Role of serotonergic system in thermoregulation in rats

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Abstract The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is involved in the regulation of several basic physiological functions such as hormone secretion, sleep-wake cycle, motor control, immune system functioning, nociception, food intake, energy balance and thermoregulation. In addition, 5-HT participates in higher brain functions, such as cognition and emotional states, by modulating synaptic plasticity and neurogenesis. Furthermore, 5-HT has recently captured the spotlight in connection with depression, synthetic narcotic drugs, hot flash, central fatigue, etc. Regarding thermoregulation, many studies have examined the relationship between 5-HT and body temperature (Tb) regulation since the 1960s. Feldberg and Myers, in pioneering experiments, first reported that microinjection of 5-HT into the cerebral ventricles or hypothalamus induced a rise in Tb. Subsequently, research on 5-HT and regulation of Tb continued and topics in recent years include resolving of 5-HT receptor subtypes, such as 5-HT1A, 5-HT3, 5-HT7, and pinpointing a local area or network for thermoregulation. In this short review, I first outline the serotonergic system in the brain, summarize the history of research on 5-HT and thermoregulation, and finally focus on recent research in the 21st century.

Keywords: serotonin, serotonergic system, thermoregulation, serotonin receptor subtype

Introduction

It is critical for homeotherms, including human beings, to maintain core body temperature (Tb) to survive. To this end, we have thermoregulatory functions that can keep Tb constant. The importance of regulating Tb increases in high temperature environments, especially with abnormal weather in recent years. Actions of neurotransmitters that promote or control nerve cell activity are very important for various mechanisms within the brain, and various reports have researched the role of neurotransmitters in thermoregulatory mechanisms1-3). It is suggested that serotonin (5-HT), dopamine, and noradrenaline are the main neurotransmitters in the thermoregulatory system12,13). Several studies have examined the relationship between 5-HT and Tb regulation since the 1960s4,5). We also reported that perfusion of tetrodotoxin (TTX) into the median raphe nucleus (MRN), which contains the cell bodies of 5-HT neurons, induced a considerable decrease in Tb6). Further, we recently examined the mechanisms of decreases in Tb after perfusion of TTX into the MRN and dorsal raphe nucleus (DRN); this decrease was due to an increase in heat loss. And the role of the 5-HT projection from the MRN and DRN in thermoregulation is primarily in the heat loss system7). Thus, the involvement of the serotonergic system in thermoregulation is generally known.

Recently, the focus of 5-HT and thermoregulation research has been in solving which 5-HT receptor subtype (such as 5-HT1A, 5-HT3, and 5-HT7) and local areas or networks are responsible for thermoregulation. In this short review, I first outline the serotonergic system in the brain, summarize the history of research on 5-HT and thermoregulation, and finally focus on recent research in the 21st century.

Outline of the serotonergic system in the brain

5-HT is an important monoaminergic neurotransmitter that is involved in the regulation of a number of physiological functions and behaviors, including sleep, sex, locomotion, food intake, pain modulation, mood, stress, and thermoregulation8,9). The identification of 14 receptor subtypes mediating 5-HT action has opened a new area to explore in 5-HT-related neurophysiology10). The profusion of 5-HT receptors should eventually allow a better understanding of the different and complex processes in which serotonin is involved. The specific 5-HT receptors that participate in regulation of Tb are described later. A role for 5-HT is also expected in the etiology of several diseases, including depression, schizophrenia, anxiety and panic disorders, migraine, hypertension, pulmonary hypertension, eating disorders, vomiting and irritable bowel syndromes11).

The two main sources of 5-HT innervation of the forebrain are the DRN and MRN12,13). These raphe nuclei send serotonergic fibers to a variety of forebrain areas, the
main targets being the olfactory bulb, hypothalamus, septal area, thalamus, caudate-putamen, hippocampal region, amygdala, and cerebral cortex. It is also clear that a functional difference exists in these two projections. For example, Kucsera et al. showed differential roles of serotonergic projections arising from the DRN and MRN in hyperlocomotion. We also recently observed differences between manipulations of the DRN and MRN in freely moving rats. Although perfusion of TTX into the DRN or MRN decreases Tb by increasing heat loss and without changing heat production, its effects on locomotor activities were different. TTX infusion into the MRN induced hyperactivity, whereas immobility was observed during infusion into the DRN. Although the projection pathways from these raphe nuclei are related, we think that this difference will relate to mood swing behavior with a Tb decrease.

