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Research Article

# Individuals with Hyperthyroidism are More Susceptible to having a Serious Serotonin Syndrome Following MDMA (Ecstasy) Administration in Rats

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**Abstract**

In a recreational use of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"), some but not all users are stricken with a serious serotonin (5-hydroxytryptamine; 5-HT) syndrome. This raises a question as to whether there exist subpopulations that are more susceptible to MDMA intoxication. The hypothesis was tested with hyperthyroid versus euthyroid rats by measuring changes in body-core temperature ($T_{cor}$) and 5-HT in the hypothalamus. In the euthyroid rats, injection of MDMA at a recreationally relevant dose had no serious effect on $T_{cor}$. In contrast, the same dose was sufficient to evoke life-threatening hyperthermia in hyperthyroid rats. Neurochemical studies revealed that there was greater 5-HT efflux in the hyperthyroid than the euthyroid rats. These effects were blocked by pretreatment with M100907, a 5-$HT_{2A}$ receptor antagonist. In summary, our data support the hypothesis that individuals with hyperthyroidism are more susceptible to having a serious serotonin syndrome following MDMA administration.

## ABBREVIATIONS

5-HT: 5-Hydroxytryptamine; MDMA: 3,4-Methylenedioxymethamphetamine; $T_{cor}$: Body-Core Temperature; $T_3$: 3,3′,5-triiodo-L-thyronine

## INTRODUCTION

High hyperthermia is a critical sign of MDMA intoxication, indicating that the syndrome is serious and likely life-threatening [1,2]. While there is no doubt that a high dose of MDMA is toxic, many users perceive recreationally relevant doses as a "safe" drug at parties [3,4]. There have been numerous reports of fatalities associated with recreational uses of MDMA [5-7]. Of those, Martin and colleagues (2007) reported that the recreational use of MDMA caused hyperthermia and then death to a 24-year-old woman who was found to have hyperthyroidism in postmortem examination [7].

Hyperthyroidism is known as a common endocrine disorder, affecting approximately 0.1% of the worldwide population [8,9]. Users with hyperthyroidism have an excess of thyroid hormones (e.g., triiodothyronine, $T_3$; thyroxine, $T_4$) that exert effects on neuronal activity through regulating gene expression, likely impairing mental function [9,10]. In rodents, hyperthyroidism is found to cause a robust presynaptic modulation at neurotransmissions, including the serotonergic system [11]. In addition, some 5-HT receptors, particularly postsynaptic 5-$HT_{2A}$Rs are likely to be up-regulated in the hyperthyroid brain, resulting in overexpression [12,13]. However, 5-$HT_{2A}$Rs are a major mediator of 5-HT action involved in MDMA-elicited autonomic dysfunction [14]. Less is known about whether these modulations of serotonergic activity in the hyperthyroid brain have an impact on serotonin syndrome caused by MDMA.

In this study, we aimed to test the hypothesis that individuals with hyperthyroidism are more susceptible to having a serious serotonin syndrome in response to MDMA administration. This hypothesis was examined in rats by measuring changes in body-core temperature ($T_{cor}$) and 5-HT in the brain. The MDMA dose examined in this study was 2 mg/kg, corresponding to recreational doses used in human [15]. For comparison, 15 mg/kg as a high dose was also examined.

## MATERIALS AND METHODS

### Animals

Adult male Sprague-Dawley rats weighing 250 - 275 g were purchased from Charles River Laboratories (Raleigh, NC, USA) and housed in pairs under a 12-h light/dark cycle (lights on 7:00 am) in a temperature- and humidity-controlled facility. Food and water were available *ad libitum* at all times. Animal use procedures were in strict accordance with the NIH Guide

for the Care and Use of Laboratory Animals and approved by the Florida Atlantic University and Ross University Veterinary School Institutional Animal Care and Use Committees (IACUCs). All efforts were made to reduce the number of animals used and their suffering.

### Drugs and chemicals

3,3′,5-Triiodo-L-thyronine ($T_3$) was purchased from EMD Chemicals (San Diego, CA, USA). MDMA and M100907 were generously obtained from the National Institute on Drug Abuse Supply Program (RTI International, Research Triangle Park, NC, USA). $T_3$ was first dissolved in 0.1 N NaOH as a high concentration and then further diluted with 0.9% NaCl to pH ~7.4. MDMA and M100907 were directly dissolved in 0.9% NaCl. Injection volume was made at 1 ml/kg of body weight.

