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Research paper

'Ecstasy' enhances noise-induced hearing loss

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ABSTRACT

'Ecstasy' or 3,4-methylenedioxy-N-methamphetamine (MDMA) is an amphetamine abused for its euphoric, empathogenic, hallucinatory, and stimulant effects. It is also used to treat certain psychiatric disorders. Common settings for Ecstasy use are nightclubs and "rave" parties where participants consume MDMA and dance to loud music. One concern with the club setting is that exposure to loud sounds can cause permanent sensorineural hearing loss. Another concern is that consumption of MDMA may enhance such hearing loss. Whereas this latter possibility has not been investigated, this study tested the hypothesis that MDMA enhances noise-induced hearing loss (NIHL) by exposing rats to either MDMA, noise trauma, both MDMA and noise, or neither treatment. MDMA was given in a binge pattern of 5 mg/kg per intraperitoneal injections every 2 h for a total of four injections to animals in the two MDMA-treated groups (MDMA-only and Noise + MDMA). Saline injections were given to the animals in the two non-MDMA groups (Control and Noise-only). Following the final injection, noise trauma was induced by a 10 kHz tone at 120 dB SPL for 1 h to animals in the two noise trauma-treated groups (Noise-only and Noise + MDMA). Hearing loss was assessed by the auditory brainstem response (ABR) and cochlear histology. Results showed that MDMA enhanced NIHL compared to Noise-only and that MDMA alone caused no hearing loss. This implies that "clubbers" and "rave-goers" are exacerbating the amount of NIHL when they consume MDMA and listen to loud sounds. In contrast to earlier reports, the present study found that MDMA by itself caused no changes in the click-evoked ABR's wave latencies or amplitudes.

1. Introduction

Ecstasy (which contains the psychoactive drug ±3,4-methylenedioxy-N-methamphetamine; MDMA) is an amphetamine derivative that is abused for its euphoric, empathogenic, hallucinatory, and stimulant effects. MDMA was developed to treat depression and anxiety disorders and is useful in treating patients with post-traumatic stress disorder (PTSD) (Mithoefer et al., 2013). First used recreationally in the 1970's, its abuse escalated in the late 1980's and continues to be a world-wide problem (Weir, 2000). Recent reports show that MDMA and other amphetamine abuse continue to increase, particularly in the adolescent and young adult populations (Johnston et al., 2011). Common settings for Ecstasy usage are nightclubs and "raves", which are dance parties where participants often consume large amounts of MDMA and dance to loud electronic music for lengthy periods of time. "Clubbers" and "rave-goers" report that consuming MDMA enhances the music experience (Weir, 2000).

People attending such venues are typically exposed to loud music for a period of 4–5 h at a time (Weir, 2000; Williams et al., 2010) with average sound levels ranging from 100 to 124 dB(A) (Gunderson et al., 1997; Sadhra et al., 2002; Serra et al., 2005; Williams et al., 2010). This is a major concern because it is well established that exposures to loud sounds for prolonged periods of time or on repeated occasions cause permanent noise-induced hearing loss (NIHL) (Gunderson et al., 1997; Sadhra et al., 2002; Serra et al., 2005; Williams et al., 2010).

Abbreviations: ABR, auditory brainstem response; ANOVA, analysis of variances; d, day; dB ppeSPL, decibels peak-to-peak equivalent Sound Pressure Level; EDTA, ethylenediaminetetraacetate; g, grams; h, hour; IHC, inner hair cell; IM, intramuscular; IP, intraperitoneal; MDMA, ±3,4-Methylenedioxy-N-methamphetamine; min, minute; NIHL, noise-induced hearing loss; OHC, outer hair cell; *p*, probability level; Pa, Pascal energy units; PBS, phosphate-buffered saline; PTSD, post-traumatic stress disorder; SD, standard deviation; SEM, standard error of the mean; SNHL, sensorineural hearing loss; wk, week.

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An added concern is that MDMA consumption may enhance the NIHL among clubbers, rave-goers, and psychiatric patients. For example, MDMA can deplete the brain neurotransmitters serotonin and dopamine (Perrine et al., 2010; Sarkar and Schmued, 2010). Both of these neurotransmitters are believed to play a protective role against acoustic trauma (Lendvai et al., 2011; Papesh and Hurley, 2012; Tong et al., 2005). Second, both high-dose MDMA administration (Sarkar and Schmued, 2010) and noise trauma (Le Prell et al., 2007) induce neurotoxicity, often by similar mechanisms as described later (see Discussion). Third, an emerging body of literature reports that loud sound and MDMA can interact whereby loud sound enhances MDMA's myocardial (Gesi et al., 2002) and neural damage (Feduccia and Duvauchelle, 2008; Gesi et al., 2004; Morton et al., 2001), and MDMA-induced stereotypy and seizures (Morton et al., 2001). Thus far, no studies have addressed the converse possibility that MDMA enhances the toxicity of loud sound exposure. This is an important health issue because of MDMA's widespread consumption and the debilitating effects of hearing loss.

To address this issue, we hypothesized that MDMA enhances NIHL and tested this hypothesis by exposing laboratory rats to high-dose MDMA, noise trauma, both MDMA and noise, or neither treatment. Hearing loss was assessed by the auditory brainstem response (ABR). The cumulative levels of noise trauma and MDMA consumption were intended to model amounts experienced by clubbers or rave-goers.

