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Effects of MDMA on body temperature in humans

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Keywords: hyperthermia, hyperpyrexia, MDMA, norepinephrine, serotonin, treatment

Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine

Hyperthermia is a severe complication associated with the recreational use of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy). In this review, the clinical laboratory studies that tested the effects of MDMA on body temperature are summarized. The mechanisms that underlie the hyperthermic effects of MDMA in humans and treatment of severe hyperthermia are presented. The data show that MDMA produces an acute and dose-dependent rise in core body temperature in healthy subjects. The increase in body temperature is in the range of 0.2-0.8°C and does not result in hyperpyrexia (>40°C) in a controlled laboratory setting. However, moderately hyperthermic body temperatures >38.0°C occur frequently at higher doses, even in the absence of physical activity and at room temperature. MDMA primarily releases serotonin and norepinephrine. Mechanistic clinical studies indicate that the MDMA-induced elevations in body temperature in humans partially depend on the MDMA-induced release of norepinephrine and involve enhanced metabolic heat generation and cutaneous vasoconstriction, resulting in impaired heat dissipation. The mediating role of serotonin is unclear. The management of sympathomimetic toxicity and associated hyperthermia mainly includes sedation with benzodiazepines and intravenous fluid replacement. Severe hyperthermia should primarily be treated with additional cooling and mechanical ventilation.

Introduction

Hyperpyrexia (body temperature >40°C) is the most important acute severe complication of the recreational use of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy). MDMA-induced hyperpyrexia is relatively rare and not observed in placebo-controlled studies in humans. However, moderate effects of MDMA on body temperature have been documented in several placebo-controlled laboratory studies in human subjects. This review summarizes the clinical studies on MDMA-induced hyperthermic effects and the potential pharmacological mechanisms that are involved in humans. Many preclinical studies (for review, see[1]) but relatively few clinical studies have evaluated the effects of MDMA on body temperature. The present review focuses on the findings from placebo-controlled studies that assessed MDMA in humans and addresses treatment options for hyperpyrexia caused by recreational Ecstasy use. The thermal effects of Ecstasy in dance clubbers have previously been described and summarized.[2]

Hyperthermia associated with Ecstasy use

The association between Ecstasy use and hyperpyrexia is well-established,[3-6] and reports were systematically compiled by Grunau and colleagues.[6] Hyperpyrexia is relatively rare, but if it occurs, then it typically leads to intravascular coagulation, rhabdomyolysis, and renal or other organ failure.[2,4-10] In particular, body temperature >41°C can result in fatalities.[4,6] Moderate forms of Ecstasy-induced hyperthermia (>38°C) are frequently observed. Increased body temperature (>37.1°C) was found in 19% of patients,[9] and hyperthermia (>38°C) was found in 4% of patients[5] who presented in emergency departments with Ecstasy-related medical problems.

Basic mechanisms involved in hyperthermia

Drug-induced hyperthermia resembles heat stroke. The basic mechanisms include increased heat production and/or decreased heat loss (**Fig. 1**). In heat stroke, heat dissipation is primarily impaired by a hot environment, and heat generation is often increased by exertion. In drug-induced hyperthermia, the drug exerts direct actions to increase metabolic heat generation and reduce heat dissipation as mostly studied in animals,[7,11-13] whereas a hot environment and exertion may act as additional permissive factors.[2,14] Additionally, in the case of drug-induced hyperthermia, central heat regulation mechanisms may be disturbed.[12] Many psychotropic substances, including both therapeutic medications and recreational drugs, alter body and brain temperature[15] and may cause hyperthermia.[12] Serotonin syndrome, which includes increases in body temperature, may result when serotonergic drugs are used at high doses or in combinations.[16] Neuroleptic malignant

