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Methamphetamine: effects on the brain, gut and immune system

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ABSTRACT

Methamphetamine (METH) is a powerful central nervous system stimulant which elevates mood, alertness, energy levels and concentration in the short-term. However, chronic use and/or at higher doses METH use often results in psychosis, depression, delusions and violent behavior. METH was formerly used to treat conditions such as obesity and attention deficit hyperactivity disorder, but now is primarily used recreationally. Its addictive nature has led to METH abuse becoming a global problem. At a cellular level, METH exerts a myriad of effects on the central and peripheral nervous systems, immune system and the gastrointestinal system. Here we present how these effects might be linked and their potential contribution to the pathogenesis of neuropsychiatric disorders. In the long term, this pathway could be targeted therapeutically to protect people from the ill effects of METH use. This model of METH use may also provide insight into how gut, nervous and immune systems might break down in other conditions that may also benefit from therapeutic intervention.

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1. Introduction

Methamphetamine (METH; also called crystal, chalk or ice) is an addictive stimulant that can be administered orally, smoked, snorted or injected. Smoking or intravenous injection delivers METH to the brain rapidly, resulting in immediate and intense euphoria (1). METH use is associated with severe neurological and physical consequences (e.g. paranoia, violent behaviour, psychosis, anxiety and depression) and has become a serious public health problem worldwide (2, 3).

METH was discovered in Japan in 1919 and was commercially used in 1938 under the brand name Pervitin. It was especially popular for tired night-shift workers and was used during WWII by Germany to treat fatigue in tired army troops (4). METH became widely available from 1943 to treat a range of disorders including narcolepsy, depression, obesity, alcoholism and attention deficit hyperactivity disorder (ADHD). As METH decreased appetite it was also well marketed to women for weight loss. Although prolonged METH use can cause severe neurological damage, prescribed METH is still legally available under the brand name Desoxyn to treat severe obesity, narcolepsy and ADHD (5-7).

In recent years METH use has increased dramatically. In the USA, approximately 1.3 million people over the age of 12 have reported using METH. According to the 2011 United Nations survey, about 2.5 % of Australians have tried METH, which is 3-5 times higher than USA, Canada and UK (United Nations, 2011). In 2013, 7 % of Australians over the age of 14 years reported having used METH, with 50 % having used ice, the purest form of METH (8).

Immediate effects of acute or short-term METH use include increased alertness, heart rate, blood pressure, body temperature and a loss of appetite. Long-term, regular METH use can lead to severe tooth decay, infection, weight loss, malnutrition, kidney damage, liver damage, respiratory issues, paranoia, violent behaviour, psychosis, severe anxiety and depression. Even when individuals stop taking METH, the symptoms may persist for many years (9-14).

METH has more potent effects in women than men. In fact, 6-fold greater vulnerability to relapse of METH-seeking behavior is evident in experimental female rats as compared to male rats (15). Changes in brain morphology, such as hippocampus volume reduction, were seen in METH-abstinent females but not in males (16). In addition, females that are undergoing treatment for METH abuse have higher instances of psychological and physical trauma compared to males (17).

Herein, we review the findings on METH-related neurological and immunological effects, particularly neuro-immune cell stability, alteration of cytokine production, inflammation, immunosuppression, signal transduction and gene regulation.

2. METH and the Blood-Brain Barrier

METH increases blood brain barrier (BBB) permeability, inducing damage by altering the structure of proteins that are involved in BBB stability in mice (18). BBB permeability is also affected by body temperature, oxidative stress and inflammation, all of which are impacted by METH use (Fig. 1). Both hyperthermia and hypothermia alter BBB permeability, although hypothermia has less effect (19). Oxidative stress and excess inflammation is also associated with BBB damage in a number of neurodegenerative disorders (20-24). Recently, liquid chromatography-mass spectrometry (LC-MS/MS) analysis of extracts from rat brains following METH exposure identified changes in 18 proteins (11 from the hippocampus and 7 in the olfactory bulb); 13 of which were upregulated and 5 were downregulated. The modified proteins were predominantly involved in cell death, inflammation, oxidation and apoptotic pathways (25). In addition, alterations of endothelial cell structure and function, with increased levels of ROS, are observed in METH-related BBB disruptions (26, 27).

METH induces peripheral kidney and liver damage that leads to toxic ammonia levels in the blood and subsequently, the brain. Ammonia that is not cleared by the liver as normal accumulates and causes oxidative damage of endothelial cells, activation of matrix metalloproteases (MMPs) and neuro-inflammation via microglia and astrocyte activation, leading to BBB disruption (28-30) (Fig. 1). Furthermore, METH alters BBB permeability via dysregulation of tight junction proteins including occludin, claudin-5, and ZO family proteins (18, 26, 27, 31). Cytoskeletal rearrangement is also perturbed, with increased actin polymerization and expression of actin-binding protein Arp2/3 complex observed following METH administration (18). Interestingly, galectin-1, which is highly expressed in endothelial cells involved in BBB remodeling, alleviates the METH-induced increase in BBB permeability, thus acting as a neuroprotective molecule (32).

3. Neurological effects of METH

The euphoric effects of METH occur due to release of the neurotransmitter dopamine, which is involved in the experience of pleasure, motivation and motor function. However, long-term use of METH causes molecular changes in the dopamine system, contributing to nerve terminal damage in the brain and leading to impaired motor skills, rapid cognitive decline, increased anxiety, psychotic disorders, violent behaviour, hallucination, delusions and depression (Fig. 2) (33). These brain changes persist for many years after METH use has ceased (34).

Acute METH use causes an increase in neurotransmitter release, leading to potential damage to the terminal ends of neurons and ultimately alters brain function. A single high dose of METH causes neurotoxicity to dopamine and serotonin producing neurons in rodents (35). Positron

emission tomography (PET) and magnetic resonance spectroscopy (MRS) studies in abstinent METH users indicate a reduction of dopamine transporters (DAT) (36, 37) and serotonin transporters (SERT) (38, 39) that lasts up to 3 years after cessation of METH use. Brain tissues from rodents exposed to METH and post-mortem brain tissues isolated from chronic METH users demonstrate decreased levels of dopamine, serotonin, DAT and SERT in areas highly innervated by dopaminergic and serotoninergic axon terminals (40).

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the brain. Disruption of inhibition via GABA receptors can lead to dopamine and serotonin dysfunction and promote depression, anxiety, stress and cognition. Similar reductions in neurotransmitters are also observed in a number of chronic neurological disorders such as Parkinson's and Alzheimer's disease (41-43).

Trace amine-associated receptor 1 (TAAR1) is a G-protein coupled receptor expressed on astrocytes, lymphocytes and neurons and negatively regulates neurotransmission via dopamine, norepinephrine and serotonin in the central nervous system (CNS) (44-46). It is an intracellular receptor predominantly found in the cytoplasm of presynaptic terminals and is poorly expressed on the cell membrane (45). Activated TAAR1 reduces dopamine receptor activity and increases cyclic adenosine monophosphate (cAMP), protein kinase A and protein kinase C activation. Subsequently, DAT is phosphorylated, leading to inhibition of dopamine transport (47, 48). TAAR1 signaling also activates transcription factor cAMP response element-binding protein (CREB) and nuclear factor of activated T-cell (NFAT), which are associated with immune cell activation and proliferation (49, 50). There are numerous studies that examine the effect of METH on TAAR1. METH directly activates TAAR1 *in vitro* and increases the intracellular cAMP levels in human HEK-393 fibroblasts (51). TAAR1 mRNA expression in resting T cells increases in response to METH administration (52). METH increases intracellular cAMP levels in human astrocytes whereas TAAR1 knockout cells have significantly reduced cAMP levels in response to METH administration (53). Interestingly, TAAR1 knockout mice show no significant difference in body weight, temperature, locomotor activity and other behaviours compared to wild-type mice; however increased firing rate of dopaminergic and serotoninergic neurons are noted (54-56). Conversely, TAAR1 transgenic mice show increased sensitivity to METH. RO5203648, a selective TAAR1 agonist, alleviates METH-induced neurochemical effects in rats, including hyperactivity, psychomotor effects and addiction (57-59).

4. Sympathetic and parasympathetic regulation of the immune system

Sympathetic and parasympathetic nervous systems play an important role in regulating the immune system. The sympathetic nervous system is involved in stress-induced remodelling of lymph

node innervation; increased norepinephrine and epinephrine levels inhibit immune cell functions and promote intestinal inflammation (60-62). The parasympathetic nervous system has an anti-inflammatory role via activation of the cholinergic anti-inflammatory pathway (63, 64). Acetylcholine decreases the production of pro-inflammatory cytokines such as TNF-α by human macrophages through nicotinic receptors (65). Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxins and intestinal inflammation (63, 66). The vagus nerve also indirectly modulates immune activity of the spleen through connections with the splenic sympathetic nerve (67, 68). However, the effects of METH on the activity of sympathetic and vagus nerves and their modulation of systemic and local immune responses have not been studied.

5. The effects of METH on the Gut-Brain axis

The rapid and sustained release of norepinephrine following METH use results in arterial vasoconstriction, leading to tachycardia and hypertension. Similar effects can also be seen in the mesenteric vessels of the gut, leading to acute intestinal ischemia (69, 70). In METH users, the most common effects of gastrointestinal (GI) vasoconstriction and bowel ischemia include abdominal or stomach cramping, severe constipation and/or diarrhoea and tissue dehydration. In some cases, loss of blood flow to GI muscles leads to severe, potentially fatal conditions such as paralytic ileus (Fig. 2) (71). Potential consequences of paralytic ileus include severe infection, tissue death (gangrene), perforation of the intestinal wall and serious disruptions in the levels of electrolytes. In severe cases, bowel infarction can lead to development of septic shock with multiple organ failure (70).

Bowel ischemia is associated with increased intestinal permeability, oxidative and nitrosative stress. Several findings suggest that dysfunction of the intestinal mucosal barrier leading to increased intestinal permeability plays an important role in the pathophysiology of anxiety, stress, depression, cognitive decline, chronic fatigue and eating and sleep disorders. All of these are common in METH users (Fig 1, 2).

Disruption of the gut wall integrity, damage to intestinal epithelial cells and derangement of tight junctions leads to the leakage of macromolecules, microbial products, and microbiota from the intestinal lumen into the circulation, mesenteric lymph nodes, spleen and liver (72). With the concurrent increase in BBB permeability following METH use, these gut-derived components have the ability to enter the brain (73). Extensive release of dopamine and norepinephrine stimulates growth of bacteria which may also influence neural activity in stress responsive brain areas (74). Therefore the intestinal microbiota may act as a mediator in the communication between the gut and the brain (75). However, the mechanisms underlying METH-induced increases in intestinal

permeability and damage to the GI tract leading to systemic immune response and neuropsychiatric disorders are not clear.

Increases in intestinal permeability may be due to the inhibition of GI motility observed in METH users (71). In the gut, dopamine and norepinephrine act on receptors of the enteric nervous system resulting in decreased bowel contractility, intestinal smooth muscle tone and alteration of the migratory motor complex (76-78). METH-mediated release of neurotransmitters might also lead to generation of oxidative stress molecules, including ROS and reactive nitrogen species (RNS) which can cause damage and death of enteric neurons and subsequent GI dysfunction.

