

# Clubbing with ecstasy

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**I**n this issue, Parrot and Young present the results of temperature measurements in young individuals “partying” with 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy). This editorial commentary briefly summarizes the main findings of their study, provides background gained from previous animal experiments, and reviews the implications for the development of future pharmacotherapies and harm reduction strategies.

Body temperature is usually viewed as a stable homeostatic parameter and any increases are typically indicative of bacterial or viral infection. However,

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**Abbreviations:** MDMA or “Ecstasy”, 3,4-methylenedioxymethamphetamine

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temperature could rise well above normal levels following exposure to a number of amphetamine-like drugs (i.e., amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy), “bath salts” drugs), which are voluntarily taken by humans to induce desired psychoactive effects. Sometimes, these temperature increases are clearly pathological, resulting in serious health complications or even death. Although most papers presented in this Special Issue describe the thermogenic effects of different drugs of abuse in laboratory animals under standard laboratory conditions, it is critically important to examine the effects of these drugs when self-administered by humans in the real world. The paper of Andrew C. Parrott and Lucy Young<sup>1</sup> is focused on this issue with respect to the highly popular party drug MDMA (Ecstasy, “Molly”).

The most important finding of this study is verification of body hyperthermia in young people partying with MDMA. Given comparable drug dose and age of participants, the temperature increases of 1.2°C (37.7°C) found in people partying with MDMA vs. drug-free party participants were much larger than 0.2–0.8°C increases induced by MDMA standard laboratory conditions.<sup>2</sup> This difference could result from 3 factors present in the rave party: drug self-intake, high level of psycho-emotional and motor activation, and specific environmental conditions associated with drug use.

MDMA is typically taken orally and given the relatively long onset latency of subjective effects and possible drug boosting, both recreational doses and temperature effects are highly variable. Even in rats under standard laboratory conditions, temperature effects of MDMA are highly variable, relatively weak, and fail to conform to a traditional dose-response curve, often showing weak decreases at low doses and weak increases at higher doses.<sup>3,4</sup>

Even at relatively large doses (9 mg/kg) that clearly exceed the range consumed by humans under real-world conditions (i.e., rave parties), temperature effects of MDMA in rats are modest (~0.8°C) and well tolerated. However, brain and body hyperthermic effects of MDMA are strongly enhanced during social interaction between 2 rats and become pathological, if not lethal, in moderately warm environments (29°C).

This state dependency and environmental modulation of hyperthermic effects of MDMA is determined by the unique properties of this drug, which induces metabolic brain activation, with excessive intra-cerebral heat production, as well as strong, prolonged cutaneous vasoconstriction, which prevents normal heat dissipation to the external environment.<sup>4</sup> Despite these effects predisposing to hyperthermia, body temperature balance remains relatively unchanged under resting conditions in cool environments but becomes clearly disturbed during psycho-physiological activation, which by itself results in intra-brain heat production and cutaneous vasoconstriction. This balance becomes dangerously tilted toward hyperthermia in a warm environment, further complicating heat loss and inducing heat accumulation. As such, the high levels of psycho-physiological and motor activation as well as the hot, humid environment typical to rave-parties/night clubs are powerful factors potentiating MDMA-induced hyperthermia. MDMA is, therefore, most commonly used under the very social and environmental conditions that enhance its toxicity.

Since physical activity is associated with robust heat production, physical activity itself may potentiate MDMA-induced hyperthermia.<sup>5</sup> However, normal body temperatures found in MDMA-free party participants suggest that intense physical activity by itself fails to increase

body temperatures. The same line of reasoning may be extended to warmth and humidity as well as high levels of psychoemotional activation typical to dance parties, which alone are not sufficient to induce hyperthermia. In rats, warm ambient temperature also did not affect basal brain and body temperatures and social interaction induced only transient hyperthermic responses. Therefore, the robust hyperthermic responses and health complications associated with MDMA use result from interactions between drug effects, individual activity states, and environmental conditions. In addition, they also depend upon multiple associated factors, including such “non-significant” ones as the type and specifics of behavioral activity, cloth, co-use of other recreational or therapeutic drugs, as well as latent health problems.

The study of Parrott and Young<sup>1</sup> also confirmed that recreational MDMA-users report feeling both hotter and thirstier than their control counterparts. Interestingly, intermediate temperature increases were also found in ecstasy-experienced individuals who had not taken ecstasy that night. The authors posit that past MDMA-use may have a long-term effect on temperature regulation and possibly on the functioning of hypothalamus given the increased ratings of “thirst.” However, these symptoms not only hint at a molecular mechanism underlying MDMA-induced hyperthermia, but also have important safety and therapeutic implications.

Although water consumption plays a very minor role in decreasing body temperature, “remember to drink lots of water” is a mantra given to recreational drug users at rave parties. However, intense water consumption could pose serious complication in MDMA-users because this drug by itself induces water retention in both the brain and body. As shown in animals, both MDMA and methamphetamine induce leakage of the blood-brain barrier, resulting in a significant rise in brain water content (vasogenic edema) as well as alterations of brain ionic balance, including increases in extracellular Na<sup>+</sup> levels.<sup>6,7</sup> These changes are tightly correlated with the degree of drug-induced temperature elevation and could be extreme during pathological hyperthermia (>40°C). Therefore, hyponatremia (i.e., decreases in Na<sup>+</sup> in the peripheral blood) found in MDMA-intoxicated individuals consuming large amounts of water may result from water retention and the redistribution of Na<sup>+</sup> from the peripheral blood into the brain extracellular environment. Since MDMA inhibits perspiration and water expulsion by urination, additional liquid intake enhances water accumulation in the body and the brain, resulting in serious health complications. Interestingly, MDMA-induced water retention poses a greater risk for females as estrogen plays a significant role in the transfer of water across cell membranes, exacerbating peripheral hyponatremia and possibly central hypernatremia as well as brain edema. It is important that Drs.

Parrott and Young discuss this issue and propose prophylactic strategies in order to reduce the risk of possible health hazards for individuals using this drug recreationally.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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