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Mirtazapine abolishes hyperthermia in an animal model of serotonin syndrome

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ABSTRACT

Serotonin (5-HT) syndrome is a potentially fatal condition associated with various combinations of serotonergic drugs. Hyperthermia is the most serious symptom of this syndrome. Hyperthermia in 5-HT syndrome is reportedly the result of activation of 5-HT_{2A} receptors. Mirtazapine is a novel antidepressant and a potent 5-HT_2 receptor antagonistic. Although mirtazapine has been reported to cause 5-HT syndrome, the pharmacological profile of mirtazapine suggests that it improves hyperthermia in 5-HT syndrome. In the present study, we evaluated whether mirtazapine attenuates hyperthermia in a rat model of 5-HT syndrome. This model was induced by administration of tranylcypromine, a nonselective monoamine oxidase inhibitor, and fluoxetine, a selective serotonin reuptake inhibitor. Upon injection of these two drugs, the rectal temperature of the rats increased to over 40 °C. Pre- and post-administration of mirtazapine abolishes hyperthermia in this model of 5-HT syndrome. Post-administration of ritanserin, a 5-HT_{2A} receptor antagonist, completely inhibited hyperthermia and pre-administration of WAY100635, a 5-HT_{1A} receptor antagonist, significantly attenuated the ability of mirtazapine to abolish hyperthermia. The results of the present study suggest that mirtazapine inhibits hyperthermia in an animal model of 5-HT syndrome by blocking the activation of 5-HT_{2A} receptors, and that it partly inhibits hyperthermia by activating the 5-HT_{1A} receptors. The present study indicates that mirtazapine is unlikely to cause 5-HT syndrome and may be a useful drug for treating this condition.

Serotonin (5-HT) syndrome is the most severe complication of serotonergic activating drugs, including those that reduce the metabolism of 5-HT (i.e., monoamine oxidase inhibitors [MAOIs]), increase the production of 5-HT (i.e., L-tryptophan), or inhibit the uptake of 5-HT (i.e., serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants). The 5-HT syndrome is thought to be induced by activation of serotonergic transmission [9]. The clinical features of 5-HT syndrome consist of autonomic nervous system symptoms (such as hyperthermia, diaphoresis, tachycardia, and diarrhea), mental status changes, and neuromuscular abnormalities (such as myoclonus, incoordination, hyperreflexia, tremors, and muscle rigidity) [21]. Among the various symptoms of 5-HT syndrome, hyperthermia is related to the most severe disease progression, leading to death in some cases [4,12,18]. Hyperthermia in 5-HT syndrome is thought to be associated with activation of the 5-HT_{2A} receptor [9,20,22]. Mirtazapine is a novel antidepressant that acts via a different mechanism from those of other antidepressants. It enhances serotonergic and noradrenergic transmission by acting as an α_2 adrenoceptor antagonist. It also has potent 5-TH_2 and 5-HT_3 receptor antagonistic effects and an indirect 5-TH_{1A} receptor-activating effect [5]. Studies have shown that mirtazapine monotherapy or the combination of mirtazapine with other antidepressants induces the 5-HT syndrome [1,7,11,30]. On the other hand, Hoes and Zeijpveld reported that mirtazapine improves 5-HT syndrome [14]. Additional investigations have suggested that 5-HT syndrome is not induced by mirtazapine [8,9,15,16]. Thus, there is a controversy with regard to whether mirtazapine induces 5-HT syndrome. We have demonstrated that 5-TH_{2A} receptor antagonists prevent and reverse serotonergic hyperactivity induced hyperthermia including animal model of 5-HT syndrome [22,26,27]. Since mirtazapine has potent 5-HT_{2A} antagonistic effects, we hypothesized that this drug could prevent hyperthermia in an animal model of 5-HT syndrome.

In the present study, we evaluate whether pre- and post-administration of mirtazapine inhibits hyperthermia in an animal model of 5-HT syndrome by measuring changes in the rectal temperature of the animals.

Male Wistar rats (Clea Japan Inc., Japan) weighing 180–220 g were used in this study. The rats were individually housed in cages maintained at 24 ± 1 °C under a 12-h light/dark cycle, and were provided free access to food and water. The animal procedures employed were approved by the Animal Investigation Committee of our institution, and were in strict accordance with the National Institute of Health (NIH) Guide for the Care and Use of Laboratory Animals.

