Methamphetamine and its immune-modulating effects

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ABSTRACT

Methamphetamine (METH, or ice) use is a global burden, which continues to pervade and plague contemporary society with estimates of up to 35 million users worldwide. METH is a psychotropic compound which acts on the central nervous system, and, in chronic doses, can induce psychotic behavior from its highly addictive nature. METH harbours the capacity to cause modulation of immune cells, enabling the drug to have lasting, long-term effects which may manifest into neuropsychiatric disorders, as well as leading to increased susceptibility to communicable diseases, such as HIV. In addition, changes to the cytokine balance have been associated with blood brain barrier compromise, resulting to alterations to brain plasticity, creating lasting neurotoxicity. Furthermore, immune-related signaling pathways are key to further evaluating how METH impacts the host immunity through these neurological and peripheral modifications. Layering this knowledge with current data on inflammatory responses can help facilitate a better understanding of how the host adaptive and innate immunity responds to METH, how this can activate premature-ageing processes and how METH exacerbates disturbances leading to non-communicable age-related diseases, including cardiovascular disease, stroke, depression and dementia.

Keywords:
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Signaling pathways

1. Introduction

Methamphetamine (METH, also known as ice), is the second most popular drug of choice worldwide [1]. In the 2014 United Nations office on drugs and crime, world drug report indicated that METH accounted for 80% of all amphetamine-type stimulant seizures [2]. In the 2017 World drug report, METH was reported to be used by around 37 million people across the globe, with other reports indicating between 14-53 million METH users globally [2]. Worrying, is the trafficking of METH around the world with data suggesting expanding METH markets in South East Asia, Oceania, along with growing concerns about METH use in North America, parts of Europe and China. In Australia, an increase of high purity crystalline METH has been documented since 2010. As a result, METH-related hospital admissions have been on the rise, from just under 2,000 hospital admissions - from 2009-2010 - to just over 10,000 cases from 2014-2015 [3]. Three forms of METH are currently found in Australia; powder methamphetamine, also known as speed; base METH, a damp oily form characterized by its yellow or brownish hue [1] and crystal METH, also known as ice, a crystalline and highly pure form of METH [4]. Crystal METH in its smoked form is the most popular choice of METH use in recreational and social settings; however, due to the attached health risks and high dependence of smoking METH there has been a substantial increase for METH treatment [5]. METH use disorders have been previously attributed to those subgroups, such as rural persons who are more likely to use METH in comparison to those residing in metropolitan areas [6]. This has been supported by reports that young people living in rural areas are twice as likely to use METH in comparison to those living in urban areas [3, 6]. Comparing the patterns and prevalence of METH users in rural and metropolitan areas, shows statistically significant differences in METH use, particularly crystal METH, in those living in rural locations [5]. These results were supported by the fact that rural men and employed rural Australians were more likely to use METH, with prevalence being mostly between the ages of 18-24 and 25-29 years – reported as higher than Australians residing in cities [5, 7]. In addition, previous data has reported that older people who are HIV seronegative who have a high level of METH use are at risk of contracting the illness [8]. In assessing the oral health and quality of life, out of 545 METH users, the majority comprised older males – median age of 45 years – with a greater degree of worsening oral health [9]. The recent statistics show that out of 390 METH users, 24.36% were aged 35-49, with 8.72% aged 50-64 [10]. METH's ease of manufacture stems from its easily obtainable ingredients, which contribute to the final METH product. This ease of manufacture has led to the prevalence of local "METH" laboratories, along with "super-labs" operated by larger organizations [11]. Overall, a lack of well-rounded knowledge and perception, other than METH's short-term effects, is available on how this drug impacts the immune system long-term. This long-term impact currently remains to be fully explored, and understanding this aspect of METH use in addiction and withdrawal scenarios can help strengthen our current perspective on METH, help inform and guide public policy, notify on

influencing communicable and non-communicable disease prevalence and risk, and impart METH's relationship to augmenting the ageing process.

2. Methodology

Searches were conducted through NCBI PUBMED using the following search terms: Methamphetamine OR METH AND population AND age, Methamphetamine OR METH AND immune system, methamphetamine OR METH AND immune dysregulation, methamphetamine OR METH AND cytokines OR chemokines, methamphetamine OR METH AND addiction, methamphetamine OR METH AND monocytes, methamphetamine OR METH AND macrophages, methamphetamine OR METH AND dendritic cells, methamphetamine OR METH AND T-cells, methamphetamine OR METH and natural killer cells, methamphetamine OR METH AND astrocytes, methamphetamine OR METH AND inflammation, methamphetamine OR METH AND immune pathways, methamphetamine OR METH AND Australia, methamphetamine OR METH AND global use, methamphetamine OR METH AND cell signalling. Articles included mainly those post-2000; and, within the reviewed articles other articles were assessed for suitability for this review. Inclusion criteria was based on peer-reviewed articles denoting experimental studies, both *in vitro* and *in vivo*, of methamphetamine and its impacts on the immune system and its constituents. Non-English language articles were excluded from being included in this review.

3. Effects of METH on immune cells

The effects of METH on the immune response have yet to be fully determined, however, there is growing evidence that METH suppresses and modulates the immune system [12, 13]. Consequently, immune dysregulation through METH abuse could lead to lasting neuropsychiatric conditions [14]. METH has significant effects on both the innate and adaptive immune responses [12, 15], with reported reductions in the numbers of natural killer (NK) cells and leukocytes [16]. In addition, macrophages stimulated by METH show increased levels of the pro-inflammatory cytokine TNF-α [17-19]. METH causes decreased levels of dendritic cells (DCs) [20], impacting the adaptive immune system and rendering individuals susceptible to certain diseases and infections [16]. Furthermore, there is growing evidence that mood disorders are related to the changing levels of pro-inflammatory cytokines and their influence on the level of monoamines; along with the dysregulation of the hypothalamic pituitary adrenal (HPA) axis, activation of microglial cells, and changes in the neuroplasticity of the brain [21].

