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Original article

Acute behavioral effects of co-administration of mephedrone and MDMA in mice

Barbara Budzynska[a,*], Agnieszka Michalak[a], Małgorzata Frankowska[b], Katarzyna Kaszubska[a], Grażyna Biała[a]

[a] Medical University of Lublin, Department of Pharmacology and Pharmacodynamics, Lublin, Poland
[b] Institute of Pharmacology, Polish Academy of Sciences, Department of Pharmacology, Kraków, Poland

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ABSTRACT

Background: Abuse of more than one psychoactive drug is becoming a global problem. Our experiments were designed to examine the effects of a concomitant administration of 3,4-methylenedioxy-methamphetamine (MDMA) and mephedrone on depression- and anxiety-like behaviors and cognitive processes in Swiss mice.
Methods: In order to investigate the drug interactions the forced swimming test (FST) – an animal model of depression, the passive avoidance (PA) test – a memory and learning paradigm, as well as the elevated plus maze (EPM) test – test for anxiety level were used.
Results: The results revealed that a concomitant administration of non-effective doses of mephedrone (1 mg/kg) and MDMA (1 mg/kg) exerted marked antidepressive effects in the FST. Also a co-administration of mephedrone (2.5 mg/kg) and MDMA (1 mg/kg) displayed a pro-cognitive action in the PA paradigm. Furthermore, even though mephedrone and MDMA can, in general, exert some anxiogenic effects in mice, the concomitant administration of nonactive doses of both drugs (0.05 and 0.1 mg/kg, respectively) in the EPM test, did not show any synergistic effect in our study.
Conclusions: The effects of mephedrone and MDMA combination on mammalian organisms were attempted to be evaluated in our study and the results are described in the present report. These results may help explain the reasons for and consequences of a concomitant administration of psychoactive substances with regards to the central nervous system, while being possibly useful in the treatment of polydrug intoxication.

Introduction

Simultaneous consumption of several psychoactive drugs is a problem among young recreational drug users [1]. Like other recreational drugs of abuse, mephedrone [(RS)-2-methylamino-1-(4-methylphenyl) propan-1-one] and MDMA, [3,4-methylene-dioxy-methamphetamine] are often used in combination. These drugs show a close structural and mechanistic convergence (see Fig. 1) which can contribute to life-threatening interactions. Mephedrone is a semi-synthetic derivative of cathinone [2]. β-ketoamphetamines (e.g., cathinone and mephedrone) exhibit a significant structural similarity to the neurotransmitters, noradrenaline (NA), adrenaline and dopamine (DA), as well as to exogenous substances that stimulate the central nervous system (CNS), such as amphetamine, methamphetamine and MDMA. Only a few behavioral and biochemical experimental studies have investigated the effects of mephedrone in laboratory animals. The results indicate that mephedrone enhances the extracellular levels of DA and serotonin (5-HT) in the nucleus accumbens and can thus be self-administered to produce locomotor activation [3–6]. *In vitro* release studies indicate that mephedrone is a nonselective substrate for transporters of plasma membrane monoamine, such as NA (NAT), DA (DAT) and 5-HT (SERT) [3,7]. MDMA, similar to mephedrone, is able to elevate DA and NA levels but in smaller amounts than 5-HT level. MDMA can also delay their metabolism by inhibition of monoamine oxidase (MAO) and bind to distinct 5-HT and NA receptors [8–10]. The above-mentioned mechanisms contribute to the general increase of extracellular monoamine level in the CNS after both drugs are taken.

Furthermore, mephedrone users describe the effects of the drug as more MDMA-than cocaine-like, including positive psychotomimetic effects, e.g., euphoria, elevated mood stimulation, as well as negative, e.g., anxiety and panic [11].

* Corresponding author.
E-mail address: basia.budzynska@umlub.pl (B. Budzynska).

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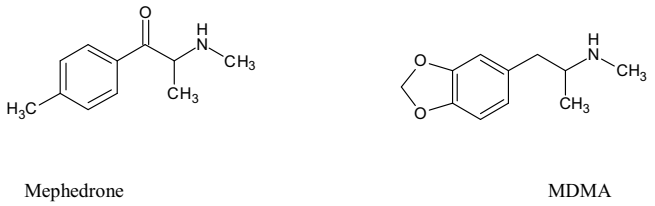

Mephedrone MDMA

Fig. 1. Chemical structure of mephedrone [(RS)-2-methylamino-1-(4-methylphenyl) propan-1-one] and MDMA [3,4-methylenedioxy-methamphetamine].

Considering these findings, it is most likely that an acute mephedrone and MDMA co-administration may contribute to behavioral changes in both humans and animals. Much research has focused on evaluating the long lasting neurotoxic effects of mephedrone, using a binge like regime in animal models [12–15]. However, to the best of our knowledge, there is no preclinical information relating to the acute, concomitant use of mephedrone with MDMA, even though the problem seems to be significant. For this reason, we chose three behavioral procedures, i.e., the passive avoidance (PA) test, the forced swimming test (FST) and the elevated plus maze (EPM) test to assess the acute effects on memory, depression- and anxiety-like behaviors, respectively, after co-administration of these drugs. The results from our experiments may explain, whether acute exposures to the two amphetamines have any short-lasting behavioral consequences.

