REVIEW ARTICLE

Toxic Effects of Methamphetamine on Perivascular Health: Co-morbid Effects of Stress and Alcohol Use Disorders

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Abstract: Methamphetamine (Meth) abuse presents a global problem and commonly occurs with stress and/or alcohol use disorders. Regardless, the biological causes and consequences of these co-morbidities are unclear. Whereas the mechanisms of Meth, stress, and alcohol abuse have been examined individually and well-characterized, these processes overlap significantly and can impact the neural and peripheral consequences of Meth. This review focuses on the deleterious cardio- and cerebrovascular effects of Meth, stress, alcohol abuse, and their comorbid effects on the brain and periphery. Points of emphasis are on the composition of the blood-brain barrier and their effects on the heart and vasculature. The autonomic nervous system, inflammation, and oxidative stress are specifically highlighted as common mediators of the toxic consequences to vascular and perivascular health. A significant portion of the Meth abusing population also presents with stress and alcohol use disorders, prompting a need to understand the mechanisms underlying their comorbidities. Little is known about their possible convergent effects. Therefore, the purpose of this critical review is to identify shared mechanisms of Meth, chronic stress, and alcohol abuse that contributes to the dysfunction of vascular health and underscores the need for studies that directly address their interactions.

Keywords: Methamphetamine, stress, alcohol use disorders, cardiovascular, cerebrovascular, blood brain barrier.

1. INTRODUCTION

Methamphetamine (Meth) is a widely used psychostimulant with high abuse potential. The 2019 National Survey on Drug Use and Health reports that 1.7 million Americans over the age of 26 have admitted to using Meth within the past year, with approximately 500k users presenting with a Meth use disorder (MUD) [1]. While these numbers alone are alarming, they do not include the homeless or incarcerated population, which is reported to have a higher percentage of Meth users than the general population [2, 3]. The 2019 World Drug Report estimated 28.9 million users of amphetamines worldwide ranging in ages from 15-64 years, with the highest prevalence of amphetamine use in North America [4]. The consequences of MUDs manifest in negative consequences, both individual and societal [5]. The long-term toxic effects of Meth-use primarily affect the central nervous system, but there is also extensive damage to peripheral organs and systems. A clear understanding of the deleterious consequences related to Meth abuse and its potential treatment requires knowledge of co-existing conditions that comprise the vast majority of individuals with MUD.

Meth use disorders are commonly comorbid with alcohol and stress. Approximately 80% of amphetamine users also present with an alcohol use disorder (AUD) [6]. Furthermore, these intoxicants are commonly used in tandem that may provide a self-medicating loop of a stimulant and a depressant [7]. Stress is a well-documented risk factor for the development of addiction and the vulnerability to relapse. The effects of stress also influence patterns of alcohol and Meth abuse [8] and can further contribute to a triad of Meth, alcohol abuse, and stress.

While the neurotoxicological and addictive effects of Meth abuse have received the most attention, vascular and perivascular effects contribute to Meth-associated coronary risk, hypertension, and cardiomyopathy [9-10] and must be considered in understanding the neurotoxicity of Meth. Similarly, alcohol and stress have been shown to contribute to deleterious effects on cardio- and cerebrovascular health and can impact the neural effects of Meth.

This critical review will focus on mechanisms underlying the toxic consequences of Meth use as they relate to cerebro- and cardiovascular integrity. Of particular consideration is the contribution from the commonly occurring co-morbid disorders of stress and alcohol abuse with Meth.

2. MECHANISMS OF METH VASCULAR TOXICITY

2.1. Central Effects of Meth Toxicity

Meth is known to rapidly accumulate in the brain parenchyma of rodents after a systemic administration [11]. The small size and lipophilicity of Meth provide a facile transport

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into the brain. In humans, uptake into the brain accounts for 10% of a single i.v. dose, whereas most go to the liver (23%) and lungs (22%) [12]. Clearance from the brain, however, is among the slowest compared to other organs and may contribute to its long-lasting central effects. The slow clearance of Meth from the brain may be explained by its accumulation and binding to catecholamine-containing vesicles and catecholamine transporters (*e.g.*, noradrenergic, dopamine, and serotonin transporters). While Meth clearance from the body occurs mainly *via* excretion through the urine, the mechanisms for clearance from the brain are unknown [13]. Regardless, it is likely that clearance is regulated by drug efflux transporter proteins such as P-glycoprotein that actively transports large hydrophobic amphipathic drugs from epithelial cells of the BBB out to the peripheral circulation [14].

The mechanism of action for Meth in the central nervous system involves the displacement of intracellular monoamines *via* the reverse action of plasmalemmal monoamine transporters, thereby increasing their concentrations in the extracellular synaptic space. The increase in available monoamines is potentiated by the inhibition of monoamine oxidases, which typically regulate monoamine degradation and reduce synaptic availability of the monoamines [15]. The toxicological consequences associated with Meth abuse include the dysregulation of catecholamine sequestration (*e.g.*, displacement of dopamine from intracellular vesicles and increased synaptic presence) and catechol-derived reactive oxygen species. In the central nervous system, dysregulation of dopamine sequestration also occurs with glutamate-mediated excitotoxicity, mitochondrial dysfunction, monoamine terminal damage, neurodegeneration, and aberrant inflammatory responses [16]. The resulting decreases in markers of dopamine terminals are evident in pre-clinical studies as well as in human Meth users[17].

The blood-brain barrier (BBB) is comprised of a unique neurovascular unit composed of tight junctions within endothelial cell surfaces of the cerebrovasculature, as well as surrounding pericytes and astrocytes that provide protection from circulating plasma components that may be toxic to neurons while permitting the passage of essential ions and signaling molecules [18-20]. A compromised BBB allows for the unregulated passage of water, proteins, or inflammatory mediators such as macrophages and neutrophils that induce brain edema and can contribute to brain damage or neurodegeneration. Meth has been shown and suggested to reversibly permeabilize the BBB and aid in the delivery of less permeable therapeutics to the brain [21]. However, the biological mechanisms that contribute to the Meth-induced permeabilization of the BBB, such as hyperthermia, reactive oxygen and nitrogen species, mitochondrial dysfunction, and inflammation, suggest more long-term permanent effects [22-26].