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The 5-HT syndrome animal model was prepared according to our previous study [25]. Rats were administered tranylcypromine, a nonselective monoamine oxidase (MAO) inhibitor (3.5 mg/kg) and fluoxetine, a selective serotonin reuptake inhibitor (SSRI) (10 mg/kg) by simultaneous intraperitoneal (i.p.) injection. The rectal temperature of the rats was measured at 30 min. intervals. A thermocouple probe connected to a digital thermometer (Shibaura Electronics Co., Tokyo, Japan) was inserted 6 cm into the rectum, and a steady temperature readout was obtained within 10 s of the probe insertion.

In addition to mirtazapine (5-HT_{1A} pK_i 5.3, 5-HT transporter pK_i < 4.5 [5]), tranylcypromine, and fluoxetine, ritanserin, a 5-HT_{2A} receptor antagonist and WAY100635, a 5-HT_{1A} receptor antagonist, were used in the experiment. All drugs were purchased from Sigma–Aldrich Co (USA). Mirtazapine and ritanserin were dissolved in 99.7% acetic acid, and the pH was adjusted to a range between 6 and 7 with NaOH. Fluoxetine was dissolved in distilled water. Tranylcypromine and WAY100635 were dissolved in saline. A volume of 2 ml/kg of each of the drugs was i.p. injected into rats. On the day of the experiment, the rats were placed in individual cages in a room maintained at 24 ± 1 °C.

The rectal temperature of the rats was measured several times, and when the temperature was observed to be stable, saline and mirtazapine (2.5 mg/kg or 5 mg/kg) were i.p. injected into the rats. Tranylcypromine and fluoxetine were i.p. injected 15 min later. Thereafter, the rectal temperature was measured at 30 min intervals (pre-administration experiment). In the post-administration experiment, tranylcypromine and fluoxetine were i.p. injected, and saline, mirtazapine (2.5 mg/kg or 5 mg/kg), and ritanserin (3 mg/kg) were i.p. injected 30 min later. In another group of rats, tranylcypromine and fluoxetine were i.p. injected at first, and saline or WAY100635 (1 mg/kg) was i.p. injected 15 min later. Mirtazapine (5 mg/kg) was then i.p. administered 15 min after injection of WAY100635 or saline. In the experiment performed to investigate the effect of mirtazapine by itself on rectal temperature, saline or mirtazapine (5 mg/kg) was i.p. injected.

The doses of mirtazapine were selected as follows. The doses of mirtazapine (2.5 mg/kg and 5 mg/kg) were selected on the basis of reports of by De Boer [5] and Pawlyk et al. [24]. The doses of other drugs were selected according to our previous study [20,25–27].

Rectal temperature changes from the baseline were calculated at 30 min for each group and statistically analyzed using analysis of variance (ANOVA) with repeated measures, followed by PLSD.

When tranylcypromine (3.5 mg/kg, i.p.) and fluoxetine (10 mg/kg, i.p.) were simultaneously administered, rats began to move intermittently from one place to another after 60 min. Behaviors specific to 5-HT behavioral syndrome (tremors, and head weaving) were observed about 90 min after administration of the drug. Continuous turning was then noted. Rectal temperature began to increase 120 min after administration of two drugs and surpassed 40 °C 240 min after drug administration (Fig. 1A).

In the group pre-injected with mirtazapine (2.5 mg/kg and 5 mg/kg), the body temperature increase of the rats was significantly inhibited and generally lower than the body temperature before drug administration (Fig. 1A). Post-administration of mirtazapine (2.5 mg/kg and 5 mg/kg) significantly inhibited hyperthermia in the 5-HT syndrome model (Fig. 1B). Administration of mirtazapine (5 mg/kg) alone significantly decreased the rectal temperature of the rats by approximately 1.5 °C (data not shown).

Post-administration of ritanserin (3 mg/kg) abolished the body temperature increase in the animal model of 5-HT syndrome (Fig. 2A). The decrease of body temperature in this case followed the same pattern as that observed for the post-administration of mirtazapine.

