

## Induction of Malignant Hyperthermia in Susceptible Swine by 3,4-Methylenedioxymethamphetamine ("Ecstasy")

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**Background:** 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") can mediate acute toxic effects such as muscle rigidity, metabolic acidosis, and hyperthermia. Because of close clinical similarities, an association between MDMA intoxication and malignant hyperthermia (MH) was suggested. The aim of this study was to investigate whether MDMA is a trigger of MH in susceptible swine.

**Methods:** MH-nontriggering general anesthesia was performed in six MH-susceptible (MHS) and six MH-normal swine. The animals were exposed to MDMA in cumulative doses of 0.5, 1, 2, 4, 8, and 12 mg/kg. The clinical occurrence of MH was defined by achievement of two of three conditions: central venous  $P_{CO_2} \geq 75$  mmHg, central venous pH  $\leq 7.20$ , and increase of body core temperature  $\geq 2.0^\circ\text{C}$ . Once MH occurred, a standardized therapy with dantrolene, sodium bicarbonate, and hyperventilation with 100% oxygen was initialized.

**Results:** Administration of 8 mg/kg MDMA triggered MH in all MHS swine. The MH-normal swine also developed clinical signs of hypermetabolism, but even after administration of 12 mg/kg MDMA, changes were moderate compared with the MHS swine. Dantrolene therapy of MDMA-induced MH crisis in the MHS swine partially counteracted the clinical signs of MH immediately.

**Conclusions:** MDMA induces MH in genetically susceptible swine in relevant doses. Therefore, MHS patients should avoid use of MDMA or related drugs. Patients with a personal or family history of MDMA-induced hyperthermia should be tested for a diagnosis of MH susceptibility. Dantrolene is effective in therapy of MDMA-induced porcine MH.

CONSUMER behavior with illicit drugs has changed during the past decade, with a clear preference for "designer drugs" or "club drugs" like 3,4-methylenedioxymethamphetamine (MDMA),  $\gamma$ -hydroxybutyrate, and ketamine.<sup>1</sup> The estimated prevalence of MDMA use in young adults varied between 2.5 and 8%.<sup>2</sup> Despite an anecdotal reputation for safety, MDMA has serious toxic effects. A major feature of patients presenting with acute MDMA toxicity is hyperthermia, often associated with other severe clinical problems such as rhabdomyolysis, renal failure after myo-

globinuria, liver damage, and/or disseminated intravascular coagulopathy.<sup>3</sup> More than 30 deaths related to hypermetabolism after MDMA ingestion have been reported up to the present.<sup>3,4</sup>

The pathophysiology of MDMA-induced hyperthermia is not yet clarified. MDMA results in relatively nonselective effects on postsynaptic serotonin (5-HT) receptors and in inhibition of 5-HT reuptake. However, MDMA also elicits large increases of the synaptic dopamine concentration. Dopamine by itself or the interaction between 5-HT and dopamine may cause the hyperthermic effect of MDMA.<sup>5-7</sup>

Emergency management of MDMA-induced hyperthermia consists primarily of supportive therapy. Basic treatment of hyperthermia includes primarily aggressive body core cooling. Other proposed therapy options are induction of general anesthesia with paralysis to reduce muscular thermogenesis.<sup>8</sup> The use of dantrolene, a peripherally acting muscle relaxant without central effects, in the therapy of MDMA-induced hyperthermia is controversial.<sup>9</sup> However, successful treatment with dantrolene has been reported.<sup>10-15</sup>

Malignant hyperthermia (MH) is an autosomal inherited, potentially lethal myopathy with a heterogeneous pathogenesis.<sup>16,17</sup> It is widely accepted that susceptibility to MH is caused by abnormal  $\text{Ca}^{2+}$  metabolism within the skeletal muscle fiber. The site of the defect in MH appears to be in the  $\text{Ca}^{2+}$  release mechanism of the sarcoplasmic reticulum in skeletal muscles, namely, in the complex of the dihydropyridine and ryanodine receptors.<sup>18,19</sup> However, alterations in second messenger systems, e.g., the 5-HT system, have been found to be associated with MH.<sup>20</sup> 5-HT receptor agonists and antagonists mediated specific effects in skeletal muscles of MH-susceptible (MHS) patients compared with MH-normal (MHN) patients *in vitro*, indicating a direct mechanism of action in skeletal muscles.<sup>21,22</sup> MH is usually triggered by volatile anesthetics and depolarizing muscle relaxants and is characterized by hypermetabolism presenting with muscle rigidity and shivering, rhabdomyolysis, hypercarboxemia, hypoxemia, acidosis, tachycardia, and increased body temperature.<sup>16,23</sup>

As a result of the highly comparable clinical symptoms of MH and MDMA intoxication, a similar pathogenesis was suggested. Therefore, one aim of this study was to investigate whether MDMA is a trigger of MH in susceptible swine. A second aim of the study was to determine the efficacy of the MH-specific antidote dantrolene as a promising option in the treatment of MDMA-induced MH syndrome.