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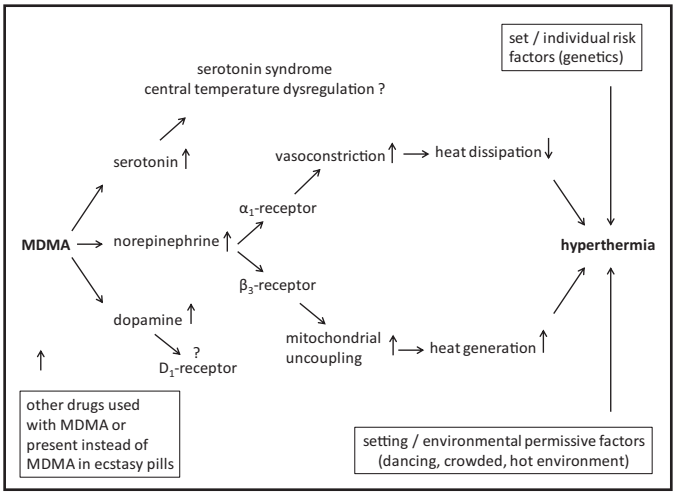

Figure 1. Basic mechanism involved in 3,4-methylenedioxymethamphetamine (MDMA)-induced hyperthermia.

syndrome is an adverse hyperthermic reaction to antipsychotic drugs.[12] MDMA releases serotonin and therefore may induce a serotonin syndrome, including increased body temperature.[17] Additionally, MDMA has been shown to induce alterations in mitochondrial energy metabolism in animals, resulting in increased heat generation instead of metabolic energy carrier (i.e., adenosine triphosphate) production.[11,18] Additionally, psychostimulants, including MDMA, constrict blood vessels via sympathetic stimulation, including adrenergic receptor stimulation, thereby reducing peripheral blood flow and heat dissipation by convection via the skin (**Fig. 1**).[19] Furthermore, central thermoregulation may be dysregulated in the case of substances that act as direct or indirect serotonin receptor agonists, such as MDMA.[20] Dopaminergic mechanisms have also been implicated in MDMA-induced hyperthermia in preclinical studies.[21] Many permissive factors have been shown to enhance the thermogenic effects of MDMA, typically in preclinical studies, and have been summarized with regard to human MDMA use.[2] Factors that increase the risk of MDMA-induced hyperthermia in animals and possibly also in humans include multiple dosing (booster) or high doses,[2,22] high ambient temperature,[7,23,24] reduced fluid intake,[23] crowded conditions, physical activity,[23] and social interaction.[24,25] Several of these risk factors are typically present in dance clubs or party settings where MDMA and other stimulant drugs are consumed. Hyperthermia is also seen in human MDMA exposure outside "rave" party settings in the absence of physical activity.[26] In placebo-controlled laboratory studies in humans, these conditions are mostly not present for safety reasons. In real-world studies of ecstasy users at dance clubs, increases in tympanic body temperature of +0.2 to +1.6°C have been measured in response to Ecstasy use (for a summary, see Parrott[2]).