### Induction of hyperthyroidism

Procedures for inducing hyperthyroid rats were based on previous studies with a minor modification [16,17]. Briefly, animals received intraperitoneal injection of 75 μg/100 g of $T_3$ once daily for consecutive 2 weeks. Control groups received only vehicle solution on the same schedule. Note that vehicle and $T_3$ pretreatments were carried out between 8:00 - 8:30 am, and experiments were performed on day 14, 4-h after the last treatment.

### Body-core temperature ($T_{cor}$)

Body temperature measurements were carried out in a temperature-controlled chamber consisting of temperature controller, heater and refrigerator as described in literature [18-20]. Rectal $T_{cor}$ was continuously measured at a 5-min interval with a flexible, 4.6-cm thermoprobe connected to a digital thermometer (Traceable®, Fisher Science; Pittsburgh, PA, *USA*). Note that the thermoprobe was secured in place throughout experiments while animals were freely behaving and thus no physical restraints interfered with the $T_{cor}$ results. Recordings included four baseline samples and 18 post-MDMA measurements. Changes in $T_{cor}$ were categorized into high hyperthermia, low hyperthermia, normothermia and hypothermia. High hyperthermia is defined as an elevation in $T_{cor}$ over +2.1°C above its baseline while hypothermia as a reduction at least -0.5°C below its baseline. Changes between -0.4 and +0.4°C are considered as normothermia, and between +0.5 and +2.0C as low hyperthermia.

### 5-HT efflux assay

*In vivo* microdialysis was used to measure 5-HT efflux in the brain. Guide cannulas were surgically implanted. Briefly, rats anesthetized by a combination of xylazine (4 mg/kg i. p.) and ketamine (80 mg/kg i. p.) were mounted in a Kopf stereotaxic frame in a flat skull position. Guide cannulas were implanted, targeting toward the hypothalamus, mainly the preoptic/anterior area (POA; AP - 1.1 mm relative to the bregma, ML 0.9 mm relative to the midline, DV -9.5 mm relative to the skull surface). After surgery, rats were allowed to recover for one week prior to experiments.

One day before microdialysis, rats were briefly anesthetized with isoflurane for a probe insertion. I-shaped microdialysis probes (molecular weight cut-off 18 kD and exchange surface 2.0 mm in length) were inserted through the guide cannulas targeting at the hypothalamus and then secured in place with the dental cement. The probe inlets were attached to a perfusion line from Raturn system (Bioanalytical System Inc., W. Lafayett, IN), and infused with the artificial cerebrospinal fluid (aCSF; containing 140 mM NaCl, 3 mM KCl, 1.5 mM $CaCl_2$, 1 mM $MgCl_2$, 0.25 mM $NaH_2PO_4$, and 1.0 mM $Na_2HPO_4$; pH: 7.4) at a flow rate of 1 μl/min. On the following day, four dialysate samples were collected to obtain basal values before administration of drugs, followed by six drug-response samples at 15-min intervals.

A reverse-phase column (150 mm×1 mm i. d., packed with a TSK gel ODS-80 TM, 5 μm particle size) was used for 5-HT separation, and its concentration was determined by HPLC-electrochemical detection (HTEC-500; EICOM, Japan). The composition of mobile phase was 0.1 M phosphate buffer (pH 6.0) consisting of 1% methanol, 500 mg/L sodium-1-octanesulfonate, and 50 mg/L ethylene diamine-tetracetic acid. The flow rate was 500 μl/min. The potential set on the graphite electrode was +450 mV (relative to an Ag/AgCl reference electrode).

Upon completion of an experiment, the rats were deeply anesthetized with pentobarbital (100 mg/kg, i.p.) for verifying probe location. After infusing the probe with a 2% fast green dye for 10 min, the animals were decapitated and brains were removed, frozen in -80°C, and then sliced freehand with a razor blade. The probe location was visually inspected by comparison to the rat brain atlas [21]. Data were excluded from analysis when probes were located outside the target boundary.

### Data analysis

To minimize individual differences, $T_{cor}$ data are expressed as a mean change relative to the respective baseline (± S.E.M), and 5-HT efflux are expressed as mean (± S.E.M) fold increases above respective baseline. Repeated measures ANOVA followed by the *post-hoc* Scheffe test were used to determine statistical difference between groups. The t-test was also used when appropriate, Statistical significance was achieved only when P-value was less than 0.05.