3.1. Monocytes and macrophages

Monocytes differentiate into both macrophages and DC as they circulate to sites of inflammation. Monocytes represent immune effector cells, in which chemokine receptors and adhesion receptors allow them to migrate from blood to sites of infection [22]. In healthy individuals, 90-95% of circulating monocytes are CD14+CD16-, whilst 5-10% are CD14+/CD16+ [23]. Macrophages secrete cytokines in response to external stimuli, which are involved in the recruitment of other immune cells to initiate a cascade of innate and adaptive immune responses [17]. In the presence of METH, macrophages secrete pro-inflammatory cytokines, interleukin-1 (IL-1) beta, IL-2, IL-6 and IL-8 [24] with IL-1β and IL-6 being significantly upregulated in the co-presence of bacterial lipopolysaccharide (LPS) [25]. Likewise, co-stimulation of macrophages with LPS and METH results in a significant increase in IL-1β, IL-8 and TNF-α [26]. Furthermore, the number of monocytes and macrophages are reduced in the presence of METH, and their cell surface marker expression are altered with the upregulation of CD80 and down-regulation of CD11b whilst there are no effects on GR-1(high) monocyte/macrophage cells [20]. In a the context of human immunodeficiency virus (HIV-1) - METH increases expression of levels of galectin-1 which is involved in HIV-1 viral absorption [27].

3.2. Dendritic cells

DCs express a diverse range of cell surface receptors in order to sense their environment and activate immune-related functions [28]. Amongst these receptors are toll like receptors (TLRs), surface pattern recognition receptors (PRRs) and NOD-like receptors which assist in detecting signals such as those associated with pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) [28]. DC are also professional antigen presenting cells, where they efficiently activate the adaptive immune system. Stimulation of DCs with METH results in altered chemokines, chemokine receptors, cytokines, G-protein signaling, cell cycle regulation and cell transcriptional regulation [16]. Specifically, METH was shown to increase HIV-1 co-receptors CXCR4 and CCR5 in human monocyte-derived DC [29]. Similar work investigating METH use and HIV-1 infection, demonstrated the differential expression of the chemokine receptor CXCR3 in immature DCs (IDC) [30]. More broadly, METH has been shown to decrease the overall abundance of splenic DCs, which renders the effectiveness of the adaptive immune response [20]. Moreover, a high-throughput investigation study of genomic changes to mature DCs noted significant increased levels of CCR5, CCR2, IL-1β TNF-α and IL8; in addition, to decreases in IL-IR3 and TGF-β [16].

3.3. T cells

T cells play an important role in the orchestration of immune responses [30]. There are few studies that document the effects of METH on T cells. In mice, chronic METH administration reduces the number of CD4 and CD8 T cells in the spleen [20]. In addition,

METH significantly increases expression of the inflammatory chemokine receptor CXCR3, suggesting that METH contributes to effector T cell function and migration [12, 31]. METH also prolongs the transition from G1 to S phase of T cells [32]. In particular, METH alters gene expression by suppressing the CDK-cyclin E complex, a critical limiting factor which is suppressed in CD4 and CD8 T-cell subsets and disrupts cell cycle progression [32]. This finding was also consistent with changes in other cell cycle genes, such as E2F1, responsible for normal cell cycle regulation [32]. Similarly, METH causes down-regulation of cell-cycle genes and proteins involved in apoptosis in a rat study addressing acute hepatic injury from METH [33]. METH also alters intracellular calcium concentrations in T cells via reactive oxygen species (ROS) production, leading to mitochondrial injury [34].

3.4. Natural Killer cells

NK cells are primarily involved in the destruction of virally-infected cells [35], and any dysfunction or numbers of NK cells, results to overall suppressed immunity [20]. METH has been shown to markedly increase the activation of NK cells [36] through an increase in simian immunodeficiency viral load and CNS damage in simian immunodeficiency virus-infected macaques. The increase in NK cells were primarily present in the brain and in peripheral sites [36]. In addition, the cell surface marker, CD107a or lysosome-associated membrane protein-1, is increased in the presence of METH [37]. However, splenic NK cells have been shown to be significantly reduced in METH treated mice [20]. These results also showed a marked reduction in CD27 and killer cell lectin-like receptor expression [20]. CD27 is an important cell surface marker of NK cells as it is involved in its cytotoxic function [38]. Thus, METH induces a dysregulated NK cell profile, one that indicates a suppressed state.

3.5. Astrocytes

Primary astrocyte cell cultures cultured in the presence of METH for 24 hours, significantly upregulates CXCL5, MAP2K5 and GPR65 as core gene network components with both neuroprotective and neuropathological roles [39]. MAP2K5 belongs to the MAP kinase family; CXCL5 has been implicated in the activation of the PI3K/AKT, MAP kinase and β-catenin pathway, and GPR65 has been described as a GCPR activated through extracellular acidic pH via protonation of histidine residues, regulating cell behavior [40]. In addition, METH increases expression of Caspase-11 and TLR4 of primary astrocyte cell cultures [39]. This study also reported the downstream expression of nuclear factor-kappaB (NF-κB) through the MyD88 independent pathway and MyD88 dependent pathway, from expression of TLR4. Consequently, increased transcription of inflammatory cytokines is found in the nucleus [39].