Effects of MDMA on body temperature in experimental clinical studies

Clinical laboratory studies that investigated the effects of MDMA using a placebo-controlled study design are summarized in **Table 1**. MDMA was administered orally in all these studies but different doses were used. A series of small experimental studies (n < 20) assessed the thermogenic effects of MDMA in healthy subjects.[27-40] These studies typically used axillary, oral, or tympanic temperature measurements. Body temperature was not the primary outcome measure in these studies, with one exception. Pooled analyses of the effects of MDMA have been reported using aggregated data from smaller studies with 27 subjects by da la Torre and colleagues,[41] 74 subjects by Liechti and colleagues,[34] and 80 subjects by Hysek and Liechti.[32] In the studies by Liechti and colleagues,[42-46] which were conducted in Zurich, Switzerland, axillary body temperature was measured in a total of 54 men and 20 women after MDMA doses of 1.35-1.8 mg/kg.[34] Peripheral body temperature was significantly increased by 0.4°C compared with placebo in male subjects, whereas MDMA-induced increases in body temperature did not reach statistical significance in the smaller group of female participants.[34] All axillary body temperatures remained below 38°C.[34] In our more recently published placebo-controlled studies performed in Basel, Switzerland, core body temperature was measured using an ear thermometer and repeatedly after the administration of MDMA at doses of 75 mg (n = 30) and 125 mg (n = 96) in a total of 126 healthy subjects.[27-33] The effects of the 75 mg dose of MDMA on body temperature were reported by Schmid et al.[47] The effects of the 125 mg dose of MDMA were reported in a pooled analysis by Hysek and Liechti (n = 80)[32] and separately for 16 additional subjects.[33,47] MDMA did not significantly alter body temperature at a dose of 75 mg compared with placebo in 30 subjects.[47] The maximum increase after MDMA was 0.35 ± 0.06°C above pretreatment baseline compared with 0.25 ± 0.06°C after placebo.[47] At a higher dose of 125 mg, MDMA robustly and significantly increased body temperature in several of our recent studies.[27,28,30,31,33] The pooled data from 5 of these studies were presented in an analysis of the autonomic effects of MDMA in 80 healthy subjects[32] and in a study of dose-response effects in the online supplemental material that accompanied the reported by Schmid et al.[47] The increase in body temperature after 125 mg of MDMA was typically 0.3-0.8°C.[32,47] As expected, a statistically significant MDMA dose-response effect on body temperature was observed.[47] Maximal temperatures occurred 2-2.5 h after MDMA administration and after subjective effects, heart rate, or blood pressure had peaked, which was at 1.5 h.[32] An analysis of the data from all 126 subjects showed a peak maximum body temperature of 37.5 ± 0.5°C. After the 75 mg dose of MDMA, tympanic temperatures remained below 38°C in all 30 subjects. However, after the 125 mg dose in a total of 96 subjects, tympanic temperatures were >38.0°C in 21 subjects (22%) and >38.5°C in 3 subjects (3%), reaching a maximum of 39.1°C in one subject (1%). Importantly, these body temperatures were measured with subjects at rest and at a mean room temperature of 22.7 ± 0.6°C. The time course of the increase in tympanic body temperature after MDMA administration at a dose of 125 mg in 96 subjects is shown in **Figure 2**. The figure shows the pooled data from all our 6 published studies using the 125 mg dose of MDMA.[27-31,33] Significant elevations in body

Table 1. Placebo-controlled studies that investigated effects of MDMA on body temperature

Reference	other drugs in study	Sample size	oral doses	measurement	effect
39	no	n = 6	0.25-1.0 mg/kg	oral	no significant change
42	no	n = 13	1.7 mg/kg	axillary	no significant change
35	amphetamine	n = 8	75 and 125 mg	oral	no significant change
[a]41	no	n = 27, pooled	50-150 mg	oral	increase after initial decrease
43	citalopram	n = 16	1.5 mg/kg	axillary	increase
46	haloperidol	n = 14	1.5 mg/kg	axillary	no significant change
44	ketanserin	n = 14	1.5 mg/kg	axillary	increase
[b]34	no	n = 74, pooled	1.35-1.8 mg/kg	axillary	increase
37	no	n = 8	0.5 and 1.5 mg/kg	finger and tympanic	no significant change
36	mCPP, amphetamine	n = 12	1 and 2 mg/kg	oral	increase
38	no	n = 9	100 mg	oral	no significant change
50	no	n = 10	2 mg/kg	[c]core body and skin	increase (core), trend-increase (skin)
49	no	n = 8	1.0 and 1.6 mg/kg	tympanic	no significant change
40	tetrahydrocannabinol	n = 16	100 mg	tympanic	increase
27	reboxetine	n = 16	125 mg	tympanic	increase
48	methamphetamine	n = 11	100 mg	oral	no significant change
29	clonidine	n = 16	125 mg	tympanic	no significant change
28	duloxetine	n = 16	125 mg	tympanic	increase
30	carvedilol	n = 16	125 mg	tympanic	increase
31	doxazosin	n = 16	125 mg	tympanic	increase
[d]32	pooled analysis	n = 80, pooled	125 mg	tympanic	increase
33	methylphenidate	n = 16	125 mg	tympanic	increase
47	methylphenidate	n = 30	75 mg	tympanic	no significant change

MDMA, 3,4-methylenedioxymethamphetamine; mCPP, metachlorophenylpiparazine.
[a]pooled data including study 35 (n = 8) and an additional 19 subjects.
[b]pooled data including studies 42, 43, 46, and 44, and data from 16 subjects from study 45.
[c]ingested radio-telemetry pill, chest, upper arm, thigh, and lower leg.
[d]pooled data including 27-31, and 33.

temperature were observed between 90 min and 4 h after MDMA administration.