Materials and methods

Animals

Male Swiss mice weighing 20–25 g were used in the experiments. The animals were maintained under standard laboratory conditions (12 h light/dark cycle, room temperature 21 ±1 °C, cage dimension of 26 × 20 × 14 cm, 8 animals per cage) with free access to tap water and laboratory chow (Agropol, Poland) and adapted to laboratory conditions for, at least, one week. Each experimental group consisted of 8–10 animals. All the experiments were conducted, according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and to the European Community Council Directive for the Care and Use of Laboratory Animals of 22 September 2010 (2010/63/EU), and were approved by the local ethics committee. Each mouse was used in one procedure only.

Drugs

The following compounds were tested: MDMA (3,4-methylenedioxy-methamphetamine hydrochloride; 0.1, 0.5, 1, 2.5, 5, 10 and 20 mg/kg; Tocris, UK) and mephedrone ((RS)-2-methylamino-1-(4-methylphenyl) propan-1-one; 0.05, 1, 2.5 and 5 mg/kg; Toronto Research Chemicals Inc., Canada). The drugs were dissolved in saline solution (0.9% NaCl), and intraperitoneally (*ip*) administered at a volume of 10 ml/kg. Fresh drug solutions were prepared on each day of experimentation. Control groups received saline injections in the same volumes and *via* the same route of administration.

The doses of mephedrone and MDMA were based on literature data [16–19] and our preliminary studies.

The FST procedure

According to Porsolt et al. [20], mice were individually placed in glass cylinders (height 25 cm, diameter 10 cm) containing 10 cm of water at 23–25 °C for 6 min. The total duration of immobility was recorded after 2 min of familiarization to the environmental conditions. Immobility was recognized when a mouse stopped struggling and continued only slight movements in order to keep its head above water level.

The animals were divided into following groups: saline + saline, saline + mephedrone (1, 2.5, 5 mg/kg, *ip*), MDMA (1, 2.5, 5, 10 mg/kg, *ip*) + saline, or mephedrone (1 mg/kg, *ip*) co-administered with MDMA (1 mg/kg, *ip*). The test was conducted in 15 min after drug administration.

The PA procedure

The apparatus and PA procedure was fully described in our previous article [21]. On the first day of experiment (pre-test), mice were individually placed in a light compartment and allowed to explore the light box for 30 s. After that time period, a guillotine door was raised and, when the mice entered a dark compartment, the guillotine door was closed again and an electric foot-shock (0.2 mA) of 2 s duration was delivered. The latency time to enter the dark compartment was recorded (TL1). In a subsequent trial (retention) 24 h later, the same mouse was again placed individually in the light compartment of the PA apparatus and the time taken to reenter the dark compartment was recorded (TL2). If the animal did not enter the dark compartment within 300 s, the test was stopped and TL2 was recorded as 300 s.

The experimental procedure involved examination of memory consolidation (the animals received injections of the substance after pre-test) [22,23].

The animals were allocated into the following drug groups: mephedrone (2.5 mg/kg, *ip*) + saline, MDMA (1, 2.5, 5, 10 mg/kg, *ip*) + saline, or mephedrone (2.5 mg/kg, *ip*) co-administered with MDMA (1 mg/kg, *ip*). The drugs were administered immediately after pre-test (memory consolidation) and the mice were re-tested 24 h later.

The EPM procedure

The apparatus, made of dark Plexiglas, was cross-shaped and consisted of a central platform (5 × 5 cm), with two open arms (30 × 5 cm) opposite to each other and two equal-sized enclosed (30 × 5 × 15 cm) arms opposite to each other. The maze was elevated to the height of 50 cm above the floor and illuminated by dim light.

The procedure was based on our recently published data [21,24]. The procedure was similar to the method of Lister [25].

The animals were divided into the following groups: saline + saline, MDMA (0.1, 0.5, 1, 2.5, 5, 10 and 20 mg/kg, *ip*) + saline, saline + mephedrone (0.05 mg/kg, *ip*), or mephedrone (0.05 mg/kg, *ip*) co-administered with MDMA (0.1 mg/kg, *ip*) The test was conducted in 15 min after drug administration.

Locomotor activity

Photoresistor actimeters (circular cages, two light beams, diameter of 25 cm, were used to measure the locomotor activity of experimental mice. The animals were individually placed in an actimeter for 40 min. The number of episodes of light beam crossing by the mice was recorded as their locomotor activity after 15 min. In order to measure the locomotor effects of mephedrone (1 mg/kg, *ip*), or MDMA (1 mg/kg, *ip*), the animals, naive for any drug treatment, were injected with the drug and immediately placed in the activity chamber. Their locomotor activity, i.e., the number of photocell beam breaks was automatically recorded.