## RESULTS AND DISCUSSION

### Results

**Experiment 1: Effects on $T_{cor}$:** The first set of experiments aimed to evaluate effects on $T_{cor}$ of drug dose levels at the normal ambient temperature of 22°C. Compared to saline (SAL) control, MDMA at 2 mg/kg, i.p., caused a time-dependent reduction in $T_{cor}$ of euthyroid rats (Figure 1A; hypothermia, $F_{(1,9)}$ =26.85, P =0.0006). Very interestingly, the high dose (15 mg/kg, i.p.) had a 'net-zero'effect on $T_{cor}$ (normothermia, $F_{(1,9)}$ =0.053, P =0.8227).

The following set of experiments was designed to explore the interaction of environments on MDMA toxicity. Previous studies showed that $T_{cor}$ would become hyperthermia as rodents were examined at a warm ambient temperature, particularly at a high MDMA dose [18]. We found that euthyroid rats were unsusceptible to having hyperthermia even though the chamber temperature being increased to 26°C ($N$ =3, data not shown), and thus further increased to 30°C. As shown in Figure 1B, the high dose eventually

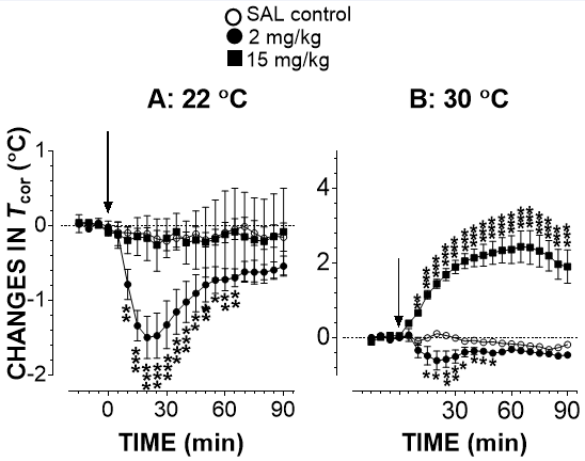


**Figure 1** Interaction of environmental temperature on MDMA-evoked changes in $T_{cor}$. All rats were euthyroid. Arrows denote the time point of vehicle or MDMA injection.
**A:** Chamber temperature was set at 22°C. Compared to SAL control ($N$ =6), the recreationally relevant dose (2 mg/kg, i.p.; $N$ =5) caused a reduction in $T_{cor}$. In contrast, the high dose (15 mg/kg, i.p.; $N$ =5) had a 'net-zero' effect on $T_{cor}$ (the increase was equal to the decrease).
**B:** Chamber temperature was set at 30°C. Compared to SAL control ($N$ =6), the recreationally relevant dose ($N$ =5) caused a smaller extent reduction in $T_{cor}$. In contrast, high hyperthermia of 2°C above baseline was elicited in euthyroid rats following the high dose ($N$ =5).
Note in this study that basal $T_{cor}$ (°C) was 38.4 ± 0.2 ($N$ =16) at 22°C and 38.7 ± 0.1 ($N$ =16) at 30°C. *$p$<0.05, **$p$<0.01, ***$p$<0.001 *vs.* the respective SAL control examined by repeated measures ANOVA followed by *post-hoc* Scheffe test.

caused an over 2.1°C increase in $T_{cor}$ (high hyperthermia; $F_{(1,9)}$ =105.511, P <0.0001) in euthyroid rats, as compared to the saline control group. In contrast, the recreationally relevant dose still caused a time-dependent reduction in $T_{cor}$ ($F_{(1,9)}$ =7.983, P =0.0199) in euthyroid rats examined at ambient temperature of 30°C. Compared to that at 22°C, the reduction was significantly attenuated ($F_{(1,8)}$ =18.957, P =0.0024).

Next, hyperthyroid rats were examined at the normal ambient temperature of 22°C. As shown in Figure 2A, the recreational relevant dose was sufficient to cause high hyperthermia ($F_{(1,10)}$ =51.166, P<0.0001). To test the involvement of 5-$HT_{2A}$Rs, 2 mg/kg M100907 was subcutaneously (s.c.) administered 15 min prior to 2 mg/kg MDMA. M100907 significantly attenuated the MDMA-induced high hyperthermia ($F_{(1,9)}$ =17.52, P =0.0024). Given that the recreationally relevant dose at 22°C already produced the life-threatening high hyperthermia, higher dose or higher ambient temperature was not investigated with hyperthyroid rats. Taken together, Figure 2B shows a remarkable difference in $T_{cor}$ between two thyroid statuses, changing from hypothermia in euthyroid rats to high hyperthermia in hyperthyroid rats following the same MDMA dosage (Figure 2B).