Recent advances in research have described the importance of gut microbiota in many neuropsychiatric conditions including autism, anxiety, depression, eating and sleep disorders. Current evidence suggests that multiple mechanisms, including immune, endocrine and neuroendocrine pathways, may be involved in gut microbiota-to-brain signalling and that the brain can in turn alter microbial composition and behaviour via the enteric nervous system (79-81). However, changes in the gut microbiota after METH use and the interplay between intestinal microbiota, immune response and neuropsychiatric manifestations associated with METH use have not been studied (Fig 2)

6. METH and its effects on the Immune System

The human immune system has a profound influence on the brain. Increasing evidence shows that there are numerous interactions between the nervous and immune systems (82). The immune system also plays an important role in the pathogenesis of neuropsychiatric disorders including cognitive decline, anxiety, mood changes and depressive states as well as increased attention, decreased fatigue and euphoria rush (80, 83, 84), which are associated with METH use (Fig. 3).

6.1. The effects of METH on Susceptibility to Infection

Chronic METH use and lack of hygiene leads to alteration in primary physical barriers and increases the occurrence of skin infections (85). METH use also increases the risk of chronic infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), human immunodeficiency virus (HIV), hepatitis and sexually transmitted diseases (3).

In the presence of METH, the number of macrophages, NK, DC, monocytes and granulocytes are reduced, further contributing to the increased susceptibility to infections (86, 87). High METH dose induces apoptotic death in rat thymic and splenic lymphocytes and produces severe immunosuppression, which could also contribute to the higher rate of infections observed in chronic

METH users (86, 88). METH also changes the cytokine response to retroviral infection in rodents (89, 90).

6.2. The effects of METH on Inflammation and inflammatory markers

Pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α) have been implicated in damaging and destroying existing neurons leading to the neurobiological manifestations of different mental states. Indeed, METH use results in IL-6 and IL-8 production by neuronal cells, leading to myelin degeneration in mice (3). Similarly, mice treated with METH show increased expression of pro-inflammatory cytokines (IL-1β) for up to 3 weeks in brain regions (91). METH-related cell activation is seen in astrocytes and leads to excessive secretion of inflammatory cytokines such as IL-6 and IL-8 inducing inflammation (86, 92), as well as enhancing expression of chemokines and chemokine receptors such as CXCR4 and CCR5 in the brain (93). In addition, METH induces a pro-inflammatory profile of *in vitro* cultured macrophages, by upregulating TNF-α, IL-8, CXCL16, CXCL1 and downregulating CCL7 (disrupting toll-like receptor 9 (TLR-9) signaling pathway) (94). Suppression of TLR-9 indicates that suppressed innate immune responses may ensue in METH users.

6.3. METH-associated Immune cell changes

Immune cell mediated neuro-inflammation and neurodegeneration is induced by METH use. METH is a weak base and alkalizes the acidic organelles within macrophages, leading to impaired phagocytosis, antigen processing and presentation (95). As a consequence, this can lead to a reduction of pathogen uptake and processing, increasing infections. Immunological factors such as cytokines, chemokines and adhesion molecules are linked with neuronal degeneration as well as neuropsychiatric complications (96, 97).

METH modifies a number of immune cell (natural killer (NK) cells, dendritic cells (DC), monocytes, macrophages and granulocytes) activities, leading to immunosuppression (86). In addition, METH affects antigen presenting cells (APCs) in the brain (microglia and astrocytes) and leads to increased secretion of pro-inflammatory cytokines (IL-1, IL-6, IL-8), interferons and TNF-α (98). Murine models show that METH modifies thymic and splenic cellularity, in turn altering peripheral T lymphocyte populations (97). Furthermore, METH suppresses adaptive immunity by altering T cell populations, specifically the CD4+/CD8+ T-cell ratio (97, 99).

Microglia and astrocytes usually perform compensatory actions during brain injury and protect the brain as excess neuro-inflammation leads to damage. However, METH activates G-protein receptors and initiates signalling of the Akt/NF-kB pathway to increase cell proliferation and cytokine secretion (IL-6 and IL-8) in astrocytes. The effect of METH-related IL-6 and IL-8 expression in

astrocytes is reduced in the presence of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), an antagonist of metabotropic glutamate receptor 5 (mGlu5) (100). Furthermore, HIV-1 envelope protein gp120 acts synergistically with METH to further increase IL-6 expression (101).

METH activates the Sigma-1 receptor which in turn activates NF-κB via SRC/ERK, thus increasing high mobility group box-1 (HMGB1) gene expression in astrocytes (102). This promotes cell proliferation and migration. HMGB1 also regulates gene transcription and acts an inflammatory mediator by activating TLR-4 (103). Activated immune cells such as macrophages and monocytes also increase the expression of HMGB1 during inflammation (104, 105).

METH also increases glutamate release from a number of brain regions such as the striatum, cerebral cortex and hippocampus (106, 107). The phosphorylation of PI3/Akt molecules via glutamate receptor engagement leads to the activation of transcription factor NF-κB and ultimately facilitates inflammation, neurotoxicity and apoptosis (108). Chronic METH exposure affects monoaminergic neurons by the loss of DAT, SERT and vesicular monoamine transporter type-2 (VMAT-2) in striatum and central gray matter of rat brain (109).

6.4. The effects of METH on the expression of death receptor PD-1 and its ligand PD-L1

Programmed cell death-1 ligand (PD-L1), is a transmembrane protein that plays a major role in suppressing the immune system. T cells express the receptor PD-1 and upon interaction with PD-L1 inhibitory signals are triggered resulting in T cell apoptosis. Cancer cells that express high levels of PD-L1 as a mechanism for immune evasion are associated with poor prognosis in patients (110-112). In inflammatory disorders the expression of PD-L1 is reduced leading to activation of T cells. Thus, PD-L1 is important in regulating immune responses. The level of PD-L1 and PD-1 expression in human brain cells under normal physiological conditions is low. However, activated neuro-immune cells such as astrocytes, microglia, T cells, B cells, macrophages, DC and non-immune cells (endothelial and epithelial cells) appear to have increased in expression (113).

The expression of PD-L1 is elevated in brain endothelial cells, on macrophages and microglia, following METH exposure (113). PD-1 signaling attenuates phosphorylation of protein kinase C (PKC), necessary for the activation of NF-kB and for production of IL-2 (114), thus METH exposure inhibits T cell activation. Overexpression of PD-1 and PD-L1 following METH exposure in macrophages may also suppress immunity by altering antigen presentation (113).

Conversely, reductions in PD-1 and PD-L1 expression are noted in astrocytes following METH exposure (113). Inhibition of PD-1/PD-L1 expression in astrocytes stimulates overproduction of inflammatory cytokines such as interleukins and leads to inflammation and neuronal damage. However, whether METH-related reduction of PD-1/PD-L1 expression in astrocytes alters PKC

activation or regulates the production of NFκB and proinflammatory mediators such as IL-1, IL-6, IL-8 and TNF-α to cause the neuronal damage by inflammation are not clear and therefore warrants further investigation.

7. Conclusion and future prospects

Recent advances in research have described the importance of gut microbiota in many neuropsychiatric conditions including autism, anxiety, depression, eating and sleep disorders. Current evidence suggests that multiple mechanisms, including immune, endocrine and neurocrine pathways, may be involved in gut-to-brain signalling and that the brain can in turn alter microbial composition and behaviour of the gut via the enteric nervous system (79-81). Though it is apparent that METH use alters numerous aspects of the nervous, immune and gastrointestinal systems, changes in gut microbiota following METH use and the interplay between intestinal microbiota, immune response and neuropsychiatric manifestations associated with METH use are yet to be studied.

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Figure 1. Schematic diagram of the complex signals activated by METH

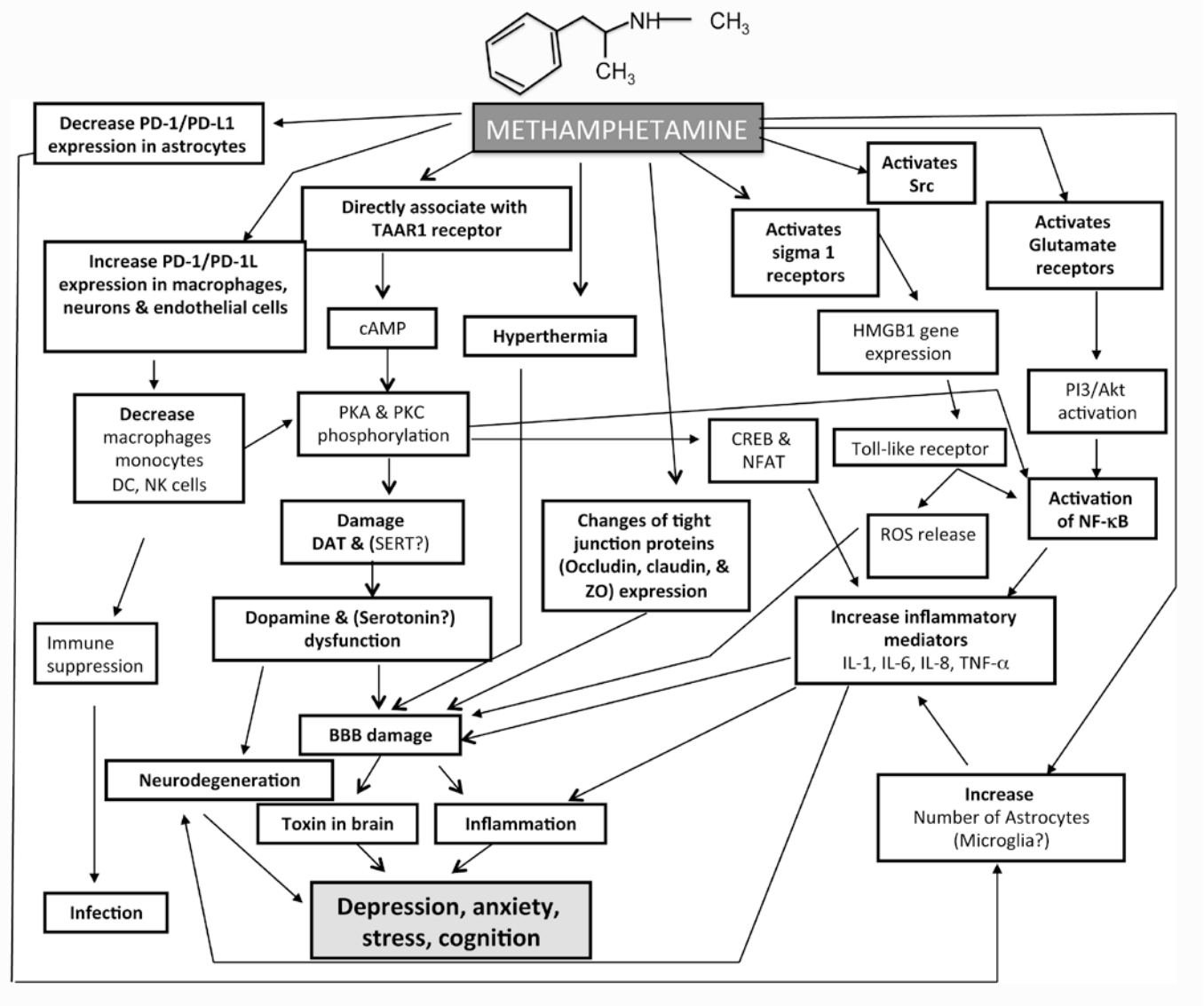

Figure 2. METH ($C_{10}H_{15}N$) and the gut-brain axis. Solid arrows are known effects of METH and dotted arrows are hypothesised effects

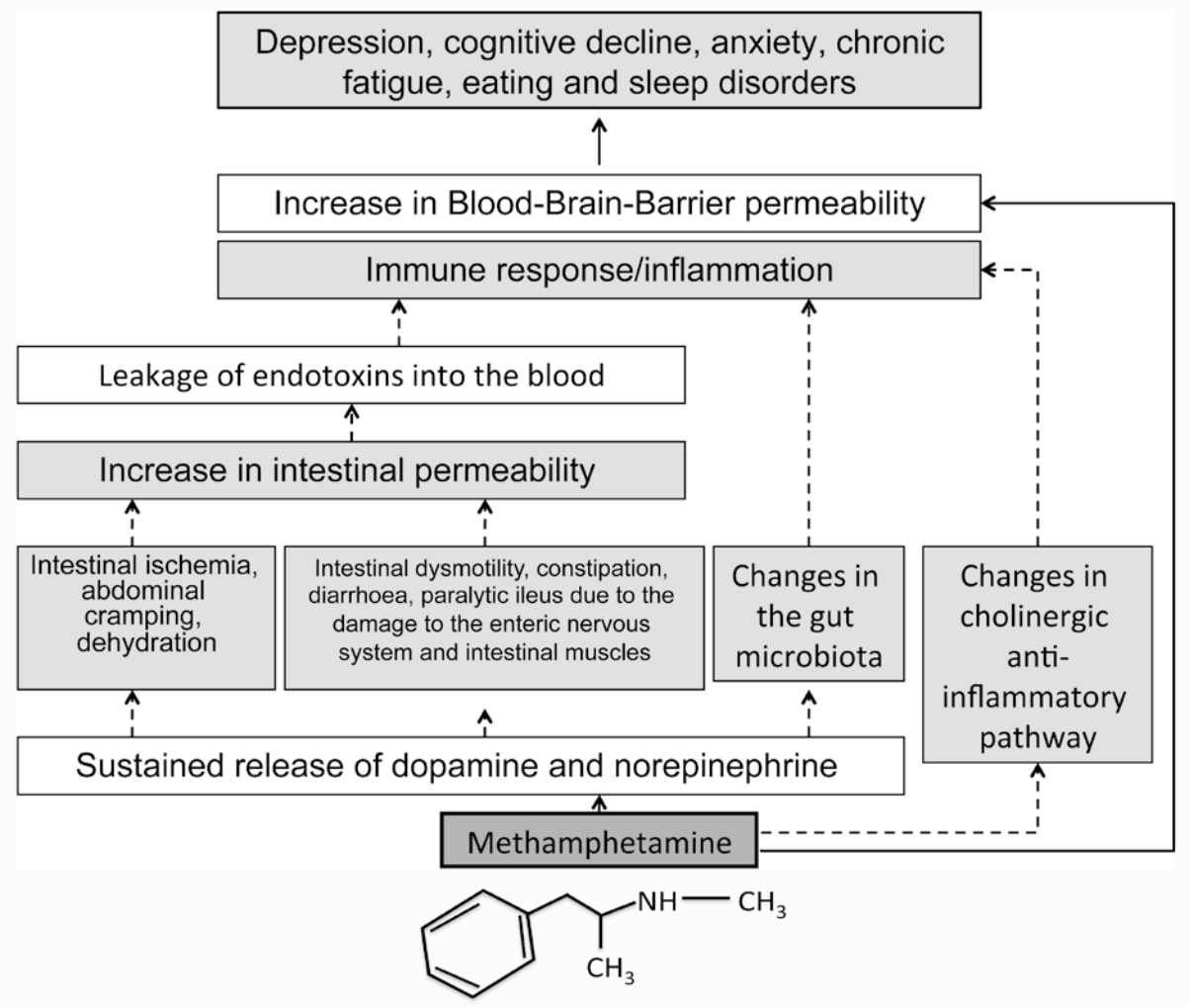

Fig. 3. Schematic diagram of the neuro-immunological affects of METH. Solid arrows are known effects of METH and dotted arrows are hypothesised effects