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The serotonin 2C receptor agonist WAY-163909 attenuates ketamine-induced hypothermia in mice

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Abstract

Anesthesia-Induced Hypothermia (AIH) has been reported to be the cause of many postoperative adverse effects, including increased mortality, decreased immune responses, cardiac events, and a greater prevalence of surgical wound infections. AIH can in some cases be minimized with pre-warming fluids and gases and forced-air heating systems, but such techniques are not always effective and can result in patient burns or other adverse effects. Stimulation of 5-HT₂ receptors has been reported to increase body temperature through a variety of mechanisms, and as such, may be a viable target for pharmacologically minimizing AIH. In the present study, we examined the effects of 5HT₂ receptor stimulation on hypothermia induced by the injectable anesthetic ketamine in Swiss-Webster mice using rectal thermometry. We report that ketamine dose-dependently induced hypothermia, and mice did not become tolerant to this effect of ketamine over the course of three injections spaced at once per week. Ketamine-induced hypothermia was significantly attenuated by pretreatment with the selective 5-HT_{2C} receptor agonist WAY-163909 but not by pretreatment with the mixed 5-HT_{2A/2C} receptor agonist 2,5dimethoxy-4-iodoamphetamine (DOI). Moreover, the blockade of ketamine-induced hypothermia by WAY-163909 was reversed by pretreatment with the selective 5-HT_{2C} receptor antagonist SB-242084. These findings demonstrate that stimulation of 5-HT_{2C} receptors can reduce AIH, at least for ketamine-induced hypothermia. They warrant further study of the pharmacological and neurobiological mechanisms underlying this interaction and its extension to other anesthetics. Furthermore, these findings suggest that the maintenance of body temperature during surgery may be a new clinical use for 5HT_{2C} receptor agonists.

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Participated in research design: Murphy and Murnane

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Keywords

Serotonin; Hypothermia; Anesthesia; 5-HT; ketamine; WAY-163909

1. Introduction:

Anesthesia is necessary for the safe and successful completion of a variety of surgeries and other procedures. However, anesthesia can compromise homeostatic thermoregulation and result in robust decreases in body temperature (Buggy and Crossley, 2000), which has been termed anesthesia-induced hypothermia (AIH). AIH is a common complication of various surgeries (Kiekkas et al., 2005; Torossian, 2008) that can result in critical adverse events. For example, AIH has been reported to be associated with increased mortality, decreased immune responses, increased risk of cardiac events, an increased prevalence of surgical wound infections, and other adverse events (Baumgartner et al., 2008; Buggy and Crossley, 2000; Shaw et al., 2017; Young and Watson, 2006). Current strategies for minimizing AIH rely on mechanical devices, such as forced air systems, to warm the patient as well as minimize patient contact with cold fluids that can exacerbate AIH (Young and Watson, 2006). However, such techniques may not provide consistent prevention of AIH (Hart et al., 2011; Shaw et al., 2017). Prewarming fluids is not always practical during emergencies or when extended fluid replenishments are required. Forced-air techniques can increase the frequency of infections or burns (Chung et al., 2012; Kabbara et al., 2002). This technique can also be contraindicated to maintain a sterile field or to keep the ambient temperature of the operating room low (Weirich, 2008). As such, it is of interest to explore alternative techniques for minimizing AIH.