The direct action of Meth on BBB integrity has been shown using organ-on-chip models of the human neurovascular unit that includes endothelial cells, pericytes, glia, and neurons [27]. By coupling three chips that model diffusion between the vascular and perivascular space, a reversible Meth dose-dependent loss of barrier function was identified. While no mechanism was proposed for the activity of Meth at the BBB in this study, mass-spectrometry analysis for each cell type revealed a disruption of the integrated signaling mechanisms between neuronal, vascular, and perivascular components that influence their metabolic states. For example, brain endothelial cells and astrocytes primarily depend on glycolysis and provide lactate as an energy source for neurons. One effect of Meth in this BBB model was to downregulate glycolysis pathways in the vascular and perivascular components with slight upregulation in the neuronal component. Other *in vitro* studies have similarly shown the direct effect of Meth on BBB integrity using cultured brain microvascular endothelial cells (BMVECs) as a model. Disruption of the modeled BBB has been attributed to modulation of tight junction protein expression [23] and increases in reactive oxygen and nitrogen species [24-25]. Not surprisingly, treatment with antioxidants during and after Meth attenuates BBB dysfunction. Similarly, Meth-induced generation of ROS has been linked to mitochondrial dysfunction and ER stress in cultured BMVECs that decreased cell viability, induced apoptosis, and disrupted tight junctions. In one study, the use of an ER-stress inhibitor, 4-phenylbutyric acid, before Meth administration blocked BBB disruption in C57BL/6J mice [28].

While Meth accumulation in the brain may provide a mechanism for the disruption of the BBB, peripheral factors are also implicated. A study by Northrop *et al.* identified the role of liver-derived ammonia in the permeabilization of the BBB *via* activation of matrix metalloproteinases (MMP9) [29]. In this study, treatment with lactulose prior to a Meth binge dose administration increased ammonia excretion and blocked MMP9 activation and BBB dysfunction. Additionally, work from this group found that local administration to the brain of ammonia and Meth, but not either species alone, produced neuronal damage similar to that seen with a systemic administration of Meth, collectively highlighting the role that peripheral mediators play in this toxic outcome [30].

Chronic methamphetamine induces hyperthermia in rodents and humans. Hyperthermia alone induces disruption of the BBB. Studies by Urakawa *et al.* indicate that localized hyperthermia (*i.e.*, the heating of rats' heads using floodlamps) increased the extravasation of systemically administered horseradish peroxidase (HRP) into the brain parenchyma [31]. A necrotic zone contained the highest HRP extravasation and also a loss of cell structure, capillary damage, and a reported "spongy" state. The reactive (2nd most affected) zone showed evidence of neuronal loss or shrinkage, infiltration of macrophages, and swelling of astrocytic endfeet, while the permeable (3rd most affected) zone only showed slightly swollen astrocytic endfeet. It was reported that HRP extravasation at the more highly disrupted zones was due to damaged endothelial cells and the induction of pinocytotic vesicles. A similar effect of Meth on the integrity of the blood-spinal cord barrier (BSCB) has been reported. A study by Kiyatkin and Sharma illustrated that a single subcutaneous injection of 9mg/kg Meth resulted in permeabilization of the BSCB and was associated with glial cell activation and edema [32]. Furthermore, they report that the effect on BSCB integrity was enhanced when the ambient temperature was increased. Interestingly, serum from mice that underwent a model of heatstroke (*i.e.*, 2h exposure to 40.1°C, 50% humidity environment) impaired the BBB integrity of iPS

cell-derived brain microvascular endothelial cells [33]. It is known that liver enzymes are increased in serum from heatstroke patients, and severe liver failure has been reported in heatstroke patients [34]. Furthermore, heat stress increases circulating ammonia in humans [35]. Thus, it is possible that Meth-induced hyperthermia in humans may influence BBB integrity by heat-induced liver toxicity that releases neurotoxic ammonia.

The gut-brain axis has been implicated in health and disease, including the effects of Meth. The bi-directional signaling that occurs between the GI tract and the central nervous system is largely mediated by the microbiome (*e.g.*, bacteria, fungi, and yeasts) that reside within the gut [36]. In addition, microbiome-derived mediators (*e.g.*, xenobiotic metabolites, short-chain fatty acids, and neurotransmitters) are known to influence the development, maintenance, and integrity of major organs such as the brain, including the BBB [37]. These mediators reach the brain *via* systemic circulation or through the vagus nerve, which originates in the brainstem and innervates the viscera, extending to the colon. Furthermore, the role of the gut microbiome and the gut-brain axis on psychological and pathological health has been associated with mood disorders and vulnerability to neurodegenerative diseases (*e.g.*, Alzheimer's, Parkinson's, and Lou Gehrig's disease) [38-39]. Meth exposure (2 mg/kg; s.c. b.i.d. for 14 days) has been shown to alter the composition, but not the abundance, of gut bacteria in male Sprague-Dawley rats. These changes were associated with depressive-like behavior, as assessed by the forced swim test [40]. Interestingly, a study performed in neonatal Wistar rats (PD 1-11) showed that exposure solely *via* breast milk from dams that were administered with Meth resulted in reduced spatial learning and memory formation in adulthood, suggesting a role for the gut-brain axis in neurodevelopment [40]. Indeed, multiple rodent studies have also identified a role for the microbiota in depressive behavior, social cognition, and the stress response, all of which are associated with the onset and persistence of addiction [41-42]. A study of the gastrointestinal microbiome among young homosexual men who frequently use Meth showed that those Meth users exhibited a microbial imbalance that favored pro-inflammatory bacteria, thus implicating the gut-brain axis in Meth use and behavior [43]. A study by Chen *et al.* showed that elevated levels of pathogenic bacteria in the colon were associated with decreased dopaminergic terminal integrity and increased markers of autophagy in the striatum of adult BALB/c mice treated with an escalating multiple-dose- binge Meth. Furthermore, an increase in intestinal autophagy flora and an accumulation of metabolites associated with the autophagy pathway was reported in fecal samples, indicating a potential gut-brain axis role in autophagy signaling [44]. Meth-induced changes in the gut microbiome have also been shown in female rodents. A study by Angoa-Perez *et al.* reported that a binge regimen of Meth in female mice induced a change in diversity and taxonomic structure of gut microbiota, following a binge regimen of Meth [45]. This study tracked dynamic changes in the microbiome composition for Meth and other drugs of abuse including substituted cathinones.