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## Materials and Methods

After approval by the Animal Research Committee of the University Hospital Hamburg-Eppendorf, six MHN (male and female German Landrace pigs weighing 19–21 kg, 2–3 months old) and six MHS swine (male and female Pietrain pigs weighing 14–22 kg, 2–3 months old) from a special breeding farm (Research Station Thalhausen, Technical University Munich, Germany) were investigated. Before the study, in all animals, genomic DNA was isolated from blood preserved in EDTA to check the presence of the Arg615-Cys point mutation on chromosome 6 indicating MH susceptibility.<sup>24</sup>

Swine were fasted overnight, with free access to water. General anesthesia was induced by administration of ketamine 10 mg/kg intramuscularly (Ketavet®, Pharmacia and Upjohn, Erlangen, Germany). After installation of a venous line into an ear vein, general anesthesia was deepened with propofol 10 mg/kg (Disoprivan® 2%, Astra-Zeneca, Plankstadt, Germany) and fentanyl 10 µg/kg (Fentanyl-Janssen®, Janssen-Cilag, Neuss, Germany) intravenously. After tracheotomy and intubation, the lungs were mechanically ventilated with an air/oxygen mixture ( $F_{IO_2}$  0.4). Anesthesia was maintained with propofol 10 mg · kg<sup>-1</sup> · h<sup>-1</sup> and fentanyl 50 µg · kg<sup>-1</sup> · h<sup>-1</sup>. Neuromuscular blocking drugs were not administered. A multilumen central venous line was installed into the right internal jugular vein. One lumen was used for withdrawal of blood samples and measurement of central venous pressure, the second for administration of MDMA and fluid infusion (5–10 ml · kg<sup>-1</sup> · h<sup>-1</sup> of lactated Ringer's solution), and the third for administration of anesthetics. Two arterial cannulas were inserted in both femoral arteries. One cannula was used for withdrawal of blood samples, the other for continuous measurement of arterial pressure and body core temperature (PiCCO®, Pulsion Medical Systems, Munich, Germany). Forced-air warming maintained normothermia; body temperature was measured continuously rectally and intravasally with the PiCCO system.

A blood gas analyzer (ABL625, Radiometer, Copenhagen, Denmark) was used for monitoring arterial and venous oxygen saturation,  $P_{O_2}$ ,  $P_{CO_2}$ , pH, potassium, and lactate. Mechanical ventilation was attuned to maintain venous  $P_{CO_2}$  at  $44 \pm 2$  mmHg, and the body core temperature was adjusted to  $38.5 \pm 0.3^\circ\text{C}$  until the experiment was started. Once a steady state was achieved for at least 30 min, baseline values were recorded for all variables.

MDMA (Sigma-Aldrich, Taufkirchen, Germany) dissolved in isotonic saline solution was administered in a dose of 0.5 mg/kg intravenously. Subsequently, MDMA was given every 20 min to reach cumulative doses of 1, 2, 4, 8, and 12 mg/kg. The clinical occurrence of MH was defined by achievement of two of three conditions: central venous  $P_{CO_2} \geq 75$  mmHg, central venous pH  $\leq 7.20$ , and an increase in body core temperature  $\geq 2.0^\circ\text{C}$  mea-

sured intravasally with the PiCCO system. In case of an MH crisis, further administration of MDMA was stopped and a standardized therapy was started. Treatment consisted of dantrolene 5 mg/kg (Dantrolen®, Procter and Gamble Pharmaceuticals, Weiterstadt, Germany) and sodium bicarbonate 1 mEq/kg intravenously; minute ventilation was doubled and performed with 100% oxygen.