Several other smaller studies have also evaluated the thermogenic effects of MDMA. Oral temperature slightly increased after doses of 75 and 125 mg MDMA in 8 subjects, but no statistically significant differences were observed compared with placebo.[35] In the same study, amphetamine at an oral dose of 40 mg was also without effects on oral temperature.[35] A similar nonsignificant increase in oral temperature was found in another small study that included 9 subjects and a dose of 100 mg.[38] The same group reported significant increases in oral temperature after MDMA administration at doses of 75, 100, and 125 mg from a pooled analysis of several studies that included doses of 50 mg (n = 2), 75 mg (n = 10), 100 mg (n = 13), 125 mg (n = 8), and 150 mg (n = 2).[41] Other small studies by different research groups were also found. Harris and colleagues measured both skin (i.e., index finger) and core (i.e., tympanic) temperature after MDMA administration (0.5 and 1.5 mg/kg) in 8 subjects.[37] Although skin temperature decreased 5.0 ± 4°C from pretreatment levels after 1.5 mg/kg, it was not significantly lower than in the placebo condition in this small study.[37] The finding of reduced finger skin temperature is consistent with reports of cold extremities after MDMA administration and very likely reflects vasoconstriction in the periphery and reduced heat dissipation.

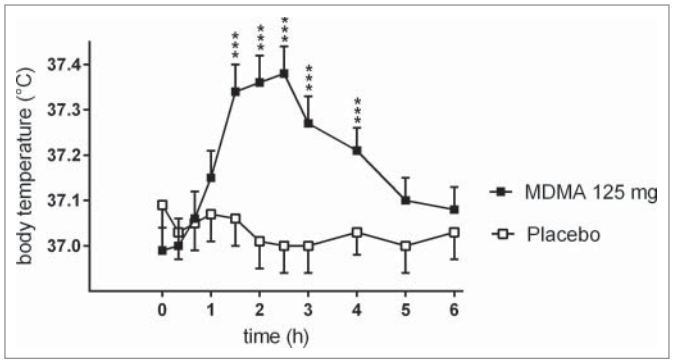

Figure 2. Effects of 3,4-methylenedioxymethamphetamine (MDMA, 125 mg orally) and placebo on core body (tympanic) temperature in healthy subjects. Absolute raw data values from all subjects who participated in our 6 placebo-controlled experimental studies using a dose of MDMA of 125 mg MDMA[27-31,33] were pooled and are presented here as mean ± SEM of absolute tympanic temperature values in 96 healthy subjects (48 male and 48 female). MDMA significantly increased body temperature compared with placebo (repeated-measures analysis of variance: time × drug interaction: $F_{10,940} = 19.72$, $P < 0.001$). *** for $P < 0.001$ indicate significant differences compared with placebo for individual time points based on Tukey post hoc test. MDMA or placebo was administered at t = 0. MDMA was administered in a quiet hospital setting and the subjects were not physically active.