The role of gut-derived mediators in Meth-induced BBB toxicity has similarly received much attention. Normally, the gastrointestinal (GI) mucosa is the intestinal barrier that nec-

essarily separates pro-inflammatory luminal contents from the systemic circulation [46]. The breakdown of the gut-blood barrier can induce an enterogenic infection that occurs by the invasion of pro-inflammatory intestinal bacteria into circulation. These infections can be exacerbated by the Meth-induced decreases in circulating leukocytes [47]. This can contribute to the disruption of vascular integrity both centrally and peripherally. Indeed, it is reported that Meth use can induce paralytic ileus, intestinal infarction, and ischemic colitis, all of which are associated with increased inflammatory mediators which compromise intestinal barrier integrity and produce downstream general vascular dysfunction [48-51]. Of particular interest has been the release of gut-derived serotonin (5-HT) into circulation that may contribute to BBB disruption. It has been shown that increases in circulating 5-HT result in hyperthermia, oxidative stress, and BBB integrity disruption. The systemic administration of a 5-HT receptor antagonist and a 5-HT synthesis inhibitor provided a protective effect from increased circulating 5-HT, further implicating the role of 5-HT in BBB breakdown [52]. Studies performed in anaesthetized rats have similarly shown that intravenous infusion of 5-HT increased BBB permeability (by Evans Blue infiltration analysis), and pretreatment with a 5-HT receptor antagonist prevented this effect [53].

2.2. Peripheral Effects of Meth Toxicity

The peripheral and vasoactive effects of Meth are largely ignored as contributors to neurotoxicity, but like the central nervous system, effects of Meth are also regulated by increases in circulating catecholamines. The acute peripheral effects of Meth use include increases in heart rate and hypertension [54] due to the increases in circulating catecholamines that activate peripheral alpha 1- and beta 1-adrenoceptors [55]. Furthermore, the central effects of amphetamine on the peripheral cardiovascular system are largely due to the increased activity of noradrenergic signaling in the brainstem that can result in toxic consequences to organs densely innervated by sympathetic neurons, such as the heart [56-57]. Moreover, catecholaminergic neurons in the brain stem are distinctly vulnerable to Meth and are linked to cardiovascular collapse [58-59]. Meth acutely increases the activity of norepinephrine in the medulla that results in hypertension and tachycardia, while long-term Meth use and subsequent sensitization may contribute to hypotension and bradycardia that may be lethal. In fact, chronic Meth exposure to rats leads to hypoperfusion and striatal hypoxia with evidence of neuronal damage [60].

Adrenergic signaling and Meth-induced activation of the sympathetic nervous system have been implicated in Meth-induced cardiomyopathies. Adrenergic neurons in the brainstem largely regulate blood pressure through activation of pre-ganglionic vasomotor neurons *via* adrenergic signaling and vasopressin release [61]. High levels of vasopressin induce vasoconstriction that, in some cases, is sufficient to induce myocardial ischemia [62]. Activation of cardiac α- and β-adrenoreceptors by an adrenergic agonist is largely responsible for the increase in heart rate, and sustained or chronic activation can elicit fibrosis, limited contractile function, and necrosis such as that seen in pulmonary arterial hypertension (PAH). In fact, a retrospective study of Meth patients with clinically determined PAH and cardiomyopathy

showed that these comorbidities contributed to significant mortality risk and disease burden [9].

Long-term users of Meth commonly present with PAH [63]. Since Meth administered i.v, accumulates in the lungs, the mode of ingestion, *i.e.*, smoking vs. i.v., is not a primary mediator of this effect. Changes in the Meth-metabolizing enzyme carboxylesterase 1 (CES1) have been associated with PAH severity in Meth users. Sequencing data from 18 Meth-PAH patients revealed a single nucleotide variant in the CES1 gene that is predicted to reduce its activity [64]. The consequence of this loss of function was verified in pulmonary microvascular endothelial cells (PMVECs) that were transfected with the mutant enzyme resulting in reduced activity, whereupon treatment with Meth resulted in increases in ROS and apoptosis of PMVECs.

Chronic Meth use has been associated with increased atherosclerotic plaque formation associated with increased endothelial cell and macrophage activation and a consequent enhanced inflammatory response [65-66]. Nazari *et al.* have shown that plasma levels of endothelial-derived microparticles (EMPs) as markers of vascular injury are increased in rats that were administered Meth [67]. The increases in circulating EMPs were detected alongside increases in biomarkers of inflammation and oxidative stress. While Meth users typically lack the traditional atherosclerotic risk factors such as obesity and elevated serum cholesterol [68], increases in endothelial cell activation, inflammatory proteins and cytokines, oxidative stress, and the recruitment of activated macrophages and white blood cells provide a local environment that is conducive to atherosclerosis [69]. A study conducted using atherosclerosis-prone apolipoprotein E-deficient (ApoE$^{-/-}$) mice showed that chronic administration of Meth (*i.e.*, 4 or 8 mg/kg/day i.p. for 24 weeks) promotes atherosclerotic aortic lesions in a dose-dependent manner [70]. Furthermore, plasma and aortic levels of pro-inflammatory mediators such as C-reactive protein, TNF-α, and INF-γ were similarly increased. Further studies by this group showed atherosclerosis-prone mice fed a high cholesterol diet also exhibited increases in splenic pro-inflammatory leukocytes and cytokines and a decrease in anti-inflammatory leukocytes and cytokines in response to chronic Meth [71].

Clinical studies have also reported Meth-induced vascular toxicity in humans. A retrospective review of Meth-related deaths in Australia from 2000 and 2005 showed that coronary artery atherosclerosis was detected in 54% of the 371 study cases, where 14% of all study cases reported cardiovascular events as the direct cause of death [72]. Similarly, a study of Meth-related deaths from 2009-2015 identified cardiovascular disease as a major cause of death [73]. The primary and secondary causes of death for this cohort were accidental drug toxicity and cardiovascular disease, respectively. This study also identified clinically significant enlarged hearts and left ventricular hypertrophy, severe coronary artery disease, and evidence of earlier ischemic events. When only patients in whom cardiovascular illness was not the primary cause of death were examined, the trends remained the same. Similar long-range studies have identified higher incidences of cardiovascular disease and stroke events that include arrhythmia and hemorrhagic stroke in Meth users [74]. Despite the apparent association with Meth, it remains to be definitively determined if Meth is a direct cause or whether the generally compromised health status of Meth abusers is the main contributor to the cardiovascular disease of these individuals.

