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Enhanced responsivity of 5-HT_{2A} receptors at warm ambient temperatures is responsible for the augmentation of the 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced hyperthermia

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Abstract

Warm ambient temperature facilitates hyperthermia and other neurotoxic responses elicited by psychogenic drugs such as MDMA and methamphetamine. However, little is known about the neural mechanism underlying such effects. In the present study, we tested the hypothesis that a warm ambient temperature may enhance the responsivity of 5-HT_{2A} receptors in the central nervous system and thereafter cause an augmented response to 5-HT_{2A} receptor agonists. This hypothesis was tested by measuring changes in body-core temperature in response to the 5-HT_{2A} receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) administered at four different ambient temperature levels: 12 °C (cold), 22 °C (standard), 27 °C (thermoneutral zone) and 32 °C (warm). It was found that DOI only evoked a small increase in body-core temperature at the standard (22 °C) or thermoneutral ambient temperature (27 °C). In contrast, there was a large increase in body-core temperature when the experiments were conducted at the warmer ambient temperature (32 °C). Interestingly, the effect of DOI at the cold ambient temperature of 12 °C was significantly reduced. Moreover, the ambient temperature-dependent response to DOI was completely blocked by pretreatment with the 5-HT_{2A} receptor antagonist ketanserin. Taken together, these findings support the hypothesis that 5-HT_{2A} receptors may be responsible for some neurotoxic effects of psychogenic drugs in the central nervous system, the activity of which is functionally inhibited at cold but enhanced at warm ambient temperature in contrast to that at standard experimental conditions.

Keywords

ambient temperature; hyperthermia; MDMA; serotonin; 5-HT_{2A} receptor

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Previous studies have demonstrated that the neurotoxic effect of psychogenic drugs is strongly dependent on the ambient temperature (T_{amb}) at which drug administration takes place. For instance, although amphetamine and its derivatives administered at the standard T_{amb} of 22 °C caused hyperthermia, this effect was alleviated when the tests were carried out at cold T_{amb} [1,17]. Conversely, warm T_{amb} facilitated the hyperthermic effect evoked by antidepressants, opiate, methamphetamine, and 3,4-methylenedioxy methamphetamine (MDMA, “ecstasy”) [3,11,12,14]. Recently, it has been revealed that the responsivity of 5-HT_{2A} receptors in the central nervous system (CNS) may depend on T_{amb} , which could be the underlying mechanism responsible for variations in neurotoxic responses to excessive 5-HT [8].

Methodologically, functional activity of 5-HT_{2A} receptors in the CNS can be estimated in vivo by measuring changes in body-core temperature in response to 5-HT_{2A} receptor agonists [13]. Physiological investigations have indicated that 5-HT_{2A} receptors are present in the thermoregulation-related regions of the brain [9]. Under the standard T_{amb} of 22 °C, it has been shown that increases in extracellular 5-HT or administration of 5-HT_{2A} receptor agonists such as 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) [9,13] and MK212 [15] are able to elicit a hyperthermic response. This effect is blocked by selective 5-HT_{2A} receptor blockers, e.g., ketanserin, ritanserin, and MDL 100,907 [4,10,16], suggesting the involvement of 5-HT_{2A} receptors. However, the role of warm T_{amb} in 5-HT_{2A} receptor-mediated hyperthermia remains to be determined. To address this question, we designed experiments in which animal tests were conducted in temperature-controlled chambers set at a warm T_{amb} of 32 °C. For comparison, animals were also examined in cold and thermoneutral temperatures. Thus, changes in functional activity of 5-HT_{2A} receptors were thoroughly examined at four different ambient temperatures: 12 °C (cold), 22 °C (standard), 27 °C (thermoneutral zone), and 32 °C (warm). By measuring changes in body-core temperature following DOI administration, we tested the hypothesis that the functional response of 5-HT_{2A} receptors can be enhanced at the warm T_{amb} .