Unfortunately, no other studies have measured finger temperature to confirm this finding in a larger sample. Kirkpatrick and colleagues found that MDMA at an oral dose of 100 mg had no effects on oral body temperature in 11 subjects.[48] This study also found no effects of methamphetamine (40 mg, orally) on body temperature.[48] Kolbrich and colleagues found nonsignificant elevations in tympanic temperature in 8 healthy subjects with MDMA doses of 1.0 and 1.6 mg/kg (46-150 mg).[49] Tancer and Johanson showed that MDMA at a dose of 2 mg/kg significantly increased oral body temperature in 12 subjects.[36] Significant increases in tympanic temperature of 0.3°C were also shown after 100 mg of MDMA in 16 subjects by Dumont and colleagues.[40] A study by Freedman, Johanson, and Tancer provided a comprehensive evaluation of the effects of 2.0 mg/kg MDMA on core and skin temperature at low (18°C) and high (30°C) ambient temperatures.[50] This also appears to be the only laboratory study of the effects of MDMA in humans in which body temperature was the primary outcome measure. In all of the other studies, body temperature was a secondary measure. Core body temperature was measured in 10 subjects using an ingested radiotelemetry pill.[50] Skin temperature was measured at the chest, upper arm, thigh, and lower leg, and a weighted average was calculated. Absolute core temperatures were higher after MDMA in the warm environment compared with the cold environment. However, core temperature was also higher in the warm environment compared with the cold environment after placebo. Thus, MDMA similarly increased core temperature at the low and high ambient temperatures compared with placebo.[50] These increases were related to increases in metabolic rate, measured by indirect calorimetry, in the same study. Skin temperature was markedly increased in the hot and decreased in the cold environment, and MDMA produced a near-significant increase in skin temperature under both temperature conditions and compared with placebo.[50]

Altogether, considering the pooled data analyses from our laboratory and those of the Freedman study, MDMA is well documented to produce an acute and dose-dependent elevation in core body temperature in healthy subjects. The increase in body temperature is also evidently rather small, in the range of 0.2-0.8°C, and does not result in hyperpyrexia (>40°C) in a controlled laboratory setting. Importantly, no laboratory study observed MDMA-induced hyperpyrexia in a controlled setting. However, moderately hyperthermic body temperatures >38.0°C were documented in a substantial number of our subjects (23% after a 125 mg dose in our sample), demonstrating that MDMA induces moderate hyperthermia even in the absence of any permissive factors and at room temperature (23°C).

Neurochemistry of the thermogenic properties of MDMA in humans

Several mechanistic studies assessed the effects of pharmacological pretreatments on the response to MDMA in healthy subjects to evaluate the mediating role of different neurotransmitters and receptors. These human studies also provide important information on the mechanisms involved in MDMA-induced increases in body temperature and likely also in the more severe hyperpyrexia associated with uncontrolled use. MDMA mainly releases serotonin and norepinephrine and to a lesser extent dopamine through the corresponding presynaptic monoamine transporters.[28,51] MDMA also interacts directly with monoamine receptors[52,53] but only at relatively high concentrations, likely making these effects less relevant in humans. Serotonin transporter inhibitors block the interaction between MDMA with the transporter to release serotonin.[28] Transporter inhibitors, therefore, can be used as pharmacological tools to investigate the role of serotonin release in the mechanism of action of MDMA. Serotonin transporter inhibitors reduced the psychotropic and most physiological effects of MDMA in healthy humans,[43,54-56] suggesting a mediating role for serotonin in most effects of MDMA in humans. Regarding the thermogenic effects of MDMA, serotonin transporter inhibition reduced MDMA-induced increases in oral[55] but not axillary body temperature.[43] The combined serotonin and norepinephrine transporter inhibitor duloxetine also tended to attenuate the MDMA-induced increase in body temperature in humans, but the effect was not significant.[28] These findings are inconclusive but are consistent with the view that both serotonin and norepinephrine are involved in the effects of MDMA on body temperature. Interestingly, in animals, serotonin transporter inhibition reduced MDMA-induced hyperthermia in mice[57] but not rats.[21] Serotonin release is the major mediator of most of the clinical effects of MDMA, but its precise role in the thermogenic response in humans remains to be determined. The serotonin 5-HT_{2A} receptor antagonist ketanserin reduced the MDMA-induced elevation in body temperature in humans,[44] consistent with studies in rats.[58] However, in humans, ketanserin alone also reduced body temperature compared with placebo, and the effects with MDMA were therefore