5-HT neurons in the medullary raphe nuclei, such as raphe pallidus, obscurus, and magnus also participate in the regulation of several physiological functions, including respiration, blood pressure, and Tb. In thermoregulation, the raphe pallidus is especially involved in forming a connection by receiving afferent and efferent information. Two reviews discussed the role of the medullary raphe nuclei in the regulation of Tb.

### History of research on 5-HT and thermoregulation

Several studies have examined the relationship between 5-HT and Tb regulation since the 1960s. Feldberg and Myers, in pioneering experiments, first reported that microinjection of 5-HT into the cerebral ventricles or hypothalamus induced a rise in Tb. Subsequently, research on 5-HT and regulation of Tb continued in the 1970s-80s by inhibition of 5-HT synthesis or direct application of 5-HT to thermosensitive neurons. For example, local application of 5-HT into the preoptic area and anterior hypothalamus (PO/AH), which are the crucial loci for maintenance of Tb, was reported to alter the activity of thermosensitive neurons. Moreover, many studies which used agonists/antagonists of 5-HT, such as cyproheptadine or methysergide, were also performed in the 1980s and reviewed by Clark and Lipton. According to this review, different results of Tb response were obtained after performing the same serotonergic pharmacological manipulations, and thus the authors concluded that the role of 5-HT in thermoregulation was obscure. This is likely because the vast majority of experiments have been pharmacological in nature. Furthermore, differences in the methodology employed, species of animals used, route of drug administration, drug dose, anesthetics used, restraint method, and ambient temperature have seriously complicated the interpretation of the collected data.

Although there is a textbook rich with information regarding the regulation of Tb by 5-HT from studies after 1990, the primary source apparently does not exist. However, Meeusen and colleagues have thoroughly reviewed research on the relationships between exercise, 5-HT, and Tb, including the central fatigue factor. Although the regulation of Tb differs between rest and exercise conditions, their research carefully addresses this issue.

### Recent research on 5-HT and thermoregulation in resting conditions

The focus of recent research regarding 5-HT and thermoregulation is on identifying the 5-HT receptor subtype and particular areas or networks involved in thermoregulation. The major studies addressing 5-HT and thermoregulation over the past ten years are shown in Table 1. Although the role of different 5-HT receptor subtypes in 5-HT-induced hypothermia attracted considerable attention, the problem cannot be considered solved. Many studies have focused on the role of 5-HT1A receptors in influencing Tb. Selective agonists of 5HT1A receptors produce a considerable hypothermic response. It was further shown that 5-HT1A receptor activation has effects on both heat loss and heat production. Not only 5-HT1A, but 5-HT3 and 5-HT7 have also captured the spotlight in recent years.

5-HT1A receptors draw attention due to their uniqueness in the brain 5-HT receptor system. 5-HT1A receptors are ligand-gated cation channels structurally and functionally distinct from all the other G-protein coupled 5-HT receptor types. Upon activation, 5-HT1A receptors permit the flow of Ca2+, Na+, and K+ ions.

5-HT7 receptors are also known to be involved in thermoregulation. Although Ootsuka and Blessing reported an effect of the 5-HT1A receptor agonist 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetratin) on thermoregulation, Naumenko et al. reported that the 5-HT7 receptor agonist LP44 (4-[2-(methylthio)phenyl]-N-(1,2,3,4-tetrahydro-2-naphthalen-1-yl)-1-piperazinenehexamide) induced a greater Tb decrease than 8-OH-DPAT. Voronova et al. also reported that the 5-HT7 receptor agonist m-CPBG (1-(3-chlorophenyl)biguanide hydrochloride) administered intracerebroventricularly resulted in a decrease in Tb. These results further demonstrated the involvement of central rather than peripheral 5-HT receptors in thermoregulation, and that both an increase in heat loss and decrease of heat production underlie the lower Tb.

Another important consideration is what region within the brain 5-HT is participating in regulation of Tb. Unfortunately, since the previous work introduced in this short review mostly utilizes intraventricular drug administration or has involved controlling activity at the 5-HT cell body, it cannot identify the locus of 5-HT action.

We have explored the particular area where 5-HT participates in thermoregulation as shown by Nagashima et al. using the microdialysis technique. This technique provides a solution to several experimental problems, such as anesthesia or restraint method, such that spe-
Table 1. Main studies of 5-HT and thermoregulation for the past 10 years.