Serotonin (5-hydroxytryptamine; 5-HT) is a monoamine neurotransmitter that acts through neuroreceptors in the central and peripheral nervous systems, as well as in nonneuronal tissues (e.g. the endocrine, cardiovascular, and gastrointestinal systems) (Hannon and Hoyer, 2008). There are seven different families of serotonin receptors (5HT₁ - 5-HT₇) with multiple subtypes within several families (Fantegrossi et al., 2008). Previous studies have linked 5-HT₂ receptor subtypes to temperature regulation. 5-HT_{2C} receptors are the most abundantly expressed serotonin receptor in the hypothalamus (Yadav et al., 2009). 5-HT₂ receptors have been reported to increase vasoconstriction in the viscera and skin (Glennon, 1990). Previous studies have linked the 5-HT_{2A} receptor to thermoregulation (Ootsuka and Blessing, 2006; Pawlyk et al., 2006; Sipe et al., 2004). Likewise, 5-HT_{2C} receptor agonists have been reported to increase body temperature and cellular metabolism. For example, YM348 (a selective 5-HT_{2C} agonist) increases body temperature and calorie expenditure, a non-shivering thermogenic response (Hayashi et al., 2004). These findings led us to the hypothesis that the activation of 5-HT₂ receptors may attenuate AIH. In the present study, we use the injectable anesthetic ketamine to assess this hypothesis because 1) its dosing can be readily controlled because it is injected rather than inhaled, 2) it is well known to induce dose-dependent hypothermia in several species (Fahim et al., 1973; Garami et al., 2017; Schmitz et al., 2016), and the role of serotonin and specific serotonin receptors in ketamine-induced hypothermia remains controversial (Fahim et al., 1973). However, it is important to note that the use of ketamine as an anesthetic in humans is limited to specific cases such as

hemorrhagic shock, hemodynamic instability, and bronchodilation (Kurdi et al., 2014), in contrast to its more extensive use as a veterinary anesthetic.

2. Material and Methods:

2.1 Subjects

The subjects of this study were adult (8–12 weeks old at 30–40 grams) male Swiss Webster mice (Charles River, Charleston, SC). Mice were housed in groups of 3 and were given food (Laboratory Rodent Diet #5001, PMI Feeds, Inc., St. Louis, MO, USA) and water *ad libitum*. The temperature of the facility was maintained at 22–23.5 °C on a 12 hour light/12 hour dark cycle. Mice were routinely handled prior to the initiation of experimental data collection to minimize stress. A total of 21 mice were used to complete all of the experiments. Mice were maintained for at least one week after arrival in the vivarium prior to testing. All studies were carried out in accordance with the Guide for Care and Use of Laboratory animals as adopted and promulgated by the National Institutes of Health, and experimental protocols were approved by the Institutional Animal Care and Use Committee at Mercer University.

2.2 Drugs

The injectable anesthetic (+/–)-ketamine and the mixed 5-HT_{2A/2C} receptor agonist (+/–)2,5-Dimethoxy-4-iodoamphetamine (DOI) (Fantegrossi et al., 2008) were purchased from Sigma-Aldrich (St. Louis, MO) and dissolved in saline. The selective 5-HT_{2C} receptor antagonist, SB-242084 (Kennett et al., 1997), was purchased from SigmaAldrich (St. Louis, MO) and dissolved in 5% Tween 80, 5% ethanol, and brought to final volume in saline. The selective 5-HT_{2C} receptor agonist, WAY-163909 (Grauer et al., 2009; Marquis et al., 2007), was provided as a gift from Pfizer (New York, NY) and dissolved in 5% Tween 80 and brought to final volume in saline. All injections were administered intraperitoneally at a volume of 0.01 ml of the drug solution per g body weight of each mouse. All doses are reported in the salt form.

2.3 Temperature Measurements

Temperature was measured by inserting a lubricated probe 1.5 cm into the rectum and recording the readout from a connected TH-8 Thermalert temperature monitor (Physitemp Instruments, Clifton, NJ, USA) using a repeated measures design. The order of doses was pseudo-randomized over the course of the testing each drug. The randomization of the dose order for the mice was conducted using Research Randomizer (<https://www.randomizer.org/>). There was a gap of at least one week between sessions in each subject. Trials were conducted 5 days per week between the hours of 12:00–17:00. On each experimental day, the mice were weighed and the tail marked. Subsequently, 6 rectal temperature readings were taken and averaged to establish the baseline temperature for that animal on that day. Following the baseline measurements, ketamine was injected by the intraperitoneal (IP) route from 50–180mg/kg and temperature recorded for an additional 18 measurements at five min intervals (90 mins). For drug interaction studies, at the end of the baseline period, DOI (1–10mg/kg, IP), WAY-163909 (0.3–3mg/kg, IP), or vehicle was injected at the end of the baseline period and 15 min prior to the ketamine injection. For the