The contribution of gut-derived serotonin (5-HT), which accounts for 95% of the total 5-HT in the body, has received much attention due to its involvement in cardiovascular diseases and the regulation of peripheral and central vascular membrane permeability [75]. High circulating 5-HT levels have been significantly associated with coronary artery disease and the occurrence of deleterious coronary events [76]. It has been shown that 5-HT signaling regulates cardiovascular tissue remodeling and can result in cardiac hypertrophy, fibrosis, and valve degradation [77]. Interestingly, the distribution of 5-HT receptors mimics that of adrenergic receptors in the heart, and the role of 5-HT receptors in vascular wall remodeling and atherosclerosis has also been identified. A study by Hayashi *et al.* showed that the administration of a 5-HT receptor antagonist attenuated the progression of atherosclerosis in a high cholesterol-induced rabbit model of cardiotoxicity [78]. Furthermore, a study performed in monkeys showed that atherosclerosis potentiates the vasoconstrictor response to circulating 5-HT, implicating the neuromodulator in chronic peripheral vascular pathology [79].

3. MECHANISMS OF STRESS AND METH VASCULAR TOXICITY

3.1. Central Effects of Stress Toxicity

It is well accepted that stress is a part of life and, in some cases, results in favorable adaptability to unexpected conditions or stimuli. Allostasis refers to the collection of physiological responses that the body engages to maintain or regain homeostasis in the presence of a stressor. Chronic stress or allostasis overload is associated with psychological, metabolic, and cardiovascular diseases, among others [80-83]. Furthermore, chronic stress can result in a maladaptive response to stress which induces long-term metabolic dysfunction that contributes to disease states [84]. The stress response is largely regulated by the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Activation of these systems results in the production and release of hormones, peptides, inflammatory mediators, glucocorticoids, and other stress-molecules that activate biological systems for escaping or adapting to the stressor, all of which overlap with the effects of Meth (Fig. **1**) [85].

Similar to Meth, chronic stress alters the integrity of the BBB. Using *in vivo* two-photon microscopy, Lee *et al.* showed that chronic restraint-stress of mice results in a general cortical decrease in cerebrovascular diameter and volume and extravasation of a 40-kDa fluorescence-conjugated dextran, indicating BBB permeability [86]. They further report increases in expression of vascular endothelial growth factor α (VGEFα) and decreases in the tight junction protein claudin-5. The authors suggest that a sustained decrease in blood flow to the brain results in a hypoxic state that increases vascular endothelial growth factor (VEGF) and its receptor, VEGFR2. Not surprisingly, the animals in this study also displayed depressive behavior in an elevated plus-maze and increased corticosterone plasma levels. Although VEGF promotes angiogenesis to restore blood supply in hypoxic
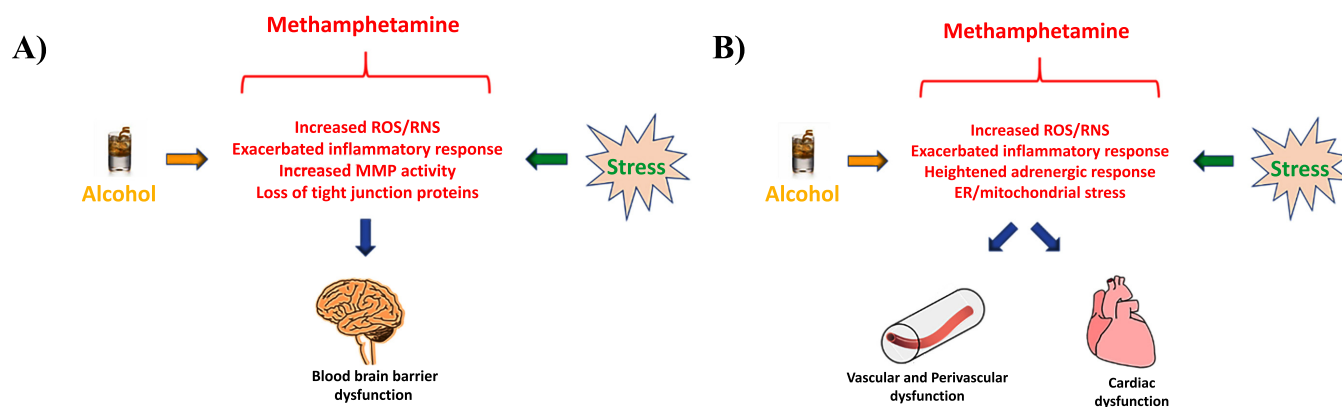
Fig. (1). Mechanistic overlap between Methamphetamine, chronic alcoholism, and stress that includes increases in reactive oxygen/nitrogen species, ER and mitochondrial stress, an exacerbated inflammatory response, and heightened adrenergic response provides insight into the toxicological consequences of their comorbidity in **A**) disruption of the blood-brain barrier and **B**) cardiovascular dysfunction. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

conditions, preclinical studies have shown it promotes BBB permeability through the breakdown of tight junction proteins [87, 88]. Likewise, a study reported by Menard *et al.* showed that chronic social defeat stress reduced BBB integrity, the tight junction protein claudin-5, increased the infiltration of the peripheral cytokine interleukin-6 into the brain parenchyma and produced depressive-like behavior [89].

The role of inflammation in stress-mediated BBB dysfunction has also been widely reported. The role of tumor necrosis factor-α (TNFα) in the disruption of the BBB and prolonged depressive-like behavior in mice was reported by Cheng *et al.* [90]. Mice that displayed prolonged depression after a learned-helplessness depression paradigm exhibited high levels of TNFα, activated glycogen synthase kinase -3 (GSK3), and interleukins in the hippocampus. Increased BBB permeability and reduced levels of tight junction proteins were similarly reported. Pharmacological inhibition of GSK3 during recovery reversed depressive-like behavior, reduced inflammatory cytokine levels, and recovered the loss of tight junction proteins. Similar results were obtained by administration of a TNFα inhibitor. The contribution of GSK3 to depression behavior in different stress models has been reported [91-92]. Its increased signaling interplay with corticosterone has also been shown in various studies [93-94]; however, the mechanism by which corticosterone modulates GSK3 activity is not known. Regardless, GSK3 activation regulates the immune response in the presence of stress [95]. For example, toll-like receptor 4 (TLR4) signaling can activate GSK3 that in turn mediates stress-induced increases in chemokines, cytokines, nuclear factor kappa B (NF- κB), and the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome [96].