4. METH and inflammation

METH abuse leads to severe dysregulation in the peripheral immune response, leading to an imbalanced expression in cytokines, chemokines and other molecular factors. In addition, expression of pro- and anti-inflammatory cytokines and chemokines have been implicated in METH-related neuronal injury which may also be related to METH addiction [41]. Further, METH-induced immune dysfunction has potential to augment HIV replication [42]. Interestingly, inflammatory responses have the ability to pass through the blood brain barrier (BBB) which can rely messages responsible for inducing changes to motor function and motivation [43].

4.1. Tumor necrosis factor-alpha

Tumour necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine which has cell signaling functions and can cause chronic and acute inflammatory responses along with having a central role in the pathophysiology of autoimmune diseases such as ulcerative colitis, rheumatoid arthritis and multiple sclerosis. TNF-α can either be membrane bound or in soluble form, with roles in apoptosis, immunity development and tumour cell necrosis. It is primarily produced by macrophages and is encoded by the TNF-α gene present on chromosome 6 and 17 [44]. TNF-α is known to be involved in activation of transcription factors such as AP-1 and NF-κB which can lead to a number of other physiological and pathological mechanisms [45]. In addition, METH stimulation of BV2 cells and primary microglial cells pre-treated with LPS, causes the expression of TNF-α via the cAMP/PKA/CREB signaling pathways [33]. Based on these findings, further studies are required that target the TNF-α cytokine pathway. Seeking to better define the role of METH in HIV-1 pathogenesis, gene and protein expression of TNF-α was markedly increased by DCs [16]. Better understanding of this pathway can help to inhibit the harmful effects caused by METH abuse.

4.2. Interleukin-1 beta

IL-1β induces catabolic effects and inflammatory reactions and is encoded by the IL-1β gene [46]. Maturation of IL-1β requires the action of enzyme caspase-1, converting it into active its IL-1β form [47]. Activation of NF-κB results in increased expression of other cytokines and chemokines [48]. The effects of IL-1β has a significant effect on the metabolism and on the extracellular matrix of the cells as seen in patients with osteoarthritis [49]. Since NF-κB is activated both in METH treatments and as a result of IL-1β stimuli, it is plausible to assume that METH may cause change in expression of IL-1β. In fact, METH stimulation of monocytic cell lines differentiated to macrophages resulted in elevated expression of IL-1β [33]. It was proposed that the pathways involved in such stimulation included NF-κB and mitogen-activation protein kinase (MAPK). Recently, in mice, METH-induced T-cell alterations of IL-1β profiles [12].

4.3. IL-10

IL-10, is an anti-inflammatory cytokine that has a role in preventing inflammatory and autoimmune pathologies [50], and is secreted by a variety of activated immune cells [39]], having pleiotropic effects on T and B cells, long with myeloid cells [51]. In addition, IL-10 has been described as a soluble factor released by type-2 T helper cells, in which also inhibits the secretion of type-1 T helper cytokines [51]. Upregulation of IL-10 has previously been reported in mice [32]. Recently, IL-10 was shown to prevent metabolic programming induced, in macrophages, by inflammatory stimuli [39]. METH has been shown to increase IL-10 in human plasma [14]. Similarly, the evaluation of METH in microglial cell (ESdM) activation showed an increased IL-10 production following 48-hr METH treatment [52]. In a comprehensive gene array overview, macrophages stimulated over a time-dependent METH dose showed considerable upregulation of IL-10 at 6 hours post METH exposure [17].

4.4. IL-12

The IL-12 family, comprising IL-12, IL-23, IL-27, and IL-35 are key players in the pathophysiology of immune responses in various disease conditions [53]. Monocytes, macrophages, DC and B-cells are able to secrete IL-12 [54]. In mouse spleen, IL-12 was shown to decrease; conversely, mouse liver and kidney revealed significantly increased expression of IL-12 [15]. Moreover, IL-12, in conjunction with other cytokines also function to inhibit HIV-1 expression and infectivity in macrophages [54].

4.5. IL-6

IL-6 is a multipotent cytokine secreted by various immune cells, such as monocytes, macrophages, fibroblasts and tumour cells [55]. Additionally, the IL-6 receptor (IL-6R) system and signal transduction mechanism has importance in immune regulation and inflammation [56]. IL-6 has been implicated in Alzheimer's disease, and may be used as a useful biomarker in determining the extent of cognitive impairment [57]. mRNA IL-6 expression is increased in mice in the hypothalamus, hippocampus, striatum, cortex and cerebellum following METH injection compared to saline treated mice [26]. In an astrocytic cell line cultured wth METH for 3 days, IL-6 RNA levels increase 4-fold. In addition, METH exposure for 24 hours increases both mRNA and protein expression of IL-6 [57]. In the same study, IL-6 expression found to be overridden by the IKK-b inhibitor SC415 [57]. Coelho-Santos et al (2012) found that microglial cells exposed to METH caused an increase in IL-6 expression and also upregulated IL-6 receptor (IL-6R-a) after 24 hours [58]. Interestingly, exogenous IL-6 expression was shown to have an anti-apoptotic effect through activation of the JAK-STAT3 pathway [58]. Assessing the anti-neurotoxic agent asiatic acid, it was noted that METH-induced neuronal cells treated with asiatic acid inhibited IL-6 secretion [59]. In addition, BV2 cells and primary glial cells treated with METH, showed an elevated expression in the levels of IL-6 along with TNF-α [60]. Likewise, an early increase in the levels of IL-6 expression in hippocampus and striatum in mouse brains is noted within 1.5 hours post METH injection [19].