**Experiment 2: Effects on 5-HT efflux:** Basal 5-HT was 0.29 ± 0.04 pg/sample (N =11) of the hypothalamus from euthyroid rats and 0.45 ± 0.09 pg/sample (N =16) in hyperthyroid rats. Time-dependent changes in hypothalamic 5-HT efflux are shown in Figure 3A. Compared to the respective SAL group, 2 mg/kg MDMA caused a remarkable increase in 5-HT efflux in both euthyroid ($F_{(1,9)}$ =101.369, P<0.0001) and hyperthyroid rats ($F_{(1,9)}$ =68.79, P <0.0001), with the maximum increase at approximately ~20-fold and 40-fold , respectively. The increase in hyperthyroid rats was significantly greater than that of euthyroid rats ($F_{(1,8)}$ =7.77, P =0.0236).

In a separate set of experiments, the involvement of 5-$HT_{2A}$Rs in MDMA-induced increase in 5-HT efflux of hyperthyroid rats was examined. In this study, 2 mg/kg M100907 (s.c.) was administered 15 min before 2 mg/kg MDMA or SAL injection. As shown in Figure 3B, M100907 alone had no effect on the 5-HT efflux, but attenuated MDMA-induced increase in 5-HT efflux ($F_{(1,10)}$ =12.336, P =0.0056).

## Discussion

The main finding of this study is that MDMA at a recreationally relevant dose that usually caused only hypothermia of a mild serotonin syndrome in the euthyroid rats would elicit high hyperthermia of a serious syndrome in hyperthyroid rats. The present study experimentally demonstrated that hyperthyroid users are susceptible to MDMA toxicity at the recreationally relevant dose.

We found that MDMA injected to euthyroid rats caused hypothermia or a reduction in $T_{cor}$. Hypothermia is not life threatening. However, it does not necessarily indicate that these MDMA doses are safe or free from adverse effects. In rodents, the syndrome exhibits a wide spectrum of $T_{cor}$ abnormalities, including hypothermia indicative of a mild syndrome,

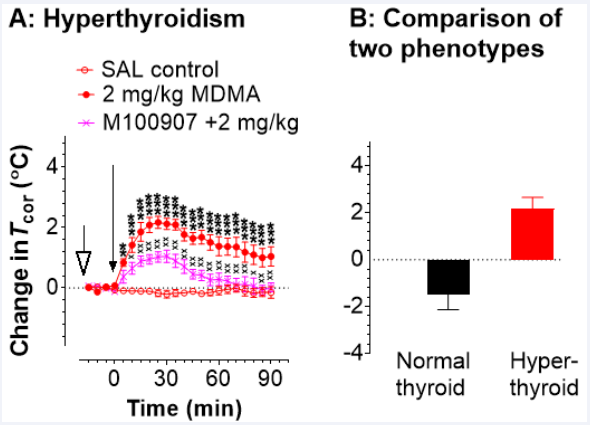


**Figure 2** Effects of thyroid status on MDMA-evoked changes in $T_{cor}$ under the chamber temperature at 22°C.
**A:** All rats were hyperthyroid. Open arrow denotes the time point of 2 mg/kg, s.c., M100907 injection and solid arrow stands for SAL or 2 mg/kg, i.p., MDMA injection. Compared to SAL control ($N$ =6), injection of the recreationally relevant MDMA dose caused high hyperthermia ($N$ =6). **$p$<0.01 and ***$p$<0.001 *vs.* the respective time point of SAL control. Pretreatment with M100907 significantly attenuated the MDMA-induced high hyperthermia. *$p$<0.05 and **$p$<0.01 *vs.* the respective time point of MDMA group examined with repeated measures ANOVA followed by *post-hoc* Scheffe test. Note that basal $T_{cor}$ (°C) was 39.0 ± 0.3 in SAL group ($N$ =6), 38.7 ±0.3 in MDMA group ($N$ =6) and 38.9 ± 0. 4 in M100907+MDMA group ($N$ =5).
**B:** Comparison of euthyroid and hyperthyroid rats in response to the recreationally relevant MDMA dose. Data are expressed as maximum changes in $T_{cor}$ (± S.E.M), replotting the response in Figure 1A and 2A.