Stress is a common risk factor in the development of addiction and relapse behavior. In Meth users, this may be due to various lifestyle factors that include childhood events, financial and housing insecurity, or poor nutrition and sleep [97-98]. While acute stress can reduce the subjective effects of a low dose of Meth in a clinical study [99], anecdotal evidence suggests that chronic stress or a maladaptive response to stress contributes to addiction behavior [100]. A longitudinal study of long-term Meth users in prolonged abstinence

reported stress as one of the most common themes in barriers to abstinence[98]. In a population of gay adult men who use Meth, there was a significant association between both poor mental health and alcohol use disorder (AUD), such that Meth and AUD severity were associated with comorbid mental health disorders [101]. Similarly, a comparison of individuals with previous life trauma to those that also self-report post-traumatic stress disorder (PTSD) showed that those with PTSD were more likely to report Meth use than those without PTSD [102]. Indeed, unresolved PTSD is largely considered to be a chronic stress disorder [103]. These studies are paralleled by pre-clinical studies in rodents reporting that stress triggers relapse to Meth and increases drug-seeking [8, 104].

Rodent studies have elucidated the interaction between stress and Meth on BBB integrity and identified mediators that are distinct to the comorbidity (*i.e.*, absent with either condition alone). Work by Northrop and Yamamoto indicates that neuroinflammation may be a point of convergence underlying the comorbidity that results in BBB dysfunction [105]. Rats exposed to a paradigm of chronic unpredictable stress (CUS) exhibited a decrease in the tight junction proteins occludin and claudin-5 and an increase in degradation of β-dystroglycan as an indicator of loss of the astrocytic endfeet component to the BBB after a Meth-binge dosage paradigm. Aside from the effects for claudin-5 and β-dystroglycan, these effects were absent in the CUS and Meth-alone cohorts, thereby indicating a synergistic toxicological profile. Not surprisingly, these results were accompanied by a loss of BBB integrity marked by extravasation into the brain of a peripherally administered fluorescein isothiocyanate (FITC)-dextran complex and evidence of brain edema. The effects on tight junction proteins and BBB integrity persisted for at least 7 days of withdrawal. While no increases in inflammatory markers were detected after 24h of withdrawal, the CUS-Meth cohort exhibited increases in the inflammatory marker cyclooxygenase-2 (COX-2), the inducible rate-limiting enzyme in the production of prostaglandins from arachidonic acid, after 7 days of withdrawal. Increases in COX-2, decreases in tight junction proteins, and extravasation of FITC-dextran were all prevented when ketoprofen,

a COX inhibitor, was given before and after a Meth binge.Surprisingly, the administration of ketoprofen during the Meth-binge did not block these effects, highlighting the temporal, progressive, and synergistic nature of the CUS-Meth toxicity to BBB integrity. This study also reported the protective effect of the prostaglandin receptor 1 (EP1) antagonist administered during withdrawal on the extravasation of FITC-dextran, further implicating the prostaglandin-mediated inflammatory response to BBB dysfunction in the CUS-Meth paradigm.

A similar study also highlights the role of COX-2 in CUS-Meth mediated dysregulation of the BBB. Natarajan *et al.* reported that rats that underwent a paradigm of 10 days of CUS followed by 7 days of unrestricted Meth self-administration (SA) exhibited decreases in tight junction proteins that were mediated by COX-2 [106]. This study identified increases in COX-2 and degradation of β-dystroglycan in cortical isolated capillaries at 3 days after the last day of Meth SA that persisted for at least 7 days, at which time point decreases in occludin were also apparent. Furthermore, these effects were detected in the CUS-Meth cohorts only and not with either drug alone. Administration of the COX-2 specific inhibitor nimesulide during withdrawal blocked the aforementioned effects. In contrast, a study of lipopolysaccharide (LPS)-mediated BBB disruption reported that permeability is exacerbated in COX-2 $^{-/-}$ *vs.* COX-2 $^{+/+}$ mice when compared to similar COX-1 mice models, suggesting that COX-2 maintains BBB integrity [107]. This seemingly contradictory involvement of COX-2 suggests its differential role in initiating or responding to BBB permeability by a drug (*i.e.*, Meth) vs. an inflammatory insult (*i.e.* LPS) and provides further evidence of a novel response to this comorbidity.

3.2. Peripheral Effects of Stress Toxicity

Similar to Meth, stress poses a risk for peripheral cardiovascular disease. Several clinical studies have identified a role for social stress in poor cardiovascular outcomes, including hypertension, cardiovascular disease, stroke, and sudden cardiac death [108]. Retrospective analyses of clinical reports show a correlation between adverse life events and cardiac pathologies. These include, among others, bereavement of a loved one, loneliness, difficult work environment, financial and home life stress, and natural disasters [109-111].

The effects of chronic stress on cardiovascular diseases can be partially attributed to the imbalance of the autonomic nervous system imposed by the activation of the sympathetic nervous system. A study by Costoli *et al.* reported that a mouse model of repeated social defeat episodes concurrent with the constant threat of further attack by a dominant mouse resulted in a 6-fold increase in cardiac reparative tissue throughout the ventricular wall when compared to mice in a controlled social environment [112]. Furthermore, real-time electrocardiogram (ECG) measurements *via* radiotelemetry indicated a shift toward increases in the sympathetic response with subsequent stress. As fibrosis of cardiac tissue is a common cause of cardiac arrhythmia, the authors claim that the increased fibrosis in socially defeated mice may be due to adrenergic stimulation and ventricular remodeling. The deleterious effects of adrenergic catecholamines on cardiocyte health and myocardial remodeling have been re-

viewed and reported elsewhere [113-115], but one central mechanism may involve calcium dysregulation *via* L-type voltage-gated calcium channels (L-VGCC) [116-117]. A likely scenario underlying both stress and Meth with regard to cardiovascular disease is that β-adrenergic stimulation increases L-VGCC phosphorylation, which increases channel availability and subsequent intracellular calcium, exacerbates cardiac activity, and induces arrhythmic behavior [118-119] upon exposure to Meth.

Similar to the effects on cerebrovascular integrity, stress-induced inflammation also plays a role in cardiovascular health. Chronic inflammation is a landmark of cardiac disease and is correlated with chronic stress [120]. Activation of the HPA axis induces a release of glucocorticoids (GC) that inhibits the expression of inflammatory mediators such as TNF-a and interleukin 6 (Il-6) [121, 122], which can further act to increase GC release. In the case of cytokine overload, this negative feedback loop is dysregulated due to decreases in GC-responsiveness that result in a chronic state of inflammation. Indeed, circulating levels of IL-6 have been reported as associated with or predictive of atherosclerosis [123].

Little is known regarding the contribution of stress to the perivascular effects of Meth, but preclinical studies provide insight into the potential mechanisms that result in cardiotoxicity. A study by Tomita *et al.* reported mice that were administered Meth and exposed to a subsequent water-restraint stress exposure for 1, 3, and 6h exhibited a significant increase in serum markers of cardiotoxicity at all time points [124]. Histological examination of cardiac muscle confirmed this effect. Furthermore, significant increases in circulating TNF-α and IL-6 were reported in the stress+Meth group when compared to either condition alone. Additionally, cardiac RNA expression for the inducible heat shock protein 70 (Hsp 70) was increased specifically in the Meth-only group that may reflect its attempt at cardioprotection [125, 126]. The protective role of Hsp70 in cardiotoxicity has been shown in various studies. Indeed, a study by Song. *et al.* reports that cultured neonatal rat cardiomyocytes that underwent a model of ischemia-reperfusion-induced injury exhibited increased Hsp70 expression, phosphorylated MAPK, calcium overload, markers of apoptosis, and expression of IL-1β and IL-6 [126]. While transfection with a short-hairpin RNA against Hsp70 exacerbated these outcomes, incubation with a MAPK inhibitor blocked the exaggerated effects of Hsp70 knockdown, implicating a protective role for Hsp70 and a deleterious role for MAPK signaling. The well-established role of MAPK in the regulation of chronic inflammation may provide an explanation for its role in cardiotoxicity [127]. A further study on the combined effects of stress and Meth reports that acute stress inhibits the Meth-induced increases in Hsp70 that results in enhanced myocardial damage in mice. Furthermore, chronic exposure to a stress+Meth paradigm resulted in a further reduction in Hsp70 expression in cardiac tissue, accompanied by an exacerbated histopathological damage to cardiac muscle [128]. While these studies indicate a shared mechanism that includes the inflammatory and heat-shock response, further studies are required to identify mechanisms underlying additive versus synergistic interactions.

Interestingly, clinical studies also implicate Hsp 70 levels with chronic stress and drug-induced mortality. A study of steelworkers who self-report chronic exposure to industry-

related stressors (*e.g.*, severe noise, dust, heat) showed high incidences (~26-40%) of plasma antibodies to Hsp 70, compared to control office workers (18%) [129]. Furthermore, there was a significant correlation between the presence of antibodies and hypertension, even when correcting for work stress. Similarly, a retrospective analysis of organ samples from 50 autopsy cases of toxicologically proven drug-induced mortality found high immunoreactivity for Hsp70 in heart, brain, and kidney of Meth, morphine, and alcohol cases [130]. While these results are not surprising for the Meth cases, since the induction of Hsp70 is considered to provide cells resistance to stressful conditions and impart thermotolerance [131], the authors report that high levels for Hsp70 were present in tissues regardless of reported hyperthermia, indicating an alternative mechanism underlying the induction of Hsp70. Indeed, adrenergic receptor stimulation has been reported to increase Hsp70 expression in vascular tissues in rats, which may explain an increase that is independent of hyperthermia [132].

The role of stress on the gut-blood barrier integrity and downstream effects has recently received attention among researchers. Numerous gastrointestinal diseases and complications arise from chronic stress [133]. Chronic stress increases inflammation in the gut mucosa and increases colon/gut-blood barrier permeability, as well as modifying the composition of the gut microbiome [134-135]. The damage produced by chronic stress initiates a pro-inflammatory cascade of cytokines such as IL-1β and TNFα released from the epithelium that ultimately degrades the tight junctions of the GI barrier to cause "Leaky Gut Syndrome" [136]. Consequently, bacteria-derived toxins such as lipopolysaccharide (LPS) are leaked into the systemic circulation and result in endotoxemia. Unsurprisingly, endotoxemia is associated with chronic non-communicable diseases that include coronary artery disease and arteriosclerosis[137]. This is likely due to the commonly occurring theme of an unmitigated hyper-inflammatory state that contributes to the pathology in these diseases. The endotoxin LPS resides on the membrane of gram-negative bacteria and binds to toll-like receptor 4 (TLR4) to induce an innate immune response that signals the activation of NFκB and COX-2 and the release of cytokines IL-1β and TNF-α [138]. Importantly, peripheral circulating cytokines and LPS can enter the brain *via* the lymphatic system or by crossing the blood-brain barrier [139-140] to cause neuroinflammation and promote BBB disruption [141]. While the combined effects of Meth and chronic stress and the contribution of gut-derived mediators on vascular dysfunction remain largely understudied, it is possible that their shared mechanisms in the gut-barrier breakdown and pro-inflammatory status would exacerbate peripheral and central vascular integrity. An additional point of convergence may reside in the interactions between circulating 5-HT known to directly modulate microbial growth [142] and changes in the gut microbiome that are induced by Meth or stress-alone.

4. MECHANISMS OF AUD AND METH VASCULAR TOXICITY

4.1. Central Effects of AUD Toxicity

Multiple lines of evidence suggest an interaction between AUD and Meth-induced vascular toxicity (Fig. **1**). For the

purpose of this review, alcohol and ethanol (EtOH) will be used interchangeably with the understanding that ethanol is the component of interest, whereas traditional consumption of alcohol by humans may contain various byproducts. Indeed, beneficial contributions from de-alcoholized red wine have been shown in human subjects [143]. Alcohol use disorders are defined as chronic diseases marked by the impaired ability to stop or control use despite recurring negative consequences [144]. The 2019 National Survey on Drug Use and Health (NSDUH) reported that 14.1 million (5.6%) of American adults aged 18 years or older self-reported with an alcohol use disorder (AUD). Furthermore, it is reported that approximately 80% of Meth users also present with an AUD and are commonly used in tandem [6-7, 145]. The popularity of the co-use of these drugs stems from the reported increases in the positive subjective effects compared to either drug alone [146] as well as the use of alcohol to blunt the negative stimulant effects of Meth. Irrespective of the reasons for their co-abuse, the high incidence of the comorbidity between alcohol and Meth imparts particular obstacles to addiction profile identification, treatment compliance and presents unique toxicological outcomes [147-149].

EtOH easily enters the brain and bypasses most biological membranes and the BBB due to its small size and lipophilicity. EtOH is metabolized and converted to acetaldehyde (Ach) by oxidative enzymes, including the inducible cytochrome P450 E1 (CYPE1) isoform, alcohol dehydrogenase (ADH), and catalase. The oxidative reaction of CYP2E1 is easily decoupled, resulting in the production of reactive oxygen species (ROS) such as superoxide [150]. Haorah *et al.* used a human BMVEC model of the BBB and showed that *in vitro* exposure to a physiologically relevant concentration of EtOH resulted in increases in CYP2E1 and ADH and the production of ROS [151]. These changes were accompanied by myosin light chain (MLC)–mediated phosphorylation of tight junction proteins, decreased BBB integrity, and monocyte migration across the BBB. Furthermore, Ach and exogenous ROS treatment recapitulated these effects. It is important to note that Ach alone, similar to Meth, increases mitochondrially-derived ROS as well as covalently modify proteins or compete with the metabolism of endogenous aldehydes [152, 153]. A similar study using the BMVEC model extended the above findings and identified decreases in the expression of tight junction proteins after long-term EtOH exposure that was mediated by PKC-α phosphorylation of the tight junction proteins [154].

Pre-clinical studies have also highlighted the vulnerability of the BBB to chronic EtOH consumption *in vivo*. A study by Ehrlich and Humpel reports that male Sprague Dawley rats exposed to vascular risk factors associated with acute ischemic stroke (*i.e.*, homocysteine, cholesterol, and 20% EtOH each separately for 5-12 months) exhibited BBB leakage in the cortex [155]. This treatment paradigm also resulted in declined spatial memory in an 8-arm radial maze. Blaker *et al.* have shown that the exposure of male Sprague Dawley rats to a 2-bottle choice (intermittent access/every other day) of water and 10% EtOH *ad libitum* for 28-days resulted in the detection of LPS in the brain parenchyma (*i.e.*, the dorsal striatum), suggestive of BBB permeabilization [148]. Similarly, Pen *et al.* reported that CD1 and B6

mice that ingested a 5% EtOH alcohol solution *ad libitum* for 2 weeks in a 2-bottle choice paradigm exhibited increased albumin and leptin permeation across the BBB [156]. Interestingly, they report that acute exposure to EtOH (*i.e.*, administration of a 20% EtOH injection i.p.) did not induce BBB disruption. The acute vs. chronic effects of EtOH consumption on the BBB illustrate seemingly contradictory findings. For instance, male Sprague Dawley rats that were allowed 7.5% EtOH *ad libitum* in a 2-bottle choice for 12 months showed no BBB permeability to systemically administered radiolabeled sucrose [157]. This was also true for the acute administration of an anesthetic dose of EtOH. However, *i.v.* administration to adult mongrel dogs of increasing amounts of EtOH resulted in the presence of systemically-administered sodium fluorescein (NaF) in cerebrospinal fluid, an indication of BBB disruption [158]. This work also showed that the extent of NaF extravasation correlated with increasing concentrations of administered EtOH. Additionally, Yorulmaz *et al.* reports that female adult Wister albino rats that were subjected to an EtOH-induced coma (*i.e.*, administration of a 4g/kg injection i.p.) did not elicit significant BBB permeability [159]. These results indicate that EtOH-mediated BBB disruption is highly dependent on multiple variables such as drinking paradigm (*i.e.*, acute *vs*. chronic), EtOH concentration, method of detection, and model (*i.e.*, *in vitro vs*. *in vivo* and species or sex).

No studies have directly identified the consequences of EtOH and Meth on BBB integrity but the mechanistic overlap of the toxic consequences on the BBB from each drug alone indicates that the effect would be at least additive. For example, various studies have indicated that Meth increases circulating LPS through dysregulation of the intestinal gut-blood barrier. Studies reported by Singh *et al.* show male alcohol-preferring rats that were allowed 70 days of a 2-bottle choice between water and 15% EtOH exhibited significant and persistent (at least 48h) BBB permeability to radio-labeled-dextran but only when challenged with an i.p. administration of LPS [160]. They further report that while LPS administration induced a transient effect on BBB integrity, there was no such effect in the rats that only consumed EtOH. Furthermore, immunohistochemical analyses of brain sections from postmortem alcoholic individuals illustrate evidence for BBB disruption in humans [161]. This analysis reports a decrease in the BBB proteins collagen-IV and claudin-5 and increases in the neuroinflammatory markers glial fibrillary acidic protein (GFAP) and allograft inflammatory factor 1 (Iba-1) immunoreactivity in the prefrontal cortex of alcoholics. Increases in MMP-9 activity and upregulation of the mitogen-activated protein kinase (MAPK) signaling pathway accompanied these changes. Indeed, Meth has been shown to similarly increase c-Jun terminal kinase and MAPK activation in human brain endothelial cells [162], thus indicating a shared mechanism of BBB disruption. A study of mice that were subjected to a binge-drinking "Drinking in the Dark" paradigm showed similar decreases in collagen-IV and claudin-5 and increases in IgG immuno-reactivity in the brain parenchyma, signs of BBB disruption[161]. These changes were similarly associated with markers of MAPK pathway upregulation. Interestingly, TLR4-knockout mice that underwent the same paradigm did not display these effects, suggestive of the role of TLR4 and potentially LPS in the alcohol-induced disruption of the BBB. The overlap in inflammatory signaling including the roles of TLR4/LPS and MMP9 activation between Meth and EtOH, may provide some evidence for their combined effects on BBB integrity.

4.2. Peripheral Effects of AUD Toxicity

Moderate consumption of EtOH is considered to be beneficial with regard to psychological, cognitive, and cardiovascular health [163-164]. A protective effect of EtOH against ischemic stroke, myocardial infarction, and hypertension has been reported in clinical studies [165-167]. This effect has been mostly attributed to decreased stress, anti-inflammatory properties, and changes in the circulating lipid profile [168-169]. However, the effects of chronic or high concentrations of EtOH on the cardiovascular system are reported to include hypertension, coronary heart disease, and arterial disease, among others [170].

Chronic alcohol exposure can result in adverse changes to the structural and functional aspects of cardiomyocytes [171]. In some cases, the result is cardiomyopathy which is commonly reported for chronic alcoholics [172]. Cardiomyopathy is marked by impaired cardiac contractility that leads to systolic dysfunction, left ventricular chamber dilation, and inefficient cardiac output that can result in congestive heart failure or even sudden death [173, 174]. Clinical studies have shown that while EtOH consumption results in vasodilation and an increase in heart rate, there was no increase in functional output [175]. Furthermore, evidence of injury to the myocardium (*i.e.*, depression of ventricular dysfunction and release of myocardial ions and transaminases) was reported in participants that received a higher dose (12oz pour of scotch) of alcohol vs. those that received a lower dose (6oz pour of scotch).