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<tr>
<th>References</th>
<th>Species</th>
<th>Manipulation</th>
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<th>Dose</th>
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specific areas of the brain can be stimulated pharmacologically or neurotransmitters released in local brain areas can be collected in freely moving animals. Microdialysis is well established in the field of neuroscience as an effective technique\(^{49}\). We have combined microdialysis (EI-COM, Kyoto, Japan) with biotelemetry (TA11CTA-F40; Data Sciences International, USA), which measures Tb, heart rate (HR), and locomotion remotely in freely moving rats. In addition, we have measured 5-HT collected by microdialysis in particular areas with high performance liquid chromatography (HPLC; EI-COM, Kyoto, Japan).

First, we measured changes in Tb and levels of extracellular 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the thermoregulatory center PO/AH during cold (5°C) and heat (35°C) exposure. We also perfused fluoxetine (5-HT re-uptake inhibitor) and 8-OH-DPAT (5-HT\(_{1A}\) agonist) into the PO/AH. During both exposures, although Tb changed significantly, no significant changes were noted in extracellular levels of 5-HT and 5-HIAA in the PO/AH. In addition, although perfusion of fluoxetine or 8-OH-DPAT into the PO/AH increased or decreased extracellular 5-HT and 5-HIAA levels in the PO/AH respectively, Tb did not change. Our results suggest that 5-HT in the PO/AH may not mediate acute changes in thermoregulation\(^{49}\).

Second, we focused on the ventral tegmental area (VTA), which is an important area for regulating heat loss\(^{45}\), to determine the relationship between 5-HT levels in the VTA and thermoregulation in freely moving rats using microdialysis/biotelemetry techniques. During heat exposure, Tb increased by approximately 1.5°C, with an increase in tail temperature (Ttail) and a decrease in HR, suggesting activation of the heat loss response. 5-HT levels in the VTA increased after 1 hour of heat exposure. During cold exposure, Tb increased by approximately 0.8°C, with an increase in HR and a decrease in Ttail, suggesting activation of the heat production response. 5-HT levels in the VTA did not change during cold exposure. Perfusion of citalopram (5-HT re-uptake inhibitor) increased 5-HT levels in the VTA, resulting in a decrease in Tb by approximately 0.5°C and an increase in Ttail, but no change in HR. Therefore, we suggest that the VTA plays an important role in the regulation of heat loss response, and that 5-HT in the VTA is a key neurotransmitter (unpublished data).

Nakamura\(^{22}\) has reviewed the research on the thermoregulatory system with respect to brain anatomy in detail. He has shown that the PO plays a central role in receiving information on thermoregulation by integrating thermoregulatory inputs. In addition, the dorsomedial hypothalamus is a key area for controlling thermoregulatory responses against both cold and heat conditions. Furthermore, the rostral medullary raphe region and spinal cord also participate in the thermoregulatory circuit. Much of the network within the brain involved in the regulation of Tb has been described. However, the neurotransmitters in the forefront are gamma-aminobutyric acid (GABA) and glutamate. GABA and glutamate are undoubtedly some of the most important neurotransmitters in the brain. We also reported that GABA in the PO/AH plays a key role in disinhibition of heat production\(^{50}\). Future study on the relationships between 5-HT, GABA, and glutamate in thermoregulation may provide new insights because 5-HT is currently thought of as a neuromodulator rather than as a classical neurotransmitter\(^{51}\).

**Future directions**

There is an increasing possibility that, in the future, we will be living in a hotter environment in connection with global warming. For this reason, research is increasingly needed on the neurotransmitters or neuromodulators in the brain that are involved in the regulation of Tb. As mentioned, research on exercise, body temperature, and neurotransmitters in the brain is moving forward. For example, Hasegawa et al.\(^{52,53}\) and Takatsu et al.\(^{54}\) suggested that the main neurotransmitter for regulation of Tb is not 5-HT but dopamine or noradrenalin during exercise in hot environments. In these studies, since the animals perform forced exercise on a treadmill, the effect of voluntary exercise becomes a factor to consider.

In addition, in our advancing research on changes in neurotransmitter levels in the brain accompanying heat acclimation, we observed that dramatic changes in 5-HT and dopamine levels occur after heat acclimation. In addition to these findings, since the relationships between 5-HT and Tb and stress connected with depression\(^{55,56}\), hot flash\(^{57,58}\), and synthetic narcotic drugs like MDMA\(^{59-61}\) are attracting attention, further research is needed.

**Conclusion**

5-HT is an important neurotransmitter for thermoregulation through both heat loss and heat production. The 5-HT receptor subtypes that participate in this regulation, especially 5-HT\(_1\) and 5-HT\(_7\), rather than 5-HT\(_{1A}\), were discussed. In terms of the anatomical brain regions that participate in this regulation, the VTