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Methamphetamine-induced toxicity: The role of autophagy?

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ABSTRACT

Methamphetamine (METH) is a highly potent and addictive drug with major medical, psychiatric, cognitive, socioeconomic, and legal consequences. It is well absorbed following different routes of administration and distributed throughout the body. METH is known as psychomotor stimulant with potent physiological outcomes on peripheral and central nervous systems, resulting in physical and psychological disorders. Autophagy is a highly conserved and regulated catabolic pathway which is critical for maintaining cellular energy homeostasis and regulating cell growth. The mechanism of autophagy has attracted considerable attention in the last few years because of its recognition as a vital arbiter of death/survival decisions in cells and as a critical defense mechanism in undesirable physiological conditions. The purpose of the current article was to review available evidence to find a relationship between METH toxicity and mechanisms associated with autophagy in different organs.

Contents

1. Introduction

Methamphetamine (METH) is a highly potent and addictive drug with major medical, psychiatric, cognitive, socioeconomic, and legal consequences [1]. It was first synthesized from ephedrine in 1893 by Nagai Nagayosh. In 1919, Akira Ogata synthesized methamphetamine hydrochloride, also known as crystal meth, by reducing ephedrine using red phosphorus and iodine, providing the basis for production of the drug on a larger scale (Fig. 1) [2].

METH comes in a variety of forms such as a pure crystalline hydrochloride salt (known as ice) or as formulated tablets. Routes of administration are intravenous injection, smoking, anal or vaginal insertion (suppository), intranasal sniffing (snorting), and oral ingestion (swallowing) [3,4].

METH is well absorbed following different routes of administration and distributed throughout the body. As METH has a relatively high lipophilicity, it distributes extensively across high lipid-content tissues such as the blood–brain barrier. METH is metabolized largely in the liver mainly involving the cytochrome isoenzyme, CYP2D6. METH is excreted mainly in the urine, and to a lesser extent through sweat and saliva. The rate of excretion into the urine heavily influenced by urinary pH. The half-life of METH is variable with a mean value between 9 and 12 h [5,6].

METH is known as psychomotor stimulant with potent

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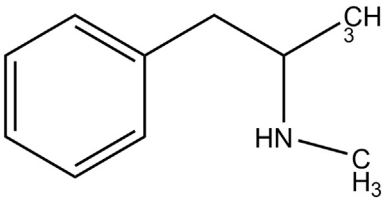

Fig. 1. Chemical structure of METH.

physiological outcomes on peripheral and central nervous systems, resulting in physical and psychological disorders [7]. It acts as a powerful releaser of monoamines by enhancing cytoplasmic concentrations of dopamine, serotonin, norepinephrine, and histamine and, to a lesser extent, inhibits their synaptic reuptake. The most common presentations associated with METH intoxication are cardiovascular risks, neuropsychiatric manifestations, and other physiological effects. Table 1 presents a summary of health factors associated with METH use [6,7].

Several studies have supported the involvement of excitotoxicity (excessive glutamate release), increase in intracellular calcium levels, generation of free radicals and nitric oxide (NO), activation of apoptotic pathways, breakdown of cytoskeletal proteins and DNA damage in METH toxicity [8]. As mentioned, one of the mechanisms of METH-induced toxicity is due to oxidative stress. These METH-derived oxidative metabolites activate different signals in cells that end up in cell death through apoptosis. During this process, METH impairs the ubiquitin–proteasome system and produces a marked activation of autophagy [9].

Autophagy is a highly conserved and regulated catabolic pathway which is critical for maintaining cellular energy homeostasis and regulating cell growth. It is known as a common physiological mechanism that may serve as a means of short-term survival, and is triggered by starvation (amino acid and nutrient deprivation), hypoxia, and metabolic stress [10,11]. The hallmark of the autophagic process is the sequestration of cytoplasmic content through the formation of double-membrane vesicles, mediated by a set of evolutionarily conserved autophagy-related (Atg) proteins. The initial phagophores are formed from the endoplasmic reticulum (ER) and enclosed to form autophagosomes. Subsequently, autophagosomes combine with lysosomes for degradation and recycling of contents to serve as new building blocks for the synthesis of macromolecules and metabolites, which were then used as the cellular energy source for cell survival [12]. The three different types of autophagy processes, namely macroautophagy, microautophagy and chaperone-mediated autophagy have been described, depending on the mechanism that mediates the transfer of cytosolic burden to lysosomes for degradation. Macroautophagy and microautophagy are conserved from yeast to mammals, while chaperone-mediated autophagy, so far, has been only described in mammals [13]. The mechanism of autophagy has attracted considerable attention in the last few years because of its recognition as a vital arbiter of death/survival decisions in cells and as a critical defense mechanism in undesirable physiological conditions [14]. The purpose of the current article was to review available evidence to find a relationship between METH toxicity and mechanisms associated with autophagy in different organs.