normothermia associated with a moderate syndrome as well as high hyperthermia linked with a severe and life-threatening syndrome [22]. In humans, relatively low doses of MDMA are sufficient to increase $T_{cor}$ to a low hyperthermia [23], and therefore the mechanisms of thermoregulation may not be the same across species. In addition to $T_{cor}$, changes in 5-HT efflux could also be used to estimate the occurrence of MDMA toxicity [24,25]. Although it is an essential neurotransmitter in the brain, too much 5-HT is toxic, causing serotonin syndrome as the extracellular level exceeds multifold above baseline [19,26]. In the present study, we found that there were over a 20-fold increase in 5-HT efflux of euthyroid rats following the recreationally relevant dose. These data are consistent with previous reports [24,25] demonstrating that the recreationally relevant MDMA dose was toxic enough to cause "excessive" 5-HT efflux in the brain. Taken together, only a mild syndrome developed in euthyroid rats following the recreationally relevant dose.

While in the chamber temperature of 22°C, we found that increasing MDMA dose up to 15 mg/kg did not cause a significant change in $T_{cor}$ of euthyroid animals. The finding seems paradoxical, which cannot be interpreted simply as that such a high dose had 'no effect' on $T_{cor}$. Given that MDMA is known to cause, not only increasing 'heat-gain' showing hyperthermia [27], but simultaneously initiating 'heat-loss' resulting in hypothermia ([28], also in this study). In rodents, the heat-loss and -gain are ascribed to activation of 5-$HT_{1A}$Rs and 5-$HT_{2A}$Rs, respectively [29-33]. It has been suggested that 5-$HT_{1A}$R-mediated heat-loss or hypothermia is neuroprotective [34]. The 5-HT binding affinity is much higher for 5-$HT_{1A}$Rs than 5-$HT_{2A}$Rs [35]. Thus at the low MDMA dose that causes a small 5-HT elevation, 5-$HT_{1A}$Rs but not 5-$HT_{2A}$Rs could have reached a full activity. Nevertheless, changes in $T_{cor}$ reflect the net effect of two opposite pathways, respectively underlying neuroprotection and toxicity [36,37]. As there is a large 5-HT elevation at the high dose, both 5-$HT_{1A}$Rs and 5-$HT_{2A}$Rs would be fully activated, resulting in the 'net-zero' effect on $T_{cor}$. Under such circumstances, MDMA induced normothermia, indicative of a moderate serotonin syndrome [22]. The results are consistent with previous reports demonstrating that MDMA is not life-threatening when examined at normal and cool environmental temperatures [18,27,37]. When experiments were conducted in the warm chamber temperature (e.g., 30°C), the activity balance between two opposite pathways was shifted towards heat-gain. Neurologically, this effect may be due to increased responsivity of 5-$HT_{2A}$Rs which show high sensitivity to the environmental temperatures [33,38]. This is consistent with the *in vitro* study that 5-$HT_{2A}$R affinity to 5-HT ligand was temperature-dependently increased [35].

In contrast to euthyroids, hyperthyroid rats had high hyperthermia in response to the recreational relevant dose. In addition, other symptoms indicating deterioration of the syndrome such as head shaking behavior, salivation, and high locomotion (naked-eye observation) were also apparent, which is worthy of further characterization. Our results demonstrated experimentally that the recreationally relevant dose was potentially life-threatening to hyperthyroid users. Although little information is available on how many people taking MDMA are hyperthyroid, this specific subpopulation may be at high risk.