antagonism study, SB-242084 (0.3mg/kg, IP) or vehicle was injected at the end of the baseline period, 15 min prior to the WAY-163909 injection, and 30 mins prior to the ketamine injection. All doses and pretreatment times were based on preliminary or published studies (Fletcher et al., 2002; Grauer et al., 2009). For the drug interaction and antagonism studies, temperature was again recorded for an additional 18 measurements at five min intervals (90 mins) after the ketamine injection. At the end of each session, the mice were observed until fully recovered from the anesthesia and then returned to the colony.

2.4 Data Analysis

All graphs were generated and statistical analyses conducted using GraphPad® Prism for windows (GraphPad Software, San Diego, California, USA). All data were normalized to the absolute change relative to the average of the baseline period for that experiment on an individual subject basis. The time course in the change in temperature post ketamine injection was converted to the area under the curve for each subject and averaged for statistical comparisons conducted using repeated measures one-way analysis of variance (ANOVA), with post-hoc comparisons by Dunnett's (Dunnett, 1955) or Tukey's (Tukey, 1949) test as appropriate. Bartlett's test was used to assess equal variance, the Shapiro-Wilk test was used to assess a Gaussian distribution, and sample size analysis was used to ensure a power (1- β) of greater than 0.8. All statistical comparisons passed each of these tests, with the exception of a few cases of unequal variance. Graphical presentation of all data depicts mean $\pm$ standard error of the mean (S.E.M.). Significance was arbitrated at $P < 0.05$.

3. Results:

In the first experiment, the effects of ketamine on temperature were assessed across a range of doses from 30 to 180 mg/kg. Ketamine induced anesthesia at both the 100 and 180 mg/kg doses. The time courses of these doses of ketamine as well as saline treatment are presented in Fig. 1, Panel A. The areas under the curve of these time courses are presented in Panel B. There was a significant main effect of ketamine ($F_{4,29} = 61.9$; $P < 0.001$) as assessed by one-way ANOVA. Post-hoc analysis by Dunnett's test revealed significant differences between saline treatment and treatment with ketamine at doses of 56, 100, and 180 mg/kg.

In the second experiment, the development of any tolerance to the hypothermia-inducing effects of ketamine on temperature was assessed over the course of three injections with each injection spaced at once per week. The time courses and areas under the curve of the effects of ketamine at 100 mg/kg are presented in Fig. 2, Panels A and C, respectively. The time courses and areas under the curve of the effects of ketamine at 180 mg/kg are presented in Fig. 2, Panels B and D, respectively. There was no significant effect of repeated injection of ketamine at 100 or 180mg/kg using this dosing regimen as assessed by one-way ANOVA.

In the third experiment, the effects of pretreatment with the mixed 5-HT_{2A/2C} receptor agonist DOI or the selective 5-HT_{2C} receptor agonist WAY-163909 on ketamine-induced hypothermia were assessed. The time courses and areas under the curve of the effects of pretreatment with DOI are presented in Fig. 3, Panels A and C, respectively. The time courses and areas under the curve of the effects pretreatment with WAY-163909 are presented in Fig. 3, Panels B and D, respectively. For DOI, one-way ANOVA revealed a

significant main effect of treatment ($F_{4,34} = 14.9$; $P < 0.001$). Post-hoc analysis by Tukey's test showed a significant difference between two injections of saline and the administration of ketamine following either saline pretreatment or pretreatment with any of the 3 doses of DOI. Moreover, there was no significant difference between pretreatment with saline and pretreatment with any of the 3 doses of DOI. For WAY163909, one-way ANOVA revealed a significant main effect of treatment ($F_{5,41} = 25.6$; $P < 0.001$). Post-hoc analysis by Tukey's test showed a significant difference between two injections of vehicle and the administration of ketamine following either vehicle pretreatment or pretreatment with any of the 3 doses of WAY-163909. However, there was a significant difference between pretreatment with vehicle and pretreatment with WAY-163909 at 1 and 3mg/kg. Of note, WAY-163909 only partially reverted the effects elicited by ketamine, even at the highest dose used of 3 mg/kg. This suggests that other mechanisms/receptors are involved.