1.1. Methamphetamine-induced autophagy

Recent evidence show that many of drugs with abuse liability are able to induce autophagy. For example, cocaine [15], heroin [16], morphine [17], tetrahydrocannabinol [18] and nicotine [19] promote autophagy. Emerging evidence show that psychostimulant drugs including 3,4-methylenedioxymethamphetamine (MDMA) [20] and METH [21] are able to induce autophagy as well. In this group, the effect of METH on autophagy has been studied in more details. One of the most important feature of METH consumption is neuronal toxicity. Previous studies show that METH is able to damage neurites selectively while leaving neuronal cell bodies undamaged [22,23]. This is suggesting that further mechanism(s) is involved in METH-induced toxicity. As the first study, Larsen and colleagues showed that METH is able to induce autophagy in the dopaminergic system. They showed that METH stimulated the formation of autophagic granules, particularly in neuronal varicosities and finally in the bodies of dopaminergic neurons [21]. They proposed that when dopamine cannot be effectively sequestered in synaptic vesicles, autophagy is promoted and induces neurite degeneration. After that, Fornai et al. found that METH induced intracellular inclusions in the nucleus and cytoplasm of striatal and substantia nigra neurons, respectively, while leaving the frontal cortex neurons intact. The same results were obtained on PC12 cell line [24]. The induced inclusions had ubiquitin, ubiquitin activating enzyme, ubiquitin protein ligase, and low and high molecular weight heat shock proteins (HSP40 and HSP70) [24]. Similarly, Kanthasamy et al., showed that cytoplasmic vacuolar structures reminiscent of autophagic vacuoles appeared within 3 h after METH exposure in mesencephalic dopaminergic neuronal cell line [25]. Interestingly, METH was also able to induce autophagy in a mouse atrial cardiac cell line. In addition, during METH treatment, huge but temporary cytoplasmic vacuolization (3–12 h) followed by an intracellular accumulation of granules (24–48 h) was reported [26]. Similar to previous studies, it was demonstrated that METH induced both autophagy and apoptosis in PC12 cells [27]. It induced autophagy through inhibition of mammalian target of rapamycin phosphorylation (*p*-mTOR) that was reversed in the presence of taurine [27]. It is worthy to mention that METH may also induce impaired autophagy [26,28]. So, this may be a new mechanism that mediate METH toxicity or protect cells against METH toxicity. Up to present, there is no agreement whether autophagy during METH- induced toxicity serves as pro-survival or pro-death. As the first researchers, Castino and colleagues did experiments to resolve this issue. They showed that METH induced autophagy in two dopaminergic neuronal-derived cell lines (PC12 and SH-SY5Y) [29]. They revealed that inhibition of autophagy by pharmacological and genetic interventions decreased the viability of both dopaminergic cell lines during METH exposure indicating that autophagy was pro-survival. The cell death was prevented by the pan-caspase inhibitor, ZVAD-fmk, implying that it was apoptotic. However, Kongsuphol and colleagues demonstrated that METH, by mTOR deactivation, induced autophagy and decreased

Table 1
Health consequences of METH use.

Cardiovascular effects	Chest pain, tachycardia, hypertension, arrhythmias, myocardial infarction, coronary artery disease, vasoconstriction and stroke
Neuropsychiatric effects	Anxiety, irritability, agitation, hallucinations, paranoia, psychosis, depression, social isolation, anorexia, vivid or lucid dreams, convulsions, headache, and insomnia
Other physiological effects	Dilated pupils, flushing, tachypnea, hyperthermia, diaphoresis, blurred vision, dry and itchy skin, hyperglycemia, renal and liver failure, pulmonary hypertension and fetal growth restriction