During the experiments, hemodynamic variables (heart rate, mean arterial pressure, central venous pressure, cardiac output), end-tidal carbon dioxide concentration ( $ET_{CO_2}$ ), rectal and intravasal body temperature ( $^\circ\text{C}$ ), blood gas concentrations ( $SaO_2$ ,  $P_{CO_2}$ , pH), and lactate levels were measured every 5 min. Every 20 min, blood probes were taken for gas chromatographic measurement of MDMA and 3,4-methylenedioxyamphetamine (MDA) blood concentrations. After all experiments were completed, the pigs were killed by use of magnesium chloride solution (10%).

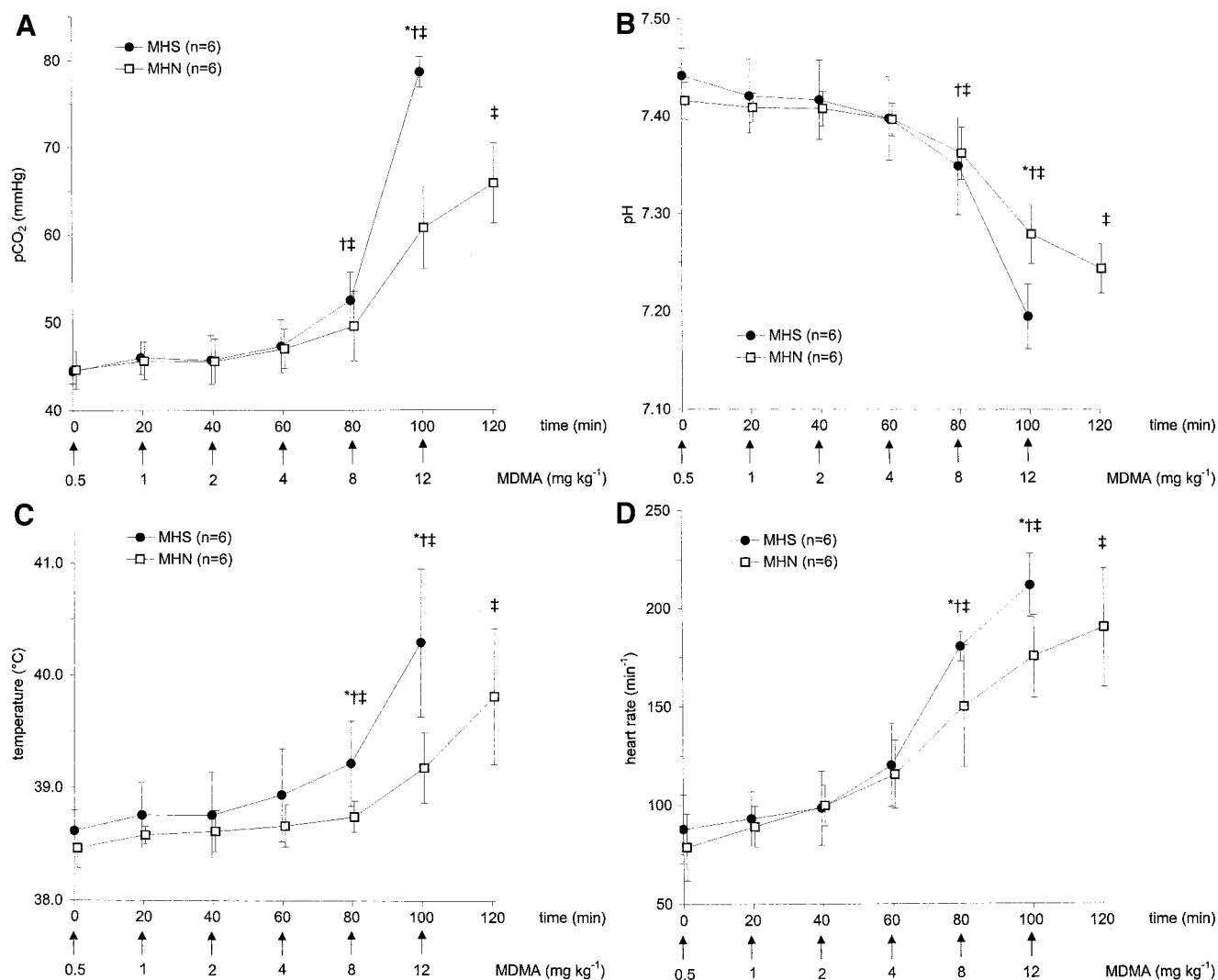
Statistical evaluation was performed by use of a computer-based program (StatView 4.57, Abacus Concepts, Berkeley, CA). All data are presented as mean  $\pm$  SD. Intergroup variations were calculated with the Mann-Whitney U test, and intragroup differences with ANOVA for repeated measures. If appropriate, subsequent comparisons were performed using Scheffé's *post hoc* method. Results were considered significant at a value of  $P < 0.05$ .