In the fourth experiment, whether the reversal of ketamine-induced hypothermia by WAY-163909 depends on its stimulation of 5-HT_{2C} receptors was tested using pretreatment with the selective 5-HT_{2C} receptor antagonist SB-242084. WAY-163909 was administered at a dose of 1mg/kg in this experiment, as it was found to be the most effective dose in the third experiment. The time courses and areas under the curve of the effects pretreatment with SB-242084 are presented in Fig. 4, Panels A and B, respectively. One-way ANOVA revealed a significant main effect of treatment ($F_{3,27} = 14.0$; $P < 0.001$). Post-hoc analysis by Tukey's test showed a significant difference between pretreatment with vehicle and SB-242084 before saline compared to treatment with ketamine after saline/vehicle or ketamine after SB-242084 and WAY-163909. Moreover, ketamine administered after vehicle plus WAY-163909 was significantly different from ketamine after SB-242084 and WAY-163909 but not significantly different from pretreatment with vehicle and SB-242084 before saline, indicating that SB-242084 fully reversed the effects of WAY-163909.

4. Discussion:

Consistent with many previous studies, we found in that ketamine dose-dependently induces hypothermia (Fahim et al., 1973; Garami et al., 2017; Schmitz et al., 2016). Furthermore, we found that mice do not become tolerant to this effect of ketamine over the course of three injections spaced at once per week. Ketamine-induced hypothermia was significantly attenuated by pretreatment with the selective 5-HT_{2C} receptor agonist WAY-163909, but not by pretreatment with the mixed 5-HT_{2A/2C} receptor agonist DOI. Finally, the blockade of ketamine-induced hypothermia by WAY-163909 was reversed by pretreatment with the selective 5-HT_{2C} receptor antagonist SB-242084, suggesting that the 5-HT_{2C} receptor is a critical mediator of the reversal of ketamine-induced hypothermia by WAY-163909. These findings demonstrate that stimulation of 5-HT_{2C} receptors can reduce AIH, at least for hypothermia induced by ketamine. They warrant further study of the pharmacological and neurobiological mechanisms underlying this interaction and its extension to other anesthetics. Furthermore, these findings suggest that the maintenance of body temperature during surgery may be a new clinical use for 5-HT_{2C} receptor agonists.

The findings of the present study have potential implications for both the basic science understanding of thermoregulation and for clinical therapy in the operating room.

Thermoregulation requires regulation of temperature within both the core and the peripheral compartments of the body, both of which are monitored and adjusted by the preoptic area in the anterior hypothalamus of the brain (Donovan and Tecott, 2013; Myers, 1981). During hypothermia, the hypothalamus receives information from thermoreceptors to activate shivering and non-shivering mechanisms of heat gain (Baumgartner et al., 2008; Buggy and Crossley, 2000; Hart et al., 2011). A critical component of AIH is loss of homeostatic responses to cold that are ablated by the anesthetic, including hypothalamic control of thermoregulation (Buggy and Crossley, 2000; Shaw et al., 2017; Torossian, 2008; Young and Watson, 2006). The hypothalamus regulates body temperature by activating sweating or shivering mechanisms, respectively. This effectively changes vascular tone or alters cellular metabolism to restore euthermia (Baumgartner et al., 2008; Fox et al., 2010). Anesthesia can prevent such responses by inhibiting the hypothalamus, causing peripheral vasodilation, or reducing cellular metabolism (Buggy and Crossley, 2000; Shaw et al., 2017; Torossian, 2008; Young and Watson, 2006). Loss of hypothalamic-mediated thermoregulation because of anesthesia is particularly problematic in the operating room as it is often kept cold and heat loss can be exacerbated by the evaporation of liquids at the surgical site, cold fluids administered intravenously, fluid deprivation prior to surgery, or unwarmed irrigation fluids (Baumgartner et al., 2008; Shaw et al., 2017). Anesthetics can also inhibit vasoconstriction of the vessels supplying the skin, preventing heat retention (Baumgartner et al., 2008). A pharmacological approach to the treatment of AIH is attractive as it has the potential to augment external sources of heat retention by normalizing hypothalamic regulation of body temperature and engaging a variety of internal processes, such as increased cellular metabolism, to regulate body temperature. Our data suggest that activation of 5-HT_{2C} receptors can induce at least a subset of these pathways.