mostly additive.[44] Additionally, ketanserin has α_1-adrenergic receptor-blocking properties[59] and may reduce peripheral vascular resistance and body temperature. The serotonin 5-HT_{1A} receptor antagonist pindolol did not alter the MDMA-induced increase in body temperature in humans,[60] also consistent with preclinical data.[58] Potential dopaminergic mediation of the effects of MDMA on body temperature has not been well-studied in humans. Preclinical data suggest a role for the dopamine D_1 receptor in the mediation of hyperthermia associated with MDMA.[21] Because no selective D_1 antagonists are available for human use, the role of the D_1 receptor has not been studied in humans. The interaction between MDMA and the dopamine D_2 receptor antagonist haloperidol was examined in healthy subjects, but MDMA did not produce significant elevations in body temperature in that study to provide meaningful results.[46] Studying the role of the dopamine transporter in MDMA-induced hyperthermia using pharmacological tools was also difficult because dopamine transporter inhibitors may not effectively block MDMA-induced dopamine release[21] or may have effects on their own.[61] In fact, the dopamine uptake inhibitor methylphenidate increased body temperature in healthy subjects when given alone but failed to alter the thermogenic response to MDMA when administered prior to MDMA.[33,47] In contrast, MDMA did not produce an increase in body temperature in humans after pretreatment with the selective norepinephrine transporter blocker reboxetine.[27] Additionally, reboxetine blocked MDMA-induced increases in norepinephrine plasma levels and elevations in heart rate and blood pressure,[27] supporting the view that norepinephrine rather than serotonin is critical in the mediation of not only the cardiovascular but also hyperthermic response to MDMA. Further human studies examined the contributing role of different adrenergic receptors. β_1-adrenergic receptors did not appear to be involved because the β_1-receptor blocker pindolol did not alter the temperature response to MDMA in humans.[60] Administration of the non-selective β-receptor antagonists propranolol or nadolol also had no effect on the thermogenic response to MDMA in rats.[62] The α_2-adrenergic receptor agonist and sympatholytic drug clonidine, which is expected to reduce central adrenergic output, lowered body temperature in humans when given alone but not the MDMA-induced elevations in body temperature.[29] In contrast, the α_1-adrenergic receptor antagonist doxazosin reduced the increase in body temperature induced by MDMA in humans.[31] This is again consistent with the view that MDMA-induced increases in norepinephrine mediate the thermogenic effects of MDMA and that increases in body temperature are linked to cutaneous vasoconstriction that results in impaired heat dissipation, and doxazosin prevents α_1-adrenergic receptor-mediated vasoconstriction. Peripheral vasoconstriction and improper heat dissipation have also been identified as critical mechanisms that underlie MDMA-induced core (brain) hyperthermia in rats treated with MDMA under conditions that simulate drug use in humans.[24] Additionally, the combined α_1- and $\beta_{1\text{-}3}$-adrenergic receptor antagonist carvedilol effectively prevented temperature elevations in healthy subjects,[30,63] consistent with preclinical data.[62] This latter finding is particularly interesting because carvedilol is expected to block both MDMA-induced heat generation by mitochondrial uncoupling[18,64], by blocking β_3-adrenergic receptor- and α_1-adrenergic receptor-mediated vasoconstriction. In fact, carvedilol more effectively reduced the hyperthermic response to MDMA compared with α_1 receptor blockade in both animals[62] and humans.[30,31] Similarly, both the α_1-antagonist prazosin and the β_3-antagonists cyanopindolol only partly attenuated body temperature increases in skeletal muscle (cyanopindolol) or core (prazosin) after MDMA and the combination of the 2 completely blocked MDMA-induced hyperthermia (muscle and core).[65] Additionally, carvedilol reduced MDMA-induced increases in both heart rate and blood pressure in healthy human subjects.[30] Thus, carvedilol reduced several signs of sympathetic activation by MDMA including the cardiostimulant and the termogenic effects.