In addition, there is an interest in MDMA's effects on brain electrophysiology. For example, studies have reported that MDMA alters electroencephalographic (Dafters et al., 1999; Gamma et al., 2000; Obrocki et al., 1999) and other measures of brain function such as the ABR (Taffe et al., 2001, 2003). Regarding the ABR, a repeated high-dose MDMA regimen in the rhesus monkey caused shortening of P3 and P4 wave latencies and prolongation of P5 wave latency that lasted up to 13 wk post-treatment (Taffe et al., 2001, 2003).

Accordingly, a second interest was to use the MDMA-only and Control rats to determine if MDMA by itself caused changes in ABR latencies such as those described in the recent monkey studies (Taffe et al., 2001, 2003), but using an animal that is lower on the phylogenetic scale and a more moderate dosing regimen. These are important issues, because the United States Animal Welfare Act requires investigators to consider the use of less traumatic procedures and animal models that are lower on the phylogenetic scale (i.e., the principles of "replacement" and "reduction"). Relatedly, the dosing regimen in the two monkey studies was relative high (4 d, 10 mg/kg IM, twice daily) (Taffe et al., 2001, 2003) compared to the standard human dose of 1 mg/kg per pill (Green et al., 2012) where a pill might be taken in a binge pattern of 2–4 times during the course of a rave party (Green et al., 2012; Johnston et al., 2011; Weir, 2000). Thus, the dosing regimen of our experiments were more relevant to the human situation while adjusting for the different metabolic rates between the rat and human (Green et al., 2012). We also sought to extend previous findings by examining both ABR amplitudes and latencies, as well as the interactive effects of MDMA administration with an auditory stressor condition (viz., rapid stimulus repetition rates). This would provide information about the best animal models, dosing regimens, stimulus parameters and general electrophysiology procedures for future studies.

2. Methods

2.1. Experiment #1 methods

2.1.1. Experimental design and subjects

All animal procedures were approved by the Wayne State University Institutional Animal Care and Use Committee and were in compliance with the National Institutes of Health and National Research Council's "Guide for the Care and Use of Laboratory Animals" (Institute of Laboratory Animal Resources (U.S.). Committee on Care and Use of Laboratory Animals, 2011). The Division of Laboratory Animal Resources maintains animal facilities accredited by the Association for Assessment and Accreditation for Laboratory Animal Care (Frederick, MD 21703-2879 USA), and animals were cared for in accordance with the Animal Welfare Act.

Male Sprague–Dawley rats (Charles River Laboratories, Portage, MI), aged ~60 d at the onset of the study, were divided into four experimental groups: (1) no MDMA and no noise trauma (Control), (2) Noise-only, (3) MDMA-only, and (4) Noise + MDMA. Each group had $n = 9$ rats, except the Control group which had $n = 10$. Rats were handled and weighed on days of treatment and ABR measurements. Otherwise, rats were left undisturbed in pair-housed conditions with ad libitum normal lab rat chow (5001 Rodent Chow; PMI Nutrition International LLC, Brentwood, MO) and water, 12 h light/dark cycle with lights on at 7 am, and standard room temperature (~22–24 °C) and humidity (~35%).

2.1.2. MDMA administration and body temperature measurements

MDMA (5 mg/kg at a solution volume of 1 ml/kg) was intraperitoneally (IP) injected in a binge pattern with MDMA administered once every 2 h for a total of four injections into the rats of the MDMA-only and Noise + MDMA groups. This paradigm of MDMA administration was chosen, because binge-pattern administration results in cumulatively high doses that consistently show serotonin depletion, behavioral effects, hyperthermia (Johnson and Yamamoto, 2010; Perrine et al., 2009, 2010) and serotonin-mediated neurotoxicity and neurodegeneration, rather than neuroplasticity (Biezonski and Meyer, 2011). Normal saline (0.9% NaCl; 1 ml/kg) was IP injected every 2 h for a total of four injections into rats of the Control and Noise-only groups. The injection site was varied from side to side to minimize discomfort and potential tissue damage that may result from multiple injections, and injections were done in the home cage environment. The MDMA-treated rats (i.e., MDMA-only and Noise + MDMA) were pair-housed together, and the saline-treated rats (i.e., Control and Noise-only) were pair-housed together. Rectal body temperature was measured between MDMA or saline injections to monitor hyperthermia, a hallmark effect of amphetamines (Sarkar and Schmued, 2010). Baseline temperatures were measured 30 min before the first MDMA (or saline) injection. Temperatures were also taken 30 min before the last (4th) injection (i.e., just before the start of noise trauma) and just after the noise trauma, using a small animal rectal thermometer (Pivia Rectal Temp; Pavia Sales Group, Inc., Plymouth, MN) coated with a lubricating jelly.

2.1.3. Noise trauma procedure

Immediately following the last (4th) MDMA or saline injection, one animal from the Noise-only and one from the Noise + MDMA condition were placed together in a 20 × 45 × 24 cm polycarbonate cage with a polycarbonate lid and filter. The caged animals were then placed inside a double-walled sound-attenuation booth (Industrial Acoustics Co., Bronx, NY). Animals were free to move about the cage. Some noise trauma studies used fully anesthetized animals during the noise trauma procedure (Cody and Robertson, 1983; Zhang et al., 2006), while others used alert and freely moving animals (Gourevitch et al., 2009; Manzoor et al., 2012; Wang et al., 2002). The anesthesia method was rejected because this would not mimic the Rave party scenario and would introduce a possible confounding effect from the co-administration of the anesthetics and the MDMA. Following procedures used by others (Gourevitch et al., 2009; Manzoor et al., 2012; Wang et al., 2002), an open field 10 kHz tone at 120 dB SPL was generated by commercial