Male Sprague-Dawley rats (Charles River Laboratories at Raleigh, NC, USA) weighing 250 – 300 g were housed two animals per cage in a temperature-controlled facility (22 ± 1 °C) with a 12-h light/dark cycle (lights on at 7:00 a.m.). Animals had free access to food and water. All animal procedures used were in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the local animal study committees. ($\pm$) DOI-hydrochloride was purchased from Sigma-RBI (St. Louis, MO, USA) and ketanserin tartrate was obtained from Tocris Bioscience (Ellisville, MO, USA). Animals were randomly assigned into control or experimental groups. On the day of the experiment, rats were allowed to habituate in a temperature-controlled test chamber for at least 2 h before starting body-core temperature measurements. The thermostatic chamber built for this study was similar to that described previously [11].

Body-core temperature was measured in the rectum by inserting a 5 cm vinyl-jacketed thermoprobe (402 model; YSI Inc., Dayton, Ohio, USA) connected with a digital thermometer (Traceable®, Fisher Scientific, Pittsburgh, USA). All experiments were carried out between 12:00 noon and 2:30 pm. Temperature recordings at 15 min intervals consisted of two measurements before drug injection and six additional measurements after DOI administration. In the case of ketanserin or vehicle pretreatment, one more measurement was taken 15 min before DOI injection. The baseline was defined as the mean of two recordings before drug administration. Changes in body temperature relative to the baseline are expressed as mean $\pm$ SEM and analyzed by ANOVA followed by *post-hoc* Scheffé's test. The significant level was set at $p < 0.05$.

The objective of the first experiment was to estimate the dose-response relationship between body-core temperature and DOI doses at the standard T_{amb} of 22 °C. Animals were assigned to one of four groups: vehicle control, 0.05 mg/kg, 0.1 mg/kg, and 0.5 mg/kg DOI groups. The baseline measurement was 38.00 ± 0.04 °C ($n = 22$). As shown in Fig. 1a, DOI administration produced a dose-dependent increase in body-core temperature. The effect became significant 15 min after administration, and the peak increase was at 30 min. This mild hyperthermia lasted for at least 90 min. Specifically, injection of 0.05 mg/kg DOI resulted in a 0.29 °C increase (± 0.09 ; $n = 6$), while 0.1 mg/kg evoked a 0.64 °C increase (± 0.06 ; $n = 5$), and 0.5 mg/kg DOI elevated the body-core temperature by 0.79 °C (± 0.06 ; $n = 5$) above the baseline. Two-way repeated measures ANOVA revealed significant main effects of treatment ($F_{3, 18} = 32.9$, $p < 0.001$), time ($F_{7, 126} = 11.0$, $p < 0.001$), and treatment $\times$ time ($F_{21, 126} = 4.6$, $p < 0.001$). *Post-hoc* Scheffe's test showed that the effect of 0.05 mg/kg DOI was not significant by comparison to the vehicle-control group ($p = 0.697$). In contrast, the body temperature was significantly elevated in response to 0.1 and 0.5 mg/kg DOI ($p < 0.01$). To further understand the time course of DOI, a one-way ANOVA followed by *post-hoc* Scheffe's test was used to analyze each time point of action between 15 – 90 min. The analyses indicated that 0.1 mg/kg DOI increased the body-core temperature at the time points of 30, 45, and 60 min, while the significant effect of 0.5 mg/kg DOI was found at 15, 30, 45, 60, and 90 min. It was observed that DOI at 0.1 mg/kg had already produced a maximal effect, and body-core temperature was not further elevated even when the dose was increased by five times up to 0.5 mg/kg under the standard T_{amb} of 22 °C. For the above reasons, the DOI dose at 0.1 mg/kg was used in the majority of the subsequent experiments to test the activity of 5-HT_{2A} receptors as described below.