Dumont and colleagues studied the interactive effects of MDMA and tetrahydrocannabinol in healthy subjects. Tetrahydrocannabinol delayed the MDMA-induced increase in temperature, and the duration of the temperature elevation was prolonged, although the mean temperature increase was comparable to administration of MDMA alone.[40] The results indicate that tetrahydrocannabinol is unlikely to protect against MDMA-induced hyperthermia, although cannabinoids decrease body temperature in rats[66] and in contrast to previous hypotheses.[67]

Several experimental human studies also tested the effects of other psychostimulants with a slightly different pharmacology than MDMA on body temperature. Various psychostimulants, including MDMA, enhance noradrenergic neurotransmission, but their relative dopaminergic vs. serotonergic activity varies. For example, Tancer and Johanson assessed the effects of MDMA, D-amphetamine (mostly a dopamine and norepinephrine releaser), and metachlorophenylpiperazine (a serotonin inhibitor and releaser) on oral temperature in the same study.[36] Both amphetamine and metachlorophenylpiperazine increased body temperature similarly to MDMA.[36] The data suggest that psychotropics with either serotonergic (metachlorophenylpiperazine) or dopaminergic (amphetamine) properties increase body temperature. Similar to amphetamine, methylphenidate (a selective dopamine and norepinephrine transporter inhibitor with no serotonergic properties) also acutely increased body temperature in humans when given at a dose of 40 mg[47] or 60 mg.[33] Cocaine enhanced the progressive increase in core body temperature during passive heating.[68] The elevation in body temperature was attributable to impaired heat dissipation, including reduced sweating and cutaneous vasodilation.[68] Similar to MDMA, cocaine has serotonergic and noradrenergic properties.[52] Importantly, all of these recreational drugs, whether serotonergic (MDMA or metachlorophenylpiperazine) or dopaminergic (amphetamine or methylphenidate) or both (cocaine), also enhance norepinephrine transmission. Therefore, norepinephrine likely contributes to the thermogenic effects of these substances, consistent with the reducing effects of carvedilol on the temperature response to MDMA.

A series of novel psychoactive substances with structural similarity to MDMA have been implicated in hyperpyrexia. In particular, para-methoxyamphetamine and para-methoxymethamphetamine, which are occasionally sold as Ecstasy,[69] have been associated with

an especially high risk of hyperthermia.[69-72] Para-methoxyamphetamine and para-methoxymethamphetamine predominantly act on the serotonin system,[73] consistent with the role of serotonin in hyperthermia. Four-Methylthioamphetamine is another serotonergic compound[73] that has been linked to hyperthermia.[74] Other novel substances, such as 3,4-methylendioxypyrovalerene, which potently inhibits dopamine and norepinephrine uptake[52] and induces marked and prolonged agitation, has also been reported to induce hyperthermia.[75] Notably, hyperthermia has also been described with the dopamine and norepinephrine transporter inhibitor methylphenidate.[76]

Altogether, the mechanistic studies in humans provide support for the conclusion that MDMA mainly increases body temperature via the release of norepinephrine, which then increases metabolic heat generation and impairs heat dissipation via vasoconstriction. Additionally, the release of serotonin may also contribute to the thermogenic effects of MDMA in humans.

Management of Ecstasy-induced hyperthermia in patients

The various treatments for hyperpyrexia induced by MDMA or other psychostimulants have not been systematically evaluated in the emergency room setting. Hyperthermic complications are relatively rare, and clinical trials are unlikely to be conducted. However, as described above, several placebo-controlled mechanistic experimental studies have been conducted with healthy subjects, which can inform us on the pharmacological mechanism of MDMA-induced hyperthermia in humans and potential effects of pharmacological treatments. As a limitation, the experimental studies used doses of pure MDMA in the range of 50-150 mg while recreational users of ecstasy pills may ingest MDMA at lager doses or repeated doses. For example, in an naturalistic observational study among 49 partying people, 34 used doses of MDMA of 0-150 mg while 15 took cumulative doses of 150-280 mg.[77] An analysis of ecstasy pills from 5,786 recreational users found an average MDMA content in the ecstasy pills of 82.5 ± 35.2 mg.[69] Approximately 20% of users presenting to emergency departments with medical problems report having ingested 2 or more pills.[5,9] Additionally, MDMA is often used in combination with other substances[5,9] many of which may also affect body temperature.