Apoptosis of the non-regenerable cardiomyocytes may explain the commonly reported alcohol-induced cardiomyopathy. A study by Guan *et al.* showed that primary rat cardiomyocytes treated with increasing amounts of EtOH for 24h resulted in concentration-dependent apoptosis, with detectable necrosis at the highest concentrations [176]. Furthermore, intracellular increases in ROS and decreases in mitochondrial membrane potential were identified. The protective effect of both vitamin E and C on ROS and apoptosis indicated that oxidative stress, presumably from mitochondria, was crucial in cardiomyocyte cell death. A similar study highlights the role of mitochondria in the EtOH-induced apoptosis in cultured cardiac cells [177]. Prolonged exposure of 48h resulted in a calcium-induced activation of the mitochondrial permeability transition pore that allowed for the release of the pro-apoptotic cytochrome c. Immunohistochemical analyses of post-mortem cardiac samples from individuals with long-term alcoholism revealed a significant increase in markers of apoptosis when compared to control subjects [178]. The results from alcoholic individuals were comparable to those from non-alcoholic subjects with long-standing hypertension and indicated similar stress to cardiac tissue. The onset of mitochondria-mediated apoptosis may also be due to the EtOH metabolite, acetaldehyde (Ach), in that Ach induces mitochondrial dysfunction and increases intracellular ROS [179]. Furthermore, inactive polymorphic variants of aldehyde dehydrogenase 2 (ALDH2), the metabolizing enzyme for Ach, have been implicated in the vulnerability to alcoholic heart disease [180].

The contribution of lipopolysaccharides (LPS) to the progression and pro-inflammatory state of atherosclerotic plaques has also been proposed. Orally ingested alcohol compromises the tight junctions of the gut-blood barrier that allows for the passage of proinflammatory mediators derived from gut bacteria (*e.g.*, LPS) into the circulation. Lipopolysaccharides from gram-negative bacteria present as a pathogen associated molecular marker (PAMP) that activates an immune response marked by increases in cytokines and other pro-inflammatory mediators. An analysis of samples from carotid and thyroid arteries from clinical patients who underwent a carotid endarterectomy that involves the removal of fatty plaque from the carotid artery revealed high immunoreactivity for LPS and TLR4 co-localized with the activated macrophage marker, CD68 [181]. Furthermore, incubation of human-derived peripheral blood mononuclear cells (PBMCs) with concentrations of LPS that mimic the clinical observations resulted in a TLR4-mediated increase in the superoxide-generating enzyme NADPH oxidase 2. Lehr, *et al.* reported rabbits that received a hypercholesterolemic diet and were challenged with a chronic administration of LPS (2.5ug, i.p. once a week for 8 weeks) or cutaneous Staphylococcus aureus infection exhibited the formation of atherosclerotic plaques that were significantly accelerated when compared to control animals [182]. Collectively, these results provide a mechanism for the pro-inflammatory nature of EtOH-induced atherosclerotic plaque pathology.

While little is known regarding the contribution of chronic EtOH to the perivascular effects of Meth, the mechanistic overlap of their individual effects may provide some insight and influence the design of necessary experiments. The role of inflammation and LPS signaling provides one aspect of focus. Persons *et al.* showed that rats that self-administered Meth (2h/day for 21 days) exhibited permeability of the gut epithelium that regulates colon barrier integrity [183]. The authors claim that dysregulation of the tight junction proteins claudin-1 and zonula occludens-1 increases colon permeability such that LPS may translocate to the circulation and contribute to systemic inflammation. Similar effects of Meth on the gut and intestinal ischemia have been reported [49-50]. The effects of EtOH on the gut-blood barrier integrity have also been discussed. The presumption is that chronic exposure to these drugs in tandem would have an exacerbated effect on the gut-blood barrier that would contribute to inflammatory mechanisms that underlie cardiovascular pathology. Furthermore, calcium signaling in cardiomyocytes may also be a point of convergence. Cardiomyocytes from human induced pluripotent stem cells that were treated with physiologically relevant doses of EtOH showed dose-dependent increases in calcium transients and contractibility [184]. These effects were paralleled by increases in ROS, cellular damage, and decreased cell viability. Similarly, Meth has been shown to induce increases in intracellular calcium levels in cardiomyocytes. Sugimoto, *et al.* have shown that Meth alters the calcium oscillation pattern in cultured cardiomyocytes from neonatal rats that were not affected by an adrenergic receptor antagonist, indicating a direct role of Meth [185]. Meth-induced increases in L-type voltage-gated calcium channels (L-VGCC) activity were verified by using the L-VGCC inhibitor nifedipine. In fact, calcium dysregulation has negative consequences on cardiomyocyte phenotype and function [186]. Moreover, the direct role of Meth identified in this study is particularly important in the comorbidity of EtOH and Meth since EtOH has been shown to inhibit the metabolism of Meth and prolong its activity [187-189]. Overall, it is clear that EtOH contributes to the perivascular effects of Meth, most likely through the mechanisms identified above.

Similar to that discussed with chronic stress and Meth, the role of gut-derived mediators in chronic alcohol-induced disorders have also received attention. Chronic alcohol consumption alters gastrointestinal tract integrity and function by modifying intestinal microbiota composition (*i.e.*, increasing "bad" while decreasing "good" bacteria), increasing oxidative stress, and inducing cell death and loss of epithelium [190-191]. The alcohol-induced overgrowth of intestinal bacteria and dysbiosis has been reported in multiple human and animal studies [192-194]. This effect leads to an increase in the release of endotoxins like LPS that promotes the inflammatory response and contribute to loss of peripheral and central vascular integrity. Similarly, the modification of the gut microbiome has also been identified for Meth and stress [195-196]. While little focus has been placed on their interactions, it can be assumed that effects would be at least additive and require further investigation.

CONCLUSION

The effects of Meth, stress, alcohol, and their comorbid effects impart distinct consequences on central and peripheral perivascular health. This review focuses on toxicological outcomes from exposure to these agents and does not focus on aspects of addiction or treatments for ongoing or chronic use. The extensive amount of clinical and pre-clinical studies that focus on one or the other of these drugs and stress is a testament to their impact on individuals, communities, and the larger population. There is a wealth of existing evidence that identifies parallel mechanisms underlying Meth, chronic stress, and alcohol abuse that compromises vascular and gastrointestinal health. Regardless, there is a need for studies that address their convergent and direct interactions as a majority of the Meth abusing population present with co-existing conditions. Fig. (**1**) illustrates overlapping roles of sympathetic activation, inflammatory status, and oxidative stress in these disorders that could guide future research that examines the vascular and perivascular effects of stress and alcohol on the neurotoxicity to Meth.

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