## Results

MDMA in doses up to 4 mg/kg induced only moderate changes in all measured parameters in MHS and MHN swine. However, administration of 8 mg/kg MDMA induced MH in all MHS swine according to the defined criteria. Furthermore, the MHS swine developed marked generalized muscle shivering and rigidity. Therefore, 8 mg/kg MDMA was the maximum dose given to MHS swine. The MHN swine developed clinical signs of hypermetabolism as well. However, even after administration of 12 mg/kg MDMA, changes in the MHN swine were moderate and did not reach the defined MH criteria.

After administration of 8 mg/kg MDMA, the  $P_{CO_2}$  increased in the MHS and MHN swine (fig. 1A). The increase in  $P_{CO_2}$  was more distinct in the MHS swine: all MHS swine developed  $P_{CO_2}$  values  $\geq 75$  mmHg and fulfilled one criterion of a MH crisis. The increase of  $P_{CO_2}$  in the MHN swine was less; therefore, a further dose to achieve 12 mg/kg MDMA was given. This dose caused a maximum  $P_{CO_2}$  of  $66.0 \pm 3.8$  mmHg in the MHN swine, but no swine exhibited  $P_{CO_2}$  values  $\geq 75$  mmHg.

The venous pH showed a slight decrease in both groups after administration of 4 mg/kg MDMA. After administration of 8 mg/kg MDMA, a further decrease of pH in both groups was observed (fig. 1B). The decrease



**Fig. 1.** Central venous  $P_{CO_2}$  (A), central venous pH (B), body temperature (C), and heart rate (D) after cumulative intravenous administration of 3,4-methylenedioxymethamphetamine (MDMA) in malignant hyperthermia-susceptible (MHS) and malignant hyperthermia-normal (MHN) swine. MDMA 12 mg/kg was given only to MHN swine. Values are mean  $\pm$  SD. \* $P < 0.05$  MHS versus MHN, † $P < 0.05$  MHS versus 0 mg/kg MDMA, ‡ $P < 0.05$  MHN versus 0 mg/kg MDMA.

was more intense in the MHS than the MHN swine. Four of six MHS swine developed a pH value  $\leq 7.20$ . In the MHN swine, administration of 12 mg/kg MDMA led to a pH of  $7.24 \pm 0.02$ , but minimum pH remained  $>7.20$  in all MHN swine.

MDMA induced a dose-dependent increase in body temperature in MHS and MHN swine (fig. 1C). However, in contrast to MHN, all MHS swine developed an increase in body temperature  $\geq 2^\circ\text{C}$  after administration of 8 mg/kg MDMA. Regarding the defined criteria, MDMA induced MH in all MHS swine but no MHN swine.