4.6. IL-2

IL-2 is reported as having specific function in T cell homeostasis and memory differentiation [61]. The addition of METH to T cells *in vitro* increases IL-2 secretion by 3-fold [34]. Furthermore, when METH was conjgated to lymphocytic choriomeningitis virus promoter, it further exacerbated IL-2 secretion by splenocyte CD4 and CD8 T cells [30]. Likewise, METH-treated mice were found to exhibit an increased expression of IL-2 in the hippocampus [14]. Additionally, METH was shown to increase the IL-2RG system and IL-2 ligand in an HIV-1 model, with the authors noting that this IL-2RG/IL-2 expression representing an important mechanism contributing to neuro-inflammation [61].

4.7. IL-8

IL-8 is a chemokine known to be associated with an inflammatory response in several neurological disorders, including Parkinson's disease [62]. In astrocytes, METH was shown to increase IL-8 in a dose-dependent manner [62]. Other work has described a moderate IL-8 upregulation in the presence of METH on macrophages [17]. Similarly, macrophages treated with METH at 48 to 72 hours resulted in significant increase in IL-8; these findings, compared to macrophages treated with LPS alone showed higher IL-8 expression [25]. Huckans et al, through hypothesising the relationship between METH, immune factors and neuropsychiatric symptoms were able to show IL-8 to be a significant marker of anxiety and depression [63].

5. Other inflammatory responses to METH

5.1. Cyclooxygenase-2

Cyclooxygenase-2 (COX-2) is expressed by stimulation from an assortment of pro-inflammatory agents, with its expression in the brain signaling physical and psychological stress [64]. METH has been shown to increase striatal expression of COX-2 protein [65, 66]. Induction of COX-2 through the NF-κB pathway results in nitric oxide, prostaglandins and inflammatory cytokine production [67]; and, induction of COX-2 might suggest drug-induced neurodegeneration [67]. METH significantly increases COX-2 protein expression in the striatum within 72 hours after METH administration to mice with no changes in COX-2 expression in the hippocampus and cerebral cortex. Interestingly, a relationship between depleted dopamine and a delay in COX-2 expression was observed. Similarly in an acute METH dose, significant reduction in COX-2 positive cells are noted in the striatum after 24-hours. In addition, upregulation of COX-2, with co-expression of NF-κB is noted after 72 hours, and this is marked by reductions in dopamine in the striatum. Reports of COX-2 expression in METH models, suggests its targeting in early METH-related neurotoxicity during METH use. Increased COX-2 expression is noted in a METH-CUS (chronic unpredictable stress) model, and this has been suggested to enhance monoaminergic depletions in both the hippocampus and striatum [64].

5.2. CXCR4

METH enhances expression of chemokine receptor CXCR4 in the brain [24]. In HIV-1 infection, METH in a dose-dependent manner caused an increase of CXCR4 expression by DCs [68]. Due to the involvement of the CXCR4 receptor, being a major co-receptor, along with CCR5 in HIV-1 infection, CXCR4 may be a likely candidate for targeting in the development of therapeutic prevention of HIV-1 entry into cells in METH addiction [27].

5.3. CXCL10

CXCL10, known also as IFN-γ-induced protein 10, is a chemoattractant for immune cells such as T-cells and monocytes [59]. In response to IFN-γ, in an appropriate inflammatory environment, CXCL10 is secreted from the host's immune cells upon activation of its receptor CXCR3 [59]. METH has been shown to significant increase CXCL10 in astrocyte cells and is involved in the activation of the innate immune system [69].

5.4. CXCL5

CXC chemokine ligand 5 (CXCL5) is a cytokine expressed in a range of cell types, including monocytes [70] and endothelial cells, along with several organs including the brain [70] and lung [71]. In the lung, and in response to microbial infection, CXCL5 orchestrates neutrophil trafficking by activating G-protein and arrestin signaling pathways [71]. Interestingly, through pro-inflammatory cytokines, CXCL5 is activated via activation of NF-κB, and produced by immune and vascular endothelial cells [70]. Additionally, tumor suppressors and oncogenes work to regulate CXCL5 expression. In astrocyte cell cultures, low to high concentrations of METH over 24-hour exposure significantly upregulates CXCL5 gene expression [39].

5.5. CXCR3

The chemokine receptor, CXCR3 is the receptor for the IFN-inducible chemokines CXCL9, CXCL10 and CXCL11 and its expression on activated T cells. In addition, CXCR3 is crucial for amplifying IFN-γ-dependent recruitment of cells in peripheral sites of infection [31]. METH has been shown to significantly differentially regulate CXCR3 protein expression in immature-DCs [72]. In addition, chronic METH exposure strongly increases CXCR3, which is important in CD8 T cell recruitment, in order to provide modulation of T cell memory [12]. CXCR3 is known to have roles in migrating T cells into the microenvironment of peripheral tissues, aiding in their interaction with antigen presenting cells leading to effector and memory T cells [31].

6. Immune pathways activated in the presence of METH

Immune pathways relating to drug addiction have been documented as falling into two categories: those pathways involved in upstream events of drug addiction; i.e. MAPK signaling and calcium signaling. The second are pathways involved in downstream effects, including those regulating glycolysis metabolism, regulation of the actin cytoskeleton and apoptosis [37]. Pathways which are impacted upon by METH, and which increase the inflammatory response have been described as the AKT-PI3K, NF-κB, MAPK [25]; [62], along with the JAK-STAT pathway [58].

6.1. NF-κB signaling

The NF-κB family of inducible transcription factor proteins exist as inactive cytoplasmic complexes, in which activation of NF-κB occurs via two main signaling pathways; canonical and non-canonical [73, 74]. NF-κB proteins involve a cascade of events which begin outside the cell, converging in the nucleus [75], promoting immunity through controlling expression inflammatory genes [73, 76, 77]. Through the action of cytokines and PAMPs, receptors such as TLRs are consequently stimulated, resulting in a cascade that activates the NF-κB [76]. The NF-κB pathway is important in activation of naive T-cells through TCR signaling, and is necessary for both the generation and maintenance of effector and memory T cells [76]. In B-cells, the NF-κB pathway mediates survival of naive B cells as well as influencing immunoglobulin class switching [74]. In METH, increases in the production of pro-inflammatory cytokines and chemokines has been attributed to dependence on the NF-κB pathway [62]. Upon the expression of pro-inflammatory cytokines and chemokines, due to extracellular signals, NF-κB is activated in which subsequent processes and regulation can include inflammation, apoptosis, cell survival, and inducing gene expression pertinent to immune and inflammatory responses [75]. Further data suggests that the NF-κB signaling pathway induces inflammatory cytokines in METH-treated macrophages. The NF-κB pathway has also been thoroughly described as influencing, and being a mediator of reward following long-term drug abuse [78], having a role in learning and memory, and increasing expression of opioid receptors and neuropeptides [78]. In neuronal cells, asiatic acid was shown to inhibit METH-induced NF-κB translocation, thus exhibiting an anti-neurotoxic effect [59]. Further, cytoplasmic and nuclear fractions of METH-exposed astrocytes showed an increased protein expression of NF-κB [39]. Heightened expression of NF-κB upregulated caspase-11 subsequently upregulating the NLRP3 inflammasome and inducing IL-1β and IL-8 expression [33]. In humans, METH induces the production of TNF-α which is involved in the BBB dysfunction. Animal and *in vitro* work using endothelial cells showed that METH initiated endothelial dysfunction, through activation of the NF-κB pathway [18]. This finding revealed the role of the NF-κB pathway in decreasing tight junction stabilization and increasing the permeability of the BBB. Conversely, blocking of the NF-κB pathway inhibits BBB dysfunction [18].

6.2. MAPK/ERK and JNK signaling

Extracellular signaling regulated kinase (ERK) and mitogen-activated proteins kinase (MAPKs) pathways have been reported to play a role in METH-mediated signaling [79, 80]. MAPK signal cascades are important intracellular signaling pathways which transmit signals from cell membrane to nucleus [81], and possess a regulatory role of pro-inflammatory cytokines [82]. ERK contained in the nucleus is known as a target of stimulants [83]. Confirmatory experiments, determining the involvement of heme-oxygenase-1 (HO-1) – a crucial cellular mechanism mitigating oxidative damage - in METH-induced toxicity, showed that the p38 MAPK pathway was involved in upregulating METH-induced HO-1 [84]. Authors of this study support the role of the p38 MAPK pathway in cellular defense against METH toxicity [84]. Single and multiple METH injections in mice revealed complex changes in MAPK-related pathways mouse striatum and frontal cortex [81]. More specifically, MAPK-related pathways significantly impacted, through repeated METH administration, included map kinase I, Erk1, Erk2 and MAP kinase 7; these MAPK-related pathways have been implicated in substance abuse [81]. Evidence supports the involvement and role of the nuclear and cytoplasmic trafficking of ERK1/2 in learning and memory and cell death [85] along with behavioral modifications in brain-specific ERK pathway expression from drug abuse [86]. Similarly, assessments and the involvement of the sigma-1 receptor found downstream activation of ERK MAPK pathway was necessary for promoting the activation of astrocytes upon stimulation via METH [87]. The c-Jun NH2-terminal kinase (JNK) signaling pathway is an evolutionary conserved group of mitogen-activated protein kinases (MAPKs) [88]. This signaling pathway has been previously implicated in its ability to respond due to activation of cytokines and exposure to extracellular signals [88]. METH has been reported to activate the Src-JNK-Jun signaling cascade [89]. In line with METH addiction, and possible neurodegeneration, the JNK signaling pathway has been suggested to possibly mediate neurodegeneration in METH addiction [90]. A further report outlines the activation of the JNK signaling pathway via METH-induced oxidative stress' ultimately, this leads to signal transduction into the nucleus through the activation of transcription factors, such as activator protein-1 (AP1) – a major target of JNK signaling [88] NF-κB and cAMP-responsive element binding protein (CREB) [91].

6.3. AKT-PI3K pathway signaling

The protein kinase B (AKT) and phosphatidylinositol-3-kinase (PI3K) pathway is vital for many aspects of cell growth and survival [92], and is triggered through the result of growth factors and regulators [92]. This signal transduction cascade also supports a role in protein synthesis, metabolism and angiogenesis, with prevention of apoptotic events [93]. METH triggers cell survival-signaling events which involve dopamine receptors, PI3K and AKT [93]. Activation of the AKT/PI3K cascade was demonstrated through pro-inflammatory cytokine and chemokine expression by METH-induced astrocytes, in which METH caused alteration of mGluR5 receptor. In turn, this was shown to activate the Akt/PI3K pathway [62]. These results were in the context of METH-mediated, NF-κB dependent increases of cytokine

and chemokine expression [62]. Similarly, the AKT/PI3K signaling pathway was also found to mediate METH-induced IL-8 and IL-1β [25]. Using topiramate (TPM) as a potential treatment for METH dependence, Niu et al (2017) were able to elucidate enrichment of PI2K-AKT signaling pathway amongst seven biologically relevant pathways [94]. Moreover, TPM's effects on METH addiction further showed a decrease in oxidative stress and increased neuroplasticity, consistent with METH's ability to increase oxidative stress through a perturbance of the PI3K-AKT pathway [94].