Next, ketanserin was used to test whether the effect of 0.1 mg/kg DOI on body-core temperature was mediated by 5-HT_{2A} receptors (Fig. 1b). In this set of experiments, a total of 26 animals was divided into 4 groups: veh + veh, veh + DOI, ket + DOI, and ket + veh. It was found that vehicle injection had no effect on body-core temperature in the veh + veh group, indicating that handling distress did not significantly contribute to the increased body-core temperature in this study. Additionally, injection of the 5-HT_{2A} receptor antagonist ketanserin (5 mg/kg, i.p.) alone did not significantly alter body-core temperature. This suggests that there is relatively little tonic activity of 5-HT_{2A} receptors in the regulation of body-core temperature at the standard T_{amb} of 22 °C. As shown in Fig. 1b, ketanserin blocked the DOI-evoked increase in body-core temperature under the standard T_{amb} of 22 °C. Two-way ANOVA test revealed significant effects of ketanserin on treatment ($F_{3, 18} = 15.9$, $p < 0.001$) and on treatment $\times$ time ($F_{24, 144} = 4.9$, $p < 0.001$). One-way ANOVA followed by *post-hoc* Scheffe's test at each time point after DOI treatment indicated that ketanserin could block the effect of DOI at the time points of 45, 60, 75, and 90 min ($p < 0.05$).

In the second set of experiments, the effects of DOI were reevaluated at the warm T_{amb} of 32 °C (Fig. 2). The basal level of body-core temperature was 37.87 ± 0.30 °C ($n = 22$). The statistical analysis showed that the basal level at warm T_{amb} had no significant difference from that at standard T_{amb} of 22 °C (Student $t = 1.5$, $p = 0.154$). This is not surprising since body-core temperature of homeothermic animals is constantly regulated by the autonomic nervous system in response to environmental changes. Additionally, the data suggest that the body-core temperature regulation is unimpaired at the warmer ambient temperature under our experimental condition. As expected, DOI evoked a dose-dependent increase in body-core temperature, showing that the peak increase was 0.50 ± 0.09 , 1.70 ± 0.25 , and 2.71 ± 0.17 °C in response to 0.05, 0.1, and 0.5 mg/kg DOI, respectively. Two-way ANOVA test demonstrated significant effects of treatment ($F_{3, 18} = 64.9$, $p < 0.001$), time ($F_{7, 126} = 106.6$, $p < 0.001$), and treatment $\times$ time ($F_{21, 126} = 30.6$, $p < 0.001$). By comparison with the vehicle

group, the *post-hoc* Scheffe's test showed that, except for 0.05 mg/kg ($p > 0.05$), both 0.1 and 0.5 mg/kg DOI produced a significant increase in body-core temperature ($p < 0.001$).

Most importantly, compared to that at the standard T_{amb} of 22 °C, the response of body-core temperature seemed to be markedly enhanced at the warm T_{amb} of 32 °C. This observation was supported by a statistical analysis, showing that the same dose caused a greater effect at warm T_{amb} of 32 °C: 0.05 mg/kg, $F_{1, 10} = 5.4$, $p < 0.05$; 0.1 mg/kg, $F_{1, 8} = 12.6$, $p < 0.01$; 0.5 mg/kg, $F_{1, 9} = 75.5$, $p < 0.001$. Thus, the new data from the present study demonstrated that warm T_{amb} facilitated the DOI-evoked hyperthermia. However, this raises the question of whether the increased hyperthermia is attributed to a direct effect of the warm T_{amb} since warm environment may compromise heat dissipation. We observed that the baseline of body temperature was somewhat altered. However, this change was not statistically significant. In addition, injection of vehicle failed to have an effect in the control group, likely arguing against the possibility that warm T_{amb} directly contributes to the increased body-core temperature.

Strikingly, we observed that the time-response curve as shown in Fig. 2a, which can be used to estimate the rate of changes in body temperature, was altered at the warm T_{amb} of 32 °C. Unlike that at the standard T_{amb} of 22 °C, the body-core temperature increase was sustained throughout the 90 min observation time, showing the upward slope of a near-perfect linear relationship between time and dose response. This change strongly suggests that the high level of hyperthermia may in turn further enhance the responsivity of 5-HT_{2A} receptors under our experimental condition (see discussion below). However, the alternative possibility that a reduced rate of heat loss in the warm T_{amb} might be the cause of the continued linear increase in body-core temperature should be taken into account in future studies. Overall, the results strongly suggest that the functional response to DOI was significantly enhanced at warm T_{amb} .

