Hyperthermia

Subjects: Cell Biology

Contributor: Riccardo Mancuso

Hyperthermia is one of the severe acute adverse effects that can be caused by the ingestion of recreational drugs, such as methcathinones. The effect of hyperthermia on neurotoxicity is currently not known. The primary aim of our study was therefore to investigate the effects of hyperthermia (40.5 °C) on the neurotoxicity of methcathinone (MC), 4-chloromethcathinone (4-CMC), and 4-methylmethcathinone (4-MMC) in SH-SY5Y cells. We found that 4-CMC and 4-MMC were cytotoxic (decrease in cellular ATP and plasma membrane damage) under both hyper- (40.5 °C) and normothermic conditions (37 °C), whereby cells were more sensitive to the toxicants at 40.5 °C. 4-CMC and 4-MMC impaired the function of the mitochondrial electron transport chain and increased mitochondrial formation of reactive oxygen species (ROS) in SH-SY5Y cells, which were accentuated under hyperthermic conditions. Hyperthermia was associated with a rapid expression of the 70 kilodalton heat shock protein (Hsp70), which partially prevented cell death after 6 h of exposure to the toxicants. After 24 h of exposure, autophagy was stimulated by the toxicants and by hyperthermia but could only partially prevent cell death. In conclusion, hyperthermic conditions increased the neurotoxic properties of methcathinones despite the stimulation of protective mechanisms. These findings may be important for the understanding of the mechanisms and clinical consequences of the neurotoxicity associated with these compounds.

Keywords: autophagy ; hyperthermia ; methcathinone ; mitochondria ; neurotoxicity

1. Introduction

New psychoactive substances (NPSs) are a broad group of drugs of abuse that are not controlled by classic international drug laws [1]. The abuse of NPSs is a major problem worldwide, since NPSs can elicit serious toxic effects on users [2]. In recent years, several synthetic cathinones, designated as “legal highs”, have emerged and their use as recreational drugs has grown rapidly [3]. Structurally, synthetic cathinones are β-keto-amphetamine derivatives, with pharmacological and toxicological properties similar to amphetamines [3]. Synthetic cathinones, such as methcathinone (MC), 4-chloromethcathinone (4-CMC), and 4-methylmethcathinone (4-MMC, mephedrone), have recently been recognized by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) as emerging NPSs [4,5,6].

Despite clinical studies with and initial use of some synthetic cathinones for the treatment of depression, appetite suppression, or smoking-cessation, none of these compounds have been approved for one of these indications, mainly due to their adverse effect profile [7]. Relevant adverse effects reported for synthetic cathinones include anxiety, paranoia, depression, stroke, seizures, hyperthermia, heart failure, liver failure, and even death [7,8].

2. Specifics

Hyperthermia, also reported as “overheating”, is one of the prominent acute severe adverse effects of stimulant drug abuse, and one of the primary causes of death [9,10]. According to clinical case reports, drug-induced hyperthermia can result in many potentially fatal complications, such as hyponatremia, rhabdomyolysis, cerebral edema, disseminated intravascular coagulation, and coma [11]. Drug-induced hyperthermia can be caused by several factors. Most psychostimulant drugs can directly increase metabolic heat production by central and/or peripheral mechanisms as well as decrease heat dissipation [9,10]. Several clinical cases of hyperthermia induced by synthetic cathinones have been reported so far [12] and a large number of animal studies have been performed in mice and rats to investigate the effect of these compounds on the body temperature [13]. Polysubstance abuse may contribute to methcathinone-induced hyperthermia. Additionally, a drug that may accidentally or deliberately be used in combination with cathinones is 3,4-methylenedioxymethamphetamine (MDMA), an amphetamine derivative with well-known effects on thermoregulation [9,14]. In addition, environmental effects that users face in dancing clubs where these drugs are usually consumed may contribute as well as to hyperthermia associated with methcathinones and MDMA [15,16].

While the capacity of cathinones and many other recreational drugs to increase the body and brain temperature is well established, the effects of hyperthermia on neurotoxicity associated with these drugs is currently less well known [13]. Barbosa et al. investigated the effect of ecstasy and ecstasy metabolites on SH-SY5Y cells under normothermic (37 °C) and hyperthermic (40 °C) conditions [17]. They found that the metabolites were more toxic than the parent compound and that the toxicity increased with higher temperature.

The aim of the current entry was to investigate in vitro the role of hyperthermia on methcathinone-induced neurotoxicity using the well-established SH-SY5Y neuronal cell model [18].