6.4. JAK/STAT signaling

The JAK/STAT signaling pathway is utilized by several diverse cytokines, chemokines, interferons and growth factors. The simplicity of the JAK/STAT pathway allows for direct communication from transmembrane receptors to the nucleus, and cytokine receptor stimulation leads to phosphorylation events that ultimately recruit STAT, translocating to the nucleus and binding specific sequences to initiate gene expression [95]. METH has been shown to increase the Bax/Bcl-2 ratio, with the cytokine IL-6 being able to prevent this effect in microglial cells [58]. METH-induced microglial cells showed that IL-6 expression served to disrupt this pro and anti-apoptotic protein ratio level [58]. The bcl-2 family of apoptotic regulators are related to cell death and survival, in which these regulators can either suppress or activate apoptosis programming. Expression of Bax proteins is correlated to pro-apoptosis; whereas Bcl-2 is related to anti-apoptosis events [96]. In addition, the same study reported that low concentration expression of TNF-α, which, with IL-6, had a protective effect – through activation of JAK/STAT signaling - on microglial cells from the toxic effects elicited from METH.

7. METH and its relationship to ageing.

METH use leads to a number of cellular changes, disrupting normal cell function which trigger events related to inflammation, oxidative stress and ageing [97]. METH abuse is also associated with neurotoxicity of the fronto-striatal region, along with morphometric alterations in the hippocampus and cortex [98]. In particular, the hippocampus remains sensitive to drug abuse from adolescence years to adulthood, as it ensures structural and functional changes crucial for hippocampus maturation and function [99]. Adult METH users also experience cognitive impairments which impact on adaptive decision making, which also has long-term effects on reversal learning [100]. Long-term METH use on the brain neuro-biochemistry have been associated to age-related cognitive decline and neurochemical alterations [98]. Also, METH causes obvious changes to inflammatory immune responses

leading to significant long-term alternations. Chronic inflammatory modifications in immune response have been linked to the 'inflammageing' phenomena [101].

7.1 METH contributes to age-related diseases, such as cardiovascular pathology, stroke and Alzheimer's Disease.

Acute and chronic METH use has been attributed to stroke [102]. Binge METH doses have been shown to significantly alter cardiovascular function leading to cardiac pathology [103]. In addition, heart rate variability (HRV) measured across a cohort of abstinent individuals with a known history of METH dependence showed impairments in several parameters of HRV in comparison to drug-free individuals [104]. A decreased HRV has been associated with cardiovascular pathology, along with psychiatric disorders such schizophrenia and bipolar disorder, and an impairment in social functioning and cognition [104]. Importantly, HRV is generally thought to decline as an individual ages [105]. Other reports have assessed METH-associated cardiomyopathy (MACM) in which METH has been attributed to negative effects on the myocardium [106]. Changes to the myocardium at a structural, molecular, cellular and functional level are all related to cardiac ageing [107]. In assessing the link between METH exposure and the development of Alzheimer's Disease (AD)-like changes, the formation of amyloid-β (Aβ) was used as a measurement to evaluate this relationship [108]. In an *in vitro* cell model, results indicated that, in a dose-dependent manner, METH increased the levels of the Aβ precursor protein (APP) [108]. Aβ accumulation is a crucial indicator of AD pathogenesis [109], in which neuroimmune cells such as astrocytes, neurons and microglia respond by upregulating NADH, COX-2 and proinflammatory cytokines [110].

7.2. Effect of METH on adolescence and adulthood, our learnings from animal models

The development of drug seeking and addiction behavior is largely shaped at the adolescent stage of life [111], governed by the chronic exposure to the neurotoxic effects of several drugs of abuse. METH use in early-life increases risk of developing Parkinson-like symptoms [112]. In fact, in adult male rats, chronic binge METH dose revealed similar impairments in metabolites within the striatum, prefrontal cortex and hippocampus. In addition, METH impacts on neurotransmitters – dopamine and serotonin in adult rats [98]. In adolescent rats, METH was modeled to assess reversal learning and the likelihood of continued METH use through to adulthood [100]. Results of this study indicated a positive correlation between METH taken at adolescent stages – specifically in the late adolescent period – to adult METH use [100]. METH was also found to have a discriminatory effect in adolescent and adult rat developmental age [99], with METH exhibiting impairments in hippocampal cell proliferation and survival in young adult rats [99].

7.3. Impacts of METH on mental health

Other than the common withdrawal symptoms associated with METH use, such as excessive sleeping and severe cravings, METH also triggers depressive-like symptoms in users [113], usually lasting for longer than two weeks of abstinence [114]. This is in stark contrast to the euphoric and elevated mood effects which METH brings on when initially consumed [115]. In a cross-sectional study using a self-reporting tool and comparing active adult METH users with early ex-users and no history of METH users, it was noted that METH-dependent users had greater anxiety and depressive symptoms; with 10 plasma immune factors being associated with, and contributing to neuropsychiatric function [63]. Another cross-sectional study evaluating the pervasiveness of major depression among 400 people accessing treatment for METH use, reported a higher proportion of individuals with depression upon entering treatment faculties [116]. Furthermore, authors noted that the high prevalence of substance-induced depression manifested greatly in symptoms associated with appetite, sleep perturbations, trouble focusing, fatigue and feelings of sadness and emptiness [116]. Comparisons between regional volumes of cortical grey matter in adults with a history of METH showed age-related grey matter loss in several regions of the brain [117]. This finding is particularly important as it suggests that adult METH-users may be at higher risk of developing neurodegenerative disorders and cognitive decline at a younger age when compared with healthy non-METH uses.

