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Review

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.

Contents

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

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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 serotonergic 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 serotonergic 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].