Tranylcypromine and fluoxetine were administered, and then saline or WAY100635 was injected 15 min later. Additionally, mirtazapine (5 mg/kg) was administered 15 min after injection of saline or WAY100635 (Fig. 2B). In the two groups injected with saline or WAY100635, the body temperature increase continued to be inhibited from the beginning of the experiment (0 min) to the end of the experiment (360 min). Relative to the group pre-injected with saline, the effect of mirtazapine on body temperature was significantly attenuated in the group pre-injected with WAY100635.

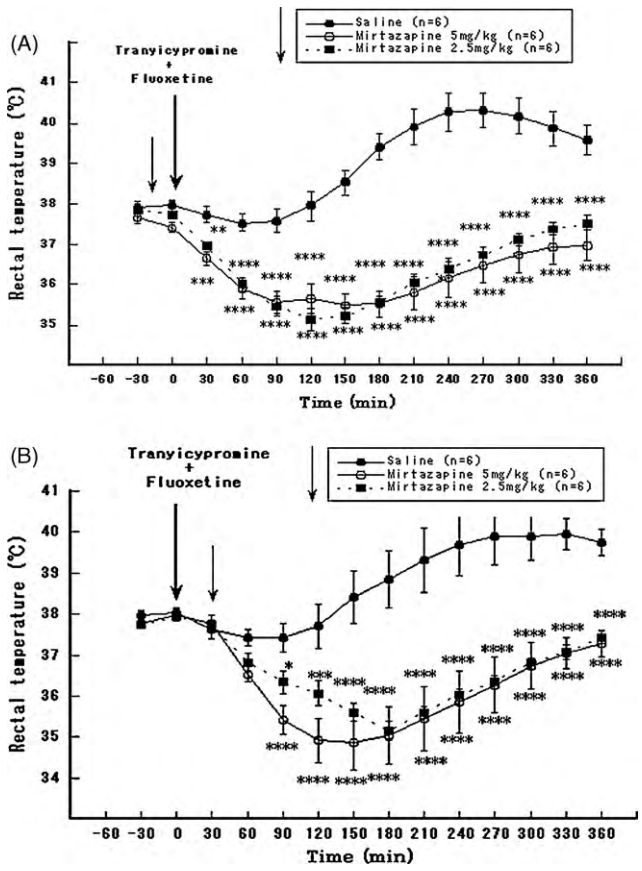

Fig. 1. Changes in rectal temperature in the 5-HT syndrome animal model and effect of pre- and post-injection of mirtazapine on hyperthermia in 5-HT syndrome. Saline or mirtazapine (2.5 and 5 mg/kg) was i.p. injected into rats, and tranylcypromine (3.5 mg/kg) and fluoxetine (10 mg/kg) were i.p. injected 15 min later (A). Tranylcypromine (3.5 mg/kg) and fluoxetine (10 mg/kg) were i.p. injected and saline or mirtazapine (2.5 and 5 mg/kg) was i.p. injected 30 min later (B). Values are represented as mean ± SEM. The statistical differences among the groups are indicated as follows: $^{*}p < 0.05$ (vs. saline), $^{**}p < 0.01$ (vs. saline), $^{***}p < 0.001$ (vs. saline), $^{****}p < 0.0001$ (vs. saline) (ANOVA followed by Fisher's PLSD).

The animal model of 5-HT syndrome used in the experiment was induced by administration of tranylcypromine and fluoxetine. Administration of these two drugs inhibits monoamine oxidase activity and reuptake of monoamines, and then reduces the metabolism of 5-HT in addition to dopamine (DA). In our previous study [25], we demonstrated that when tranylcypromine and fluoxetine were simultaneously administered, the concentrations of both 5-HT and DA in the anterior hypothalamus were remarkably increased. The 5-HT_{2A} receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) induces hyperthermia in animals [20]. In the present study, the 5-HT_{2A} antagonist ritanserin is found to prevent hyperthermia in the animal model of 5-HT syndrome. The results of our studies and those of other investigators have led us to propose that hyperthermia in 5-HT syndrome is mainly the result of 5-TH_{2A} receptor activation induced by an increased concentration of 5-HT.

In the present study, we demonstrated that pre- and post-injection of mirtazapine abolishes hyperthermia in the animal