Next, ketanserin was employed to further explore the underlying mechanism for the enhanced functional response. Animals were divided into 4 groups: veh + veh, veh + DOI, ket + DOI, and ket + veh. As shown in Fig. 2b, vehicle injection had no effect in the veh + veh group, suggesting that changes in body-core temperature could not be simply ascribed to physical distress in the handling of body temperature measurement at the warm T_{amb} of 32 °C. Results from the veh + DOI group confirmed the previous observation demonstrating that DOI at 0.1 mg/kg evoked a near-perfect linear increase in body-core temperature at the warm T_{amb} of 32 °C. Interestingly, injection of ketanserin alone slightly reduced the body temperature. However, this effect was not statistically different from that of the veh + veh group ($p > 0.05$). It was found that the enhanced functional effect of DOI was blocked by ketanserin injected 15 min before DOI. A two-way ANOVA test demonstrated significant main effects of treatment ($F_{3, 17} = 28.1$, $p < 0.001$), time ($F_{8, 136} = 7.4$, $p < 0.001$), and treatment $\times$ time ($F_{24, 136} = 19.3$, $p < 0.001$). Compared to the veh + DOI group, *post-hoc* Scheffe's test showed that ketanserin pretreatment blocked the DOI-induced increase in body temperature ($p < 0.001$). Further one-way ANOVA analyses of body temperature to DOI treatment indicated that ketanserin effectively blocked the enhanced effect at each of the time points ($p < 0.01$). Thus, the results of the ketanserin data agree with the hypothesis that 5-HT_{2A} receptors are involved in the molecular mechanisms responsible for the enhanced effect of DOI at warm T_{amb} .

The purpose of the final set of experiments was to test whether cold T_{amb} in contrast to warm T_{amb} exerts an opposite effect on the functional response of 5-HT_{2A} receptors to DOI administration. Experiments were conducted at cold T_{amb} of 12 °C, standard T_{amb} of 22 °C and warm T_{amb} of 32 °C. For comparison, one group of animals was exposed to the thermoneutral zone of 27 °C in which the metabolic rate is near minimum [6]. The basal

levels of body temperature were 38.08 ± 0.13 °C ($n = 6$), 37.71 ± 0.12 °C ($n = 5$), 37.33 ± 0.15 °C ($n = 6$) and 37.72 ± 0.10 °C ($n = 5$) at the T_{amb} of 12, 22, 27, and 32 °C, respectively. After two baseline samples, animals were injected at time zero with 0.1 mg/kg DOI. As shown in Fig. 3, DOI produced a T_{amb} -dependent increase in body-core temperature. The maximal increase was 0.20 ± 0.07 , 0.69 ± 0.06 , 0.99 ± 0.13 , and 1.45 ± 0.23 °C at the T_{amb} of 12, 22, 27, and 32 °C, respectively. Two-way repeated measures ANOVA test revealed significant effects of treatment ($F_{3, 18} = 25.2$, $p < 0.001$), time ($F_{7, 126} = 29.6$, $p < 0.001$), and treatment $\times$ time ($F_{21, 126} = 8.3$, $p < 0.001$). *Post-hoc* Scheffe's test showed that, compared to that at 22 °C, the DOI-evoked increase in body temperature was reduced at the T_{amb} of 12 °C ($p < 0.05$) but enhanced at 32 °C ($p < 0.01$), indicating that functional activity of 5-HT_{2A} receptors appears to be reduced in a cold environment but enhanced in a warm environment. However, changes at the T_{amb} of 27 °C were not significantly different from that at 22 °C.