We propose that 5-HT_{2C} receptor activation stimulates the hypothalamus to activate nonshivering mechanisms of heat gain, most likely by increasing cellular metabolism. This hypothesis is supported by reports that serotonin systems have anatomical, physiological, and pharmacological properties amenable to reversing AIH. Serotonin transporters and receptors are expressed in the hypothalamus (Donovan and Tecott, 2013), with the 5HT_{2C} receptor being the most abundant (Yadav et al., 2009). Brain injections of 5-HT or its precursor 5-hydroxytryptophan (5-HTP) have been shown to increase cellular metabolism (Le Feuvre et al., 1991; Rothwell and Stock, 1987). Cell metabolism can also be increased by specific drugs that activate serotonin systems, such as fenfluramine, which acts as a substrate-based releaser of 5-HT (Le Feuvre et al., 1991; Rothwell and Stock, 1987). Likewise, the mixed stimulant/psychedelic 3,4-methylenedioxymethamphetamine (MDMA) (Murnane et al., 2009), which acts as a substrate-based releaser of 5-HT (Murnane et al., 2010) as well as a 5-HT_{2A} receptor agonist (Murnane et al., 2012a), can increase body temperature (Murnane et al., 2012b). We have also focused on 5-HT_{2C} receptors because selectively stimulating these receptors increases body temperature and cellular metabolism (Hayashi et al., 2004).

The selective induction of a non-shivering thermogenic responses by 5-HT_{2C} receptor agonists could provide an excellent clinical strategy for reversal of AIH. Our findings with ketamine act as a proof of principle that 5-HT_{2C} receptor activation can counteract AIH. However, much further research is necessary to understand how this effect generalizes to

other anesthetics and other conditions. In particular, it is important to note that the use of ketamine as an anesthetic in humans is limited to specific cases such as hemorrhagic shock, hemodynamic instability, and bronchodilation (Kurdi et al., 2014), and it would be useful to study the effects of 5-HT_{2C} receptor stimulation in combination with inhaled agents that are more commonly as anesthetics in humans than ketamine. As operating rooms are often kept below typical room temperature, it would also be useful to study the effects of 5-HT_{2C} receptor stimulation in a variety of ambient conditions. Moreover, WAY-163909 only partially reverted the effects elicited by ketamine, even at the highest dose used of 3 mg/kg. This implies that other mechanisms/receptors are involved. Nevertheless, the emergence of 5-HT_{2C} receptor stimulation as a novel approach to, at least partially, reverse of AIH could have a significant impact as lorcaserin is a 5-HT_{2C} receptor agonist that is currently marketed for weight loss. The use of lorcaserin could be possibly be extended for the reversal of AIH, or newer agents could be developed, but this idea remains speculative as the effectiveness of lorcaserin is not yet known and the generalization of 5-HT_{2C} receptor agonism to other anesthetics is also not known.