Paramedics and emergency department personnel must recognize hyperthermia in subjects with acute substance-induced disorders. It is not uncommon that agitated subjects die of hyperpyrexia because body temperature was not measured, and elevations in body temperature went unrecognized. Agitated subjects should not be restrained. Sedation with benzodiazepines and intravenous fluid replacement are the most important acute supportive care measures in patients with substance-induced sympathomimetic toxidromes and/or agitation.[3,5,78] The management of hyperpyrexia includes cooling (fanning, water, ice packs, ice bath, cooling blankets) and mechanical ventilation.[10] Dantrolene, which acts at skeletal muscles to inhibit the release of calcium, has also been used.[6,10,79] However, dantrolene does not inhibit the thermogenic effects of MDMA,[80] and the drug does not modulate the mechanism of MDMA-induced hyperthermia discussed above. Nevertheless, case reports support its benefits in cases of extreme hyperpyrexia (>42°C).[6]

Antipsychotics, such as haloperidol, should not be used as a routine treatment of drug-induced agitation or only with great care and after treatment with benzodiazepines. Antipsychotics are associated with hyperthermia in the context of neuroleptic malignant syndrome and some (e.g., phenothiazines) also act as anticholinergics and potentially reduce sweating and thus heat dissipation by evaporation. Additionally, haloperidol has been shown to enhance acute anxiety and the negative mood effects of MDMA[46] and psilocybin.[81] Thus, the use of this antipsychotic medication may actually enhance adverse drug effects, at least in certain situations. The atypical antipychotic clozapine has been shown to reverse hyperthermia and cutaneous vasoconstriction induced by MDMA in rats or rabbits[82] but human data to support its clinical use are lacking. Hyperthermia is often associated with other signs of sympathomimetic stimulation, including agitation, tachycardia, and hypertension. Benzodiazepines are also beneficial in the treatment of these symptoms. However, additional hypertensive treatment with vasodilators, such as nitrates, may be needed. Adrenergic receptor antagonists can be useful. However, β blockade without α blockade should be avoided in drug-induced sympathomimetic toxicity because of the unopposed α-adrenergic receptor stimulation that enhances vasoconstriction[83] and results in further increases in blood pressure[60,84] and possibly body temperature. In contrast, α blockade reduced the blood pressure response to MDMA and elevations in body temperature,[31] and combined α/β blockade reduced MDMA-induced increases in blood pressure, heart rate, and body temperature[30,63] and blood pressure response to cocaine.[85-87] Accordingly, α blockers (e.g., phentolamine) or α/β blockers (e.g., carvedilol) could be useful in situations of extreme sympathomimetic stimulation, although real-world clinical data are mostly lacking. Phentolamine was successfully used to treat a hypertensive emergency caused by amphetamine overdose.[88]

Besides from hyperthermia, brain edema is another severe complication of MDMA use. MDMA induces a syndrome of inappropriate secretion of antidiuretic hormone[89-91] which may lead to symptomatic hyponatremia including brain edema in particular in women.[92-94] Thus, excessive water consumption but also fluid treatment can be potentially dangerous in the prevention or the treatment of MDMA-induced hyperthermia. Additionally, animal studies indicate that the blood-brain barrier is disrupted during MDMA-induced hyperthermia also leading to brain edema.[95]

Conclusion

MDMA increases body temperature in humans. However, hyperpyrexia (>40°C) is not seen in controlled laboratory settings. The MDMA-induced elevations in body temperature in humans appear to depend on the MDMA-induced release of norepinephrine and involve cutaneous vasoconstriction and likely also enhanced metabolic heat generation. The role of serotonin needs further clarification. The management of overdose cases

includes sedation treatment with benzodiazepines, intravenous fluid replacement, and additional cooling and mechanical ventilation in severe cases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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