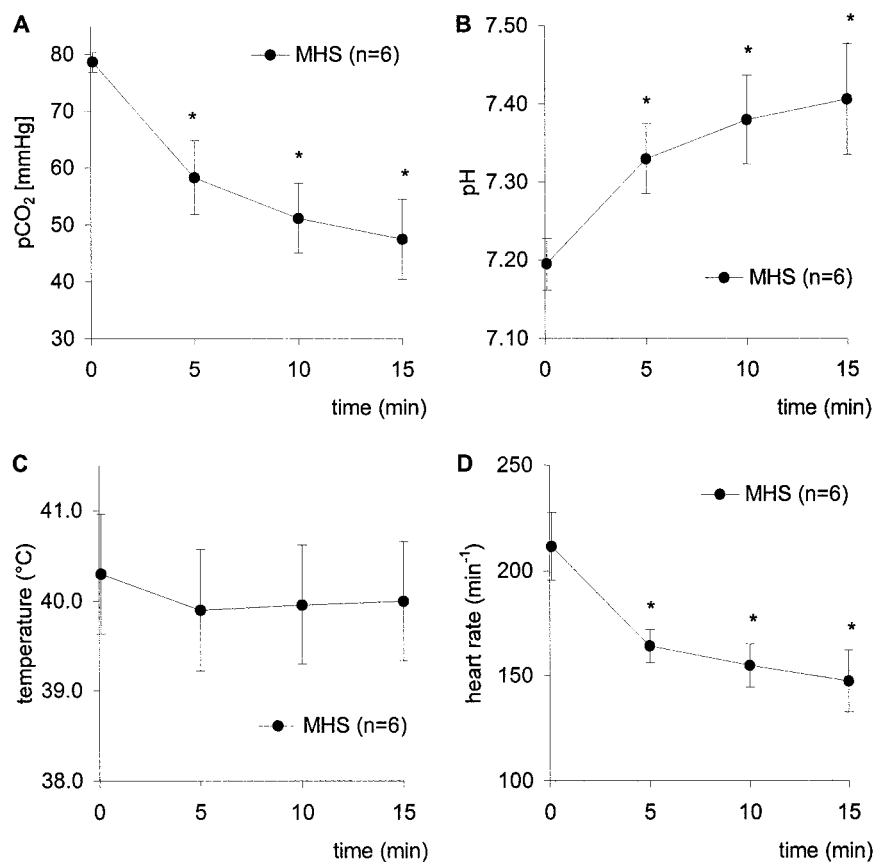
Administration of MDMA induced tachycardia in all swine, more obviously in the MHS group (fig. 1D). After 8 mg/kg MDMA, heart rate was increased to  $219 \pm 18$  beats/min in the MHS swine. Maximum heart rate in the MHN swine after 12 mg/kg MDMA was  $182 \pm 23$  beats/min. The starting mean arterial pressure of  $62 \pm 10$  mmHg in the MHS and  $58 \pm 5$  mmHg in the MHN swine increased after

administration of 0.5 mg/kg MDMA. After administration of 8 mg/kg MDMA, the mean arterial pressure was increased to  $79 \pm 12$  mmHg in the MHS and  $87 \pm 11$  mmHg in the MHN group.

There were no differences in blood concentrations of MDMA and the active metabolite MDA between MHS and MHN swine. Blood concentrations of  $913 \pm 133$  ng/ml MDMA and  $252 \pm 65$  ng/ml MDA were measured after administration of 8 mg/kg MDMA in all swine. When 12 mg/kg MDMA was given to the MHN swine, blood concentrations of  $1336 \pm 109$  ng/ml MDMA and  $450 \pm 83$  ng/ml MDA were measured.

Standardized therapy of MDMA-induced MH crisis in the MHS swine performed with dantrolene, sodium bicarbonate, and hyperventilation with an  $F_{IO_2}$  of 1.0 partially cleared the clinical signs of MH immediately (fig. 2). The venous  $P_{CO_2}$  of  $78.7 \pm 1.8$  mmHg before therapy decreased to  $47.4 \pm 7.0$  mmHg. The venous pH of

Fig. 2. Course of central venous  $\text{PCO}_2$  (A), central venous pH (B), body temperature (C), and heart rate (D) after therapy with 5 mg/kg dantrolene and sodium bicarbonate 1 mEq/kg, and hyperventilation with pure oxygen, in malignant hyperthermia-susceptible (MHS) swine with malignant hyperthermia (MH) induced by 8 mg/kg 3,4-methylenedioxymethamphetamine (MDMA). Values are mean  $\pm$  SD. \* $P < 0.05$  MHS after therapy versus MHS before therapy.



$7.19 \pm 0.03$  increased to  $7.41 \pm 0.07$ . The body temperature of  $40.3 \pm 0.7^\circ\text{C}$  remained unchanged 15 min after therapy induction. The heart rate also stabilized after therapy. The heart rate decreased from  $212 \pm 16$  to  $147 \pm 15$  beats/min. The mean arterial pressure remained stable at  $82 \pm 17$  mmHg before and  $96 \pm 14$  mmHg 15 min after therapy.