There are some areas of note with the present findings. It was surprising to us that DOI was less effective than WAY-163909. Previous studies have linked the 5-HT_{2A} receptor and thermoregulation (Ootsuka and Blessing, 2006; Pawlyk et al., 2006; Sipe et al., 2004). Sipe and colleagues reported that R(-)-DOI prevents increases in tail skin temperature following naloxone withdrawal in two rodent models of ovariectomy-induced thermoregulatory dysfunction, and this effect of DOI is reversed by the selective 5-HT_{2A} receptor antagonist M100907, suggesting that central 5-HT_{2A} receptors can restore temperature regulation (Sipe et al., 2004). We do not yet have an explanation for this other than stimulation of 5-HT_{2A} receptors seems to attenuate 5-HT_{2C} receptor mediated reversal of AIH. This is consistent with previous studies that 5-HT_{2A} and 5-HT_{2C} receptors oppose one another's actions (Filip et al., 2004, 2006; McMahon et al., 2001), but surprising in the context of temperature regulation. It is also of note that 5-HT₂ receptors have been reported to increase vasoconstriction in the viscera and skin (Glennon, 1990), and vasodilation is a major driver of AIH. It will be important in future studies to examine whether doses of 5-HT_{2C} receptor agonists that reverse AIH are concomitantly increasing blood pressure, which could be contraindicated during surgery, although lorcaserin is approved for use in the obese with comorbid hypertension and does not appear to have a pronounced cardiovascular risk profile (Khera et al., 2018).

Moreover, the current experiments were conducted at typical ambient temperatures. In contrast, the temperature in operating rooms is often lower (Weirich, 2008), and it is known that ambient temperature can alter the effects of MDMA on body temperature in rodents (Malberg and Seiden, 1998) and primates (Banks et al., 2007). It would therefore be of interest to assess the influence of 5-HT_{2C} receptor agonists on AIH across a range of ambient temperatures. Notwithstanding these issues, the findings reported herein warrant further study of the pharmacological and neurobiological mechanisms underlying the role of serotonin systems in thermoregulation and AIH, and suggest that the maintenance of body temperature during surgery may be a new clinical use for 5-HT_{2C} receptor agonists.

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Fig. 1: Dose-related effects of ketamine on body temperature (N =7). Panel A shows the time course of rectal temperature before and after treatment with vehicle (saline) or various doses of ketamine normalized as an absolute change in temperature relative to the pre-injection baseline temperature. Panel B shows the integrated areas under of the curve of the time courses from the 0 to 90 min time points. All values represent the mean + S.E.M. ** = $P < 0.01$, *** = $P < 0.001$ as assessed by one-way analysis of variance followed by Dunnett's multiple comparison test.

Fig. 2: Effects of repeated administration of ketamine once per week for a total of 3 administrations (N = 7). Panel A shows the effects of repeated administration of ketamine at 100 mg/kg. Panel B shows the effects of repeated administration of ketamine at 180 mg/kg. All values represent the mean + S.E.M. There was no significant effect of repeated treatment at either dose as assessed by one-way analysis of variance.

Fig. 3: Dose-related effects of pretreatment with 5-HT_{2C} receptor agonists on ketamine-induced hypothermia (100mg/kg, IP). Panel A shows the effects of the non-selective 5HT_{2A/2C} receptor agonist 2,5-Dimethoxy-4-iodoamphetamine (DOI) on ketamine-induced hypothermia (N =7). Panel B shows the effects of the selective 5-HT_{2C} receptor agonist WAY-163909 on ketamine-induced hypothermia (N =7). The integrated areas under of the curve of the time courses from the 0 to 90 min time are shown for DOI in Panel C and WAY-163909 in Panel D. All values represent the mean + S.E.M. # = P < 0.05, ## = P < 0.01, and ### = P < 0.01 relative to vehicle pretreatment; ** = P < 0.01, and *** = P < 0.01 relative to ketamine administration, as assessed by one-way analysis of variance followed by Tukey's multiple comparison test.

Fig. 4: Effects of pretreatment with the selective 5-HT_{2C} receptor antagonist SB-242084 (0.3mg/kg, IP) on suppression of ketamine-induced hypothermia (100mg/kg, IP) by the selective 5-HT_{2C} receptor agonist WAY-163909 (1mg/kg, IP). Panel A shows the time course of rectal temperature before and after treatment as an absolute change in temperature relative to the pre-injection baseline temperature. Panel B shows the integrated areas under of the curve of the time courses from the 0 to 90 min time points. All values represent the mean + S.E.M. ## = P < 0.01 relative to treatment with ketamine following two vehicle pretreatments; *** =

$P < 0.01$ relative to pre-treatment with SB-242084 and vehicle as assessed by one-way analysis of variance followed by Tukey's multiple comparison test.

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