7.4. METH-induced inflammation and link to ageing.

METH creates an immune imbalance where changes in immune cell function, inflammatory cytokines and chemokines are apparent. METH creates an environment which disturbs the balance between oxidative stress and antioxidant defence [118]. IL-6, is over-expressed in METH addicted individuals, and has been linked to the ageing process [119]. Moreover, IL-6 has been described as a central aspect of 'inflamm-ageing' [120], with an increase of this cytokine in serum is characteristic of ageing [121]. IL-6 has also been implicated in poor physical performance, with loss of muscle strength. Similarly, TNF-α, a cytokine impacted upon by METH, has also been associated with the ageing process [121]. Post-mortem analysis from human tissues have aligned METH with diseases characteristic of old age [122]. It was noted that METH fast-tracked cellular senescence and activated genes involved in the cell cycle and inflammation [122]. Moreover, METH caused an increase in ceramide biosynthesis, a process known to play a role in cellular replicative senescence, which led to the expression of senescent-associated biomarkers, IL-6 and TNF-α. Results of this study indicated that METH initiated a cascade of genetic changes observed in rapid health decline, character sic of chronic inflammation and ageing [122]. Indeed, the immune changes from chronic and acute METH (increased inflammation and oxidative stress) have been suggested to lead towards a reduction in telomere length [123]. Shortened telomere length is associated to increased cellular ageing as well as a range of non-communicable age-related diseases, including hypertension, cardiovascular disease, stroke, diabetes and dementia. In fact, drug abusers on METH, heroin or diazepam have shorter telomere length and accelerates cellular senescence [122, 124].

8. Conclusion and Future prospects

METH carries out its immunomodulatory effects via a number of key changes to both pro- and anti-inflammatory cytokines, leading to a cascade of signaling responses in both innate and adaptive immune cells. Alterations to IL-6, TNF-α, IL-10, COX-2 and IL-1β all play a vital role in METH-induced neurotoxicity. Although knowledge relevant to the effects of METH on several human cell types and in *in vivo* models has been well-established, there lacks a well-described, accumulated understanding of METH's immune-modulatory and immune-metabolomic effects. In addition, human peripheral immune cells have gained attention in recent years for their potential in being a valuable source for discovering biomarkers. Data supports the case that METH lowers an effective immune response in humans, leading to susceptibility of transmitting sexually transmitted diseases and infections. However, data is limited on the immune and oxidative-related pathways activated and maintained from changes in immune cell metabolism – glycolytic fluxes, mitochondrial respiration and reactive oxygen species generation, which are disturbed through METH use. In particular, the Nod-like receptor pyrin containing 3 inflammasome (NLRP3), a multiprotein complex related to infection and inflammation, and its activation, could be relevant in METH abuse. The NLRP3 pathway ties immunity to cell metabolism, which holds significance in assessing the pathogenesis of psychiatric disorders and further research in this inflammasome complex might uncover peripheral markers associated with METH use for assessing major depressive disorders. Furthermore, a better understanding of the link between METH use in the younger years, and its consequence to health outcomes in the long term (after METH has been stopped) in regards to increased risk of communicable and non-communicable diseases and accelarating the ageing process are required.

Contributors

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Figure Legends

Figure 1. METH elicits changes to the innate and adaptive immune response, causing changes to pro-inflammatory cytokines and related oxidative stress molecules. METH also impacts frequencies of T cell subsets (CD4+ and CD8+) along with proliferation.