## Discussion

The results of this study show for the first time that MDMA induces MH in susceptible swine. MH susceptibility in swine is associated with the presence of the Arg615-Cys point mutation at a homozygous level. In contrast, MH in humans is a genetically heterogeneous disease, most often with a heterozygous carrier status.<sup>16,17</sup> Despite the genetic differences between MH in swine and humans, we suspect that MDMA triggered a clinical MH syndrome in some case reports of MDMA-induced hypermetabolic syndrome. Therefore, patients with MDMA-induced hypermetabolic syndrome and their relatives are possibly at high risk of MH after anesthesia with MH trigger substances or repeated MDMA abuse. These persons should undergo standardized MH diagnostics using the halothane and caffeine *in vitro* contracture test according to the established protocols of the European MH Group or the Northern American MH group.<sup>25,26</sup>

Tablets sold as "ecstasy" contain primarily MDMA, usu-

ally in a dose of approximately 50 to 150 mg, but also other ingredients, such as amphetamines or analogues, caffeine, or theophylline.<sup>3,27,28</sup> The adverse reactions to MDMA are not clearly dose-dependent, and occurrence of toxic side effects is not predictable by the number of tablets ingested. In patients with fatal hypermetabolic reaction, the number of tablets ingested varied between 1 and 10 tablets, although the exact dose was unknown in most cases.<sup>3</sup> The postmortem blood concentrations varied between  $<100$  and  $3700$  ng/ml in 22 patients whose deaths were causally related to MDMA ingestion.<sup>4</sup> Doses of 50, 75, and 125 mg MDMA given to healthy volunteers resulted in peak blood concentrations of 106, 131, and 236 ng/ml, respectively.<sup>29</sup> For this experiment, we calculated the administration of MDMA in doses between 0.5 and 12 mg/kg to achieve comparable blood concentrations. These doses induced MH in susceptible swine. Pharmacokinetic data for intravenous application of MDMA in swine are not available. However, plasma elimination half-time of MDMA after oral administration was measured between 7.7 and 8.6 h in men; therefore, elimination of MDMA during an experimental time of 120 min could be assumed to be moderate.<sup>29</sup> The MDMA dose of 8 mg/kg was comparable to ingestion of 4 to 8 tablets of "ecstasy" in adults, depending on the purity of the tablets. Blood concentration after this dose was  $913 \pm 133$  ng/ml MDMA. The number of tablets and the

blood concentration are comparable to data in patients after MDMA recreational abuse in a nonmedical setting.

MDMA was thought to take effect by activation of 5-HT and/or dopamine receptors.<sup>5-7</sup> However, 5-HT<sub>2</sub> receptor agonists like 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane or lysergic acid diethylamide have been found to be triggers of MH in susceptible swine as well.<sup>30</sup> Further experiments have demonstrated that symptoms of 5-HT<sub>2</sub>-induced MH were reduced or counteracted by administration of the 5-HT<sub>2</sub> receptor antagonists ketanserin or ritanserin, indicating a primary involvement of 5-HT<sub>2</sub> receptors in the pathophysiology of MH.<sup>30</sup> Furthermore, 5-HT exerts direct *in vitro* effects at 5-HT receptors in porcine and human skeletal muscle. *In vitro* investigations with 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane demonstrated distinct differences between human MHS and MHN skeletal muscle preparations as well.<sup>21</sup> These results indicated a direct alteration in 5-HT regulation of MHS skeletal muscles. Therefore, it is tempting to speculate that MDMA might have specific effects in skeletal muscles, especially in MHS skeletal muscles leading to a clinical MH syndrome.

MDMA induced only minor hypermetabolism in MHN swine in this investigation. It could be assumed that MHN patients can develop MDMA-induced hyperthermia as well. The hyperthermic reaction to MDMA is a multifactorial event. Environmental temperature, physical activity, dehydration, or mixed intoxications are supposed cofactors of MDMA-induced hyperthermia.<sup>31</sup>

We have shown that dantrolene is effective in therapy of MDMA-induced porcine MH. Therefore, we recommend administration of dantrolene to every patient with life-threatening MDMA-induced hyperthermia immediately. Furthermore, dantrolene might be useful to prevent further increase in body temperature as a result of hypermetabolism by blockade of muscular thermogenesis. Therefore, it is important to enable immediate access to dantrolene not only for anesthesiologists but also for all medical practitioners dealing with MDMA-intoxicated patients, *e.g.*, emergency doctors, internists, and neurologists.

In summary, MDMA induces MH in genetically susceptible swine in relevant doses. Therefore, MHS patients should in any case avoid use of MDMA or related drugs. Dantrolene is effective in therapy of MDMA-induced porcine MH. Furthermore, immediate access to dantrolene in all emergency departments and intensive care units dealing with MDMA-intoxicated patients should be guaranteed. Patients with a personal or family history of MDMA-induced hyperthermia should be tested for a diagnosis of MH susceptibility.

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