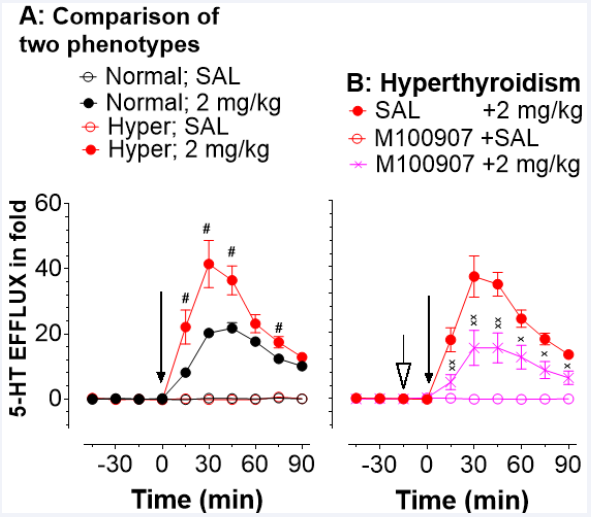


**Figure 3** Effects of thyroid status on MDMA-evoked changes in 5-HT efflux in the hypothalamus under the chamber temperature at 22°C. Basal 5-HT was 0.29 ± 0.04 pg/sample in euthyroid rats ($N$ =11) and 0.45 ± 0.09 pg/sample in hyperthyroid rats ($N$ =16).

**A:** Arrow denotes the time point of SAL or 2 mg/kg, i.p., MDMA injection. The recreationally relevant dose produced a significant increase in extracellular 5-HT in both hyperthyroid and euthyroid rats. There was a significant difference between euthyroid and hyperthyroid rats. $^{\#}p<0.05$ *vs.* The respective time point of euthyroid group.

**B:** Open arrow denotes the time point of SAL or 2 mg/kg, s.c., M100907 injection and solid arrow stands for SAL or 2 mg/kg, i.p., MDMA injection. Pretreatment with M100907 significantly attenuated the MDMA-induced increase in hypothalamic 5-HT efflux. $^{\times}p<0.05$ and $^{\times\times}p<0.01$ *vs.* the respective time point of MDMA alone.

In addition to the potentiated effect on $T_{cor}$, basal 5-HT was higher in hyperthyroid rats than the normal control rats. This is consistent with a previous study demonstrating that the 5-HT neurotransmission can be centrally upregulated by hormonal $T_3$ [11]. Furthermore, MDMA elicited more 5-HT in hyperthyroid rats, seemingly supporting there was more toxicity with this phenotype. However, accumulative evidence suggests that there is no direct proportional relationship between the 5-HT level and syndrome intensity [19,24], suggesting the causing mechanisms different from the development of a syndrome. While an excess of 5-HT efflux is known as the initial cause, the syndrome development to a mild or life-threatening intensity is likely attributed to postsynaptic circuits and 5-HT receptor components that can be functionally altered by environmental factors and hormones. In the brain, the thyroid hormones exert a broad action in regulating gene expression, resulting in up-regulation of 5-$HT_{2A}$Rs [12,13]. Under such a circumstance, the 5-$HT_{2A}$R response to 5-HT would be greater than 5-$HT_{1A}$Rs, thereby aggravating toxicity, which may interpret our findings that the low dose to the hyperthyroid rats caused high hyperthermia. Our data showed that pretreatment with M100907 partially but significantly attenuated the recreationally relevant dose-induced hyperthermia and 5-HT efflux, supporting the suggestion that 5-$HT_{2A}$R upregulation is likely one of the mechanisms responsible for the syndrome intensification in the hyperthyroid rats. The finding that M100907 could not completely block the effect of

MDMA in hyperthyroid rats suggests that, in addition to 5-$HT_{2A}$R upregulation in the brain, other mechanisms may also contribute to the syndrome intensification. Muscle contraction is known to generate heat for hyperthermia in the serotonin syndrome [39]. Thyroid hormones have been shown to facilitate the activity of uncoupling protein-3(UCP3) in the skeletal mitochondria, resulting in hyperthermia [40,41]. However, how thyroid hormones modulate 5-$HT_{2A}$Rs or UCP3 is still unknown, and thus further investigation is warranted.

## CONCLUSION

In summary, the $T_{cor}$ and 5-HT response to a recreationally relevant MDMA dose have been experimentally examined with hyperthyroid rats compared to the control group with the normal thyroid function. All results indicate that the recreationally relevant dose that was not life-threatening to the euthyroids was sufficient to cause severe intoxication manifested as high hyperthermia in hyperthyroid rats. This study has important clinical implications that MDMA users with hyperthyroidism are at high risk in MDMA abuse [7] and also other 5-HT-promoting drugs [42]. Thus, we propose that hyperthyroid animals could be used as a model organism for understanding the neurological aspects of a molecular process involving life-threatening serotonin syndrome.

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## ETHICS APPROVAL

Animal handling and tests were approved with a number of A1005 by the Florida Atlantic University and Ross University School of Veterinary Medicine Institutional Animal Care and Use Committee (IACUC).

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