In conclusion, the main finding of this study is that the responsivity of 5-HT_{2A} receptors in the CNS is strongly dependent on the ambient temperature. It has been demonstrated that neurotoxicity induced by amphetamine derivatives is ambient temperature-dependent [1,3,11,14]. Thus, the results of the present study may have a significant impact on understanding the neurotoxic effects of these psychogenic drugs. Neurochemical studies have shown that a recreational dose of MDMA elicits an 8 fold increase in extracellular 5-HT in the CNS under normal laboratory conditions [2,7]. This level of 5-HT is unlikely able to over-activate the low affinity 5-HT_{2A} receptors for inducing severe neurotoxicity [8,10], which is contrary to the clinical observation that MDMA can cause severe toxicity at club. We suggest that the hot environment at clubs may be responsible since the affinity of 5-HT to 5-HT_{2A} receptors can be increased in a temperature-dependent manner [5]. Taken together, the present study provides the functional evidence that the 5-HT_{2A} receptor may be the key molecule responsible, at least in part, for ambient temperature-dependent neurotoxic effects of psychogenic drugs.

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Fig. 1. Effect of DOI on body-core temperature at the standard ambient temperature (T_{amb}) (22 °C)

The y-axis indicates changes in body-core temperature (ΔT_{cor}) plotted against the time of measurement expressed in the x-axis (min). *a*, DOI at the doses of 0.05, 0.1 and 0.5 mg/kg, s.c., was administered at time of zero as indicated by an arrow. Injection of DOI at the standard T_{amb} produced a dose-dependent increase in body-core temperature. * $p < 0.05$, 0.1 mg/kg vs. vehicle; # $p < 0.05$, 0.5 mg/kg vs. vehicle (one-way ANOVA followed by *post-hoc* Scheffe's test). *b*, Ketanserin (Ket, 5 mg/kg, i.p.) was administered 15 min before 0.1 mg/kg DOI injection. Pretreatment with ketanserin blocked the DOI-induced increase in T_{cor} . * $p < 0.05$ vs. vehicle + DOI (one-way ANOVA followed by *post-hoc* Scheffe's test). Each value is the mean $\pm$ SEM of 5–8 animals.

Fig. 2. Effect of DOI on body-core temperature at the warm ambient temperature (32 °C)

The y-axis indicates changes in body-core temperature (ΔT_{cor}) plotted against the time of measurement expressed in the x-axis (min). *a*, DOI at the doses of 0.05, 0.1 and 0.5 mg/kg (s.c.) were administered at time zero. Similar to that at the standard T_{amb} , DOI at the warm T_{amb} evoked a dose-dependent increase in T_{cor} . * $p < 0.05$, 0.1 mg/kg vs. vehicle; # $p < 0.05$, 0.5 mg/kg vs. vehicle (one-way ANOVA followed by *post-hoc* Scheffe's test). The increased body-core temperature at the warm T_{amb} was significantly greater than that under the standard condition (see text). *b*, Ketanserin pretreatment (Ket, 5 mg/kg, i.p.) blocked the increase in body-core temperature induced by DOI (0.1 mg/kg, s. c.) at the T_{amb} of 32 °C. * $p < 0.05$ vs. vehicle + DOI (one-way ANOVA followed by *post-hoc* Scheffe's test). Data are expressed as mean $\pm$ SEM relative to baseline ($n = 5-8$ animals).

Fig. 3. Effect of ambient temperatures (12, 22, 27, and 32 °C) on the increased body-core temperature induced by DOI

The y-axis indicates changes in body-core temperature (ΔT_{cor}) while the x-axis shows the time of measurement (min). DOI at the dose of 0.1 mg/kg, s.c., was administered at time zero as indicated by the arrow. DOI produced a T_{amb} -dependent increase in body-core temperature ($p < 0.001$, main effect). Values are expressed as changes in body-core temperature relative to baseline. The baseline was the mean of two measurements before drug administration. Each value is the mean $\pm$ SEM of 5–8 animals.