Figure 1

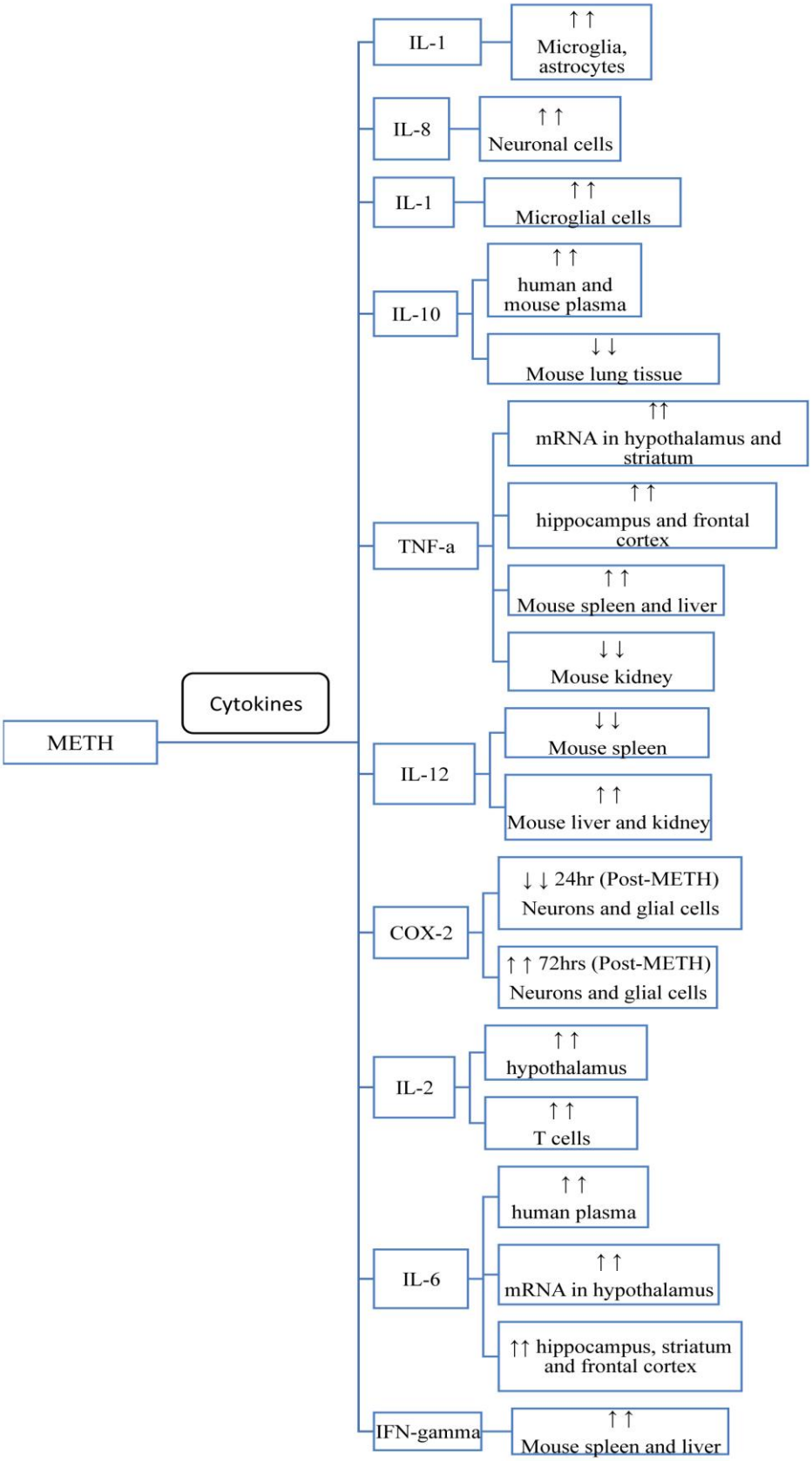
METH
Cytokines
IL-1
↑↑ Microglia, astrocytes
IL-8
↑↑ Neuronal cells
IL-1
↑↑ Microglial cells
IL-10
↑↑ human and mouse plasma
↓↓ Mouse lung tissue
TNF-a
↑↑ mRNA in hypothalamus and striatum
↑↑ hippocampus and frontal cortex
↑↑ Mouse spleen and liver
↓↓ Mouse kidney
IL-12
↓↓ Mouse spleen
↑↑ Mouse liver and kidney
COX-2
↓↓ 24hr (Post-METH) Neurons and glial cells
↑↑ 72hrs (Post-METH) Neurons and glial cells
IL-2
↑↑ hypothalamus
↑↑ T cells
IL-6
↑↑ human plasma
↑↑ mRNA in hypothalamus
↑↑ hippocampus, striatum and frontal cortex
IFN-gamma
↑↑ Mouse spleen and liver

Table 1. Effects of METH on immune cells.

Cell type	Impacts by METH	Reference
Monocytes	↑↑ Dose escalation mouse model assessing immune subsets	[20]
	↓↓ THP-1 cell viability (after 24 hrs) Cytotoxicity on LPS-stimulated IL-1β THP-1 monocytes	[125]
Macrophages	↑↑ IL-8, IL-1β and TNF-α in LPS-treated macrophages	[25]
	↑↑ Activated brain macrophages	[36]
T cells	↓ CD4 ↑ CD8 Effect of METH on systemic immune system	[126]
	↓ CD4 *In vivo* lymphocytic choriomeningitis virus infection model	[30]
	CD8+ and CD4+ cell cycle progression disrupted (*in vitro*)	[32]
	↓↓ frequency of CD4+ ↓↓ frequency of CD8+	[126]
	Dysfunction of primary human T cells (mitochondrial oxidative damage.)	[34]
	Inhibition of T cell proliferation	[15]
Dendritic cells	Dose escalation mouse model assessing immune subsets	[20]
	↑↑ infectivity of human immunodeficiency virus-1 in monocyte-derived DC	[29]
	Modulation of genes in pathogenesis of human immunodeficiency virus-1.	[16]
Natural killer cells	↑↑ Activation of NK cells	[36]
	↓↓ Splenic NK lymphocytes	[127]

Table 2. METH causes changes in expression to several known pathways.

Pathway	METH-induction	Reference
JAK-STAT	↑ TNF-α and IL-6 ↓ Bax/Bcl-2 ratio (microglial cells)	[58]
JNK	Activation of Src-JNK-Jun signaling cascade	[89]
	Activation via METH-induced oxidative stress	[88]
AKT-PI3K	Activation by pro-inflammatory cytokines and chemokines	[62]
	Mediation of IL-8 and IL-1β	[25]
MAPK/ERK	↑ METH-induced HO-1	[84]
	Activation of p38 MAPK pathway (METH toxicity)	[84]
	Changes in MAPK pathways in mouse striatum and frontal cortex	[81]
	ERK1/2 activation via D1 and D2 receptors	[128]
NF-κB	Pro-inflammatory cytokine and chemokine activation	[62]
	Inflammation, apoptosis, cell survival, gene expression: immune and inflammatory response	[129]