF and other neurotrophins that are crucial in post-injury neuronal recovery (Ikeda et al. 2000; Sofroniew et al. 2001; Zhou et al. 2003).

Interestingly, IL-10, which is an anti-inflammatory cytokine that inhibits several macrophage functions, including pro-inflammatory cytokine production, was shown to be elevated post-TBI. The paradoxical presence of elevated IL-10 along with the pro-inflammatory cytokines IL-1β and IL-6 can be attributed to the time-dependent expression of these markers. Our study, which evaluated these cytokines after 24 h, may not express the true dynamic changes in these cytokines, as revealed in one rat TBI study by Kamm et al. which showed that IL-1β elevation precedes IL-10 elevation; however, 8 h after injury, IL-1β concentration starts declining, with sustained IL-10 levels (Kamm et al. 2006). Thus, a better assessment of these cytokines would be obtained by evaluating their concentration at different time points.

Cytokine evaluation following METH injection was measured 24 h post-treatment; this was based on our previously published data showing that the maximal effect of METH-induced neurotoxicity occurs 24 h after administration (Warren et al. 2005, 2006a, 2006b). In our current study, our data revealed that acute METH treatment exhibited similar cytokine elevation (IL-1β, IL-6, and IL-10) as that of TBI, as shown in Figs. 3 and 4. This was accompanied by behavioral findings of significant weight loss (Fig. 1) along with teeth loss, increased fighting tendencies, and excessive sweating which can be related to increased locomotor activity (Ginawi et al. 2005, 2004).

Recent studies have provided substantial evidence on immunomodulatory effects following drug abuse (Asanuma et al. 2004; House et al. 1994; Kuhn et al. 2006; Yu et al. 2002). These studies have focused on inflammatory cytokines such as IL-6 as a contributing factor, leading to neuronal cell death in METH abuse, where it was shown that METH-induced neurotoxicity is attenuated in mice with IL-6 null mutation (Ladenheim et al. 2000). In other studies, IL-1β was shown to be significantly upregulated in the hippocampus following METH treatment (Yamaguchi et al. 1991).

In another study by Yu et al. (2002), METH was shown to increase the secretion of TNF-α and to have a differential effect on the Th1 and Th2 cytokines by enhancing Th2 cytokine secretion while suppressing those of Th1 cells. Taken together, our data and others may indicate that an immune response is elicited following METH treatment; however, our study showed serum elevation of IL-1β and IL-6 that is not brain-derived, as shown in previous studies. This raises the question of the ability of these cytokines to infiltrate the brain. Interestingly, an elegant study by Bowyer et al. has shown that at high dosage of METH (40 mg/kg) in mice, METH can induce BBB disruption, coupled with microglial activation and macrophage infiltration (Bowyer and Ali 2006). Thus, our data showing increased pro-inflammatory cytokines may hint at neuronal degeneration mediated by the neurotoxic role of IL-6 on neuronal cells (Benveniste 1998; Gruol and Nelson 1997).

Indeed, the effects of METH use on BBB integrity have been previously described (Ho et al. 2009; Kousik et al. 2012). In experiments with animal models, Bowyer et al.

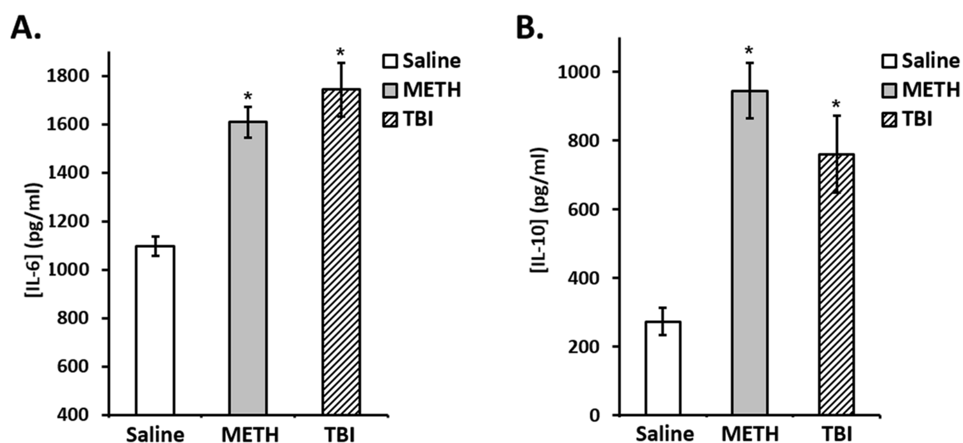


Fig. 4 ELISA quantitation of serum IL-6 and IL-10 after acute METH administration and TBI insult. Serum concentrations of IL-6 and IL-10 after saline treatment (white bars), acute METH treatment (gray bars), and TBI insult (dashed bars). IL-6 and IL-10 levels were increased significantly in a similar manner after acute METH treatment and TBI insult. Results are expressed as mean ± SEM (pg/ml). Student's *t*-test was used to check for statistical significance ($p < 0.05$ for each). *Significant result at the level of $p < 0.05$. The white panel represents the Saline, the grey panel represents the METH group and the lined panel represents the TBI animals

showed that high doses of METH administration (40 mg/kg) in mice can induce BBB disruption through the coupled action of microglial activation and macrophage infiltration (Bowyer and Ali 2006). Other plausible mechanisms of METH-induced BBB injury include disturbances of the tight junction proteins of the barrier and oxidative stress (Sajja et al. 2016). Currently, BBB dysfunction is thought to be a long-term cerebrovascular complication evident throughout the different phases of METH use, both in humans and animal models (Sajja et al. 2016). Such dysfunction can further contribute to central immune toxicity by increased leukocyte and monocyte transmigration across the endothelium and into the central nervous system (Mahajan et al. 2008; Park et al. 2013; Ramirez et al. 2009). Furthermore, matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) have been shown to play a crucial role in functional and structural remodeling of the cellular architecture, including BBB integrity, mainly by modulating the cleavage of ECM proteins and the bioavailability of cytokine and growth factors (Sternlicht and Werb 2001; Yong et al. 2001). Several studies suggested the involvement of TIMP-1 in neuronal plasticity including tissue reorganization and synaptic activity (Mizoguchi et al. 2007, 2011; Rivera et al. 1997). The expression of TIMP-1 has been reported to elevate during acute IL-1β activation and to fall only during chronic activation (Borgmann and Ghorpade 2015). Theodore et al. showed that levels of TIMP-1 along with other pro-inflammatory cytokines remained significantly increased in rat striatum 24 h after METH injections (Theodore et al. 2006). In fact, MMP/TIMP balance is highly important in the development of the CNS, in which uncontrolled proteolysis has been involved in different neuropathologies including brain injuries (Rivera et al. 1997; Siman et al. 1989). Interestingly, repeated METH exposure was found to induce the expression of MMP-2 and MMP-1, which in turn increased dopamine release, thus indicating that the MMP/TIMP system is also involved in regulating METH-induced behavioral sensitization (Mizoguchi et al. 2007, 2008).

In one study by Asanuma et al. (2004), utilizing genomic tools to investigate gene expression in METH-induced neurotoxicity, a number of genes belonging to the cytokine family were shown to be upregulated. This study focused on pro-inflammatory genes reflecting on the paradigm of inflammatory process in inducing neuronal cell death. It is suggested that METH activation of cycloxynase-2 (COX-2) and nitric oxide leads to the induction of inflammatory cytokines (Asanuma et al. 2004; Hirata and Cadet 1997; Itzhak and Ali 1996). This novel approach was evaluated by studying the effect of nonsteroidal anti-inflammatory drugs (NSAIDS) in ameliorating METH-induced neurotoxicity. Interestingly, using indomethacin, an NSAID, prior to an acute regiment of METH treatment (4 mg/kg × 4 i.p. at 2 h intervals), it was shown that reduction in dopamine transporters and microglial activation were attenuated in a dose-dependent manner (Asanuma et al. 2004). This highlights the role of immune activation after METH use.

Taken together, these data indicate that an inflammatory response activation may be involved in the METH-induced neurotoxicity. Thus, these data suggest using anti- inflammatory agents aiming at suppressing cytokine production and/or the activation of different inflammatory cells, such as macrophages and lymphocytes that produce them. This indeed, presents a novel strategy in treating METH-induced toxicity.

Finally, our data showed an elevation of IL-10, and although generally considered an immunosuppressive molecule, IL-10 exhibits some immunostimulatory properties, as shown in different studies. In this context, several studies have shown that IL-10 enhances the function

of natural killer cells which lead to antigen presentation by antigen-presenting cells (Lauw et al. 2000; Mocellin et al. 2003; Zheng et al. 1996). Whether IL-10 is acting as an immuno-suppressive agent, attenuating the inflammatory actions of IL-1β and IL-6, or as an inflammatory stimulant, its serum elevation would be detected in a similar pattern following a TBI insult so as to quell the damage of the secreted pro-inflammatory cytokines.

The findings in this study raise several research questions that demand further investigations. Firstly, a more in-depth analysis of the serum cytokine elevation needs to be conducted. In addition, future experiments need to examine whether serum or central nervous system cytokines are first to be elevated following METH use. This will provide more insights into the mechanism of action of the peripheral inflammatory response in METH neurotoxicity Lastly, understanding the role of IL-10 in modulating METH-induced inflammatory response is also important as it seems to play a vital role in the process.

Conclusion

In conclusion, the cytokine data reported in this study are indicative of a peripheral immunomodulation process occurring following acute METH exposure and TBI insults. The dual elevation of the pro-inflammatory cytokines IL-1β and IL-6 suggests a potentially harmful inflammatory response that could be contributing to either METH-induced neurotoxicity or TBI. Future work would necessitate an in-depth evaluation of serum cytokine levels at different time points following METH treatment and brain trauma. This information would provide a better understanding of the peripheral immune system's involvement in the neurotoxic effects of METH use or TBI. Finally, the finding that pro-inflammatory cytokines are present after acute METH administration reiterates the possible use of anti-inflammatory agents in treating METH-induced toxicity. Gaining further insights into the involvement of a heightened immune response in METH-induced neuronal damage may revolutionize the current approach to treatment.

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Authors' Contributions FK, KW, and MSG conceived and designed the study. FK and ZS collected the data. FK, SEH, and ZS contributed to data analysis. FK performed the experiments, WM, ZS, and SEH drafted the manuscript. All authors reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Material All data generated or analyzed during this study are included in this published article

Declarations

Ethics Declarations and Consent to Participate All the animal experiments in our study were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Florida.

Consent for Publication All authors read and approved the final manuscript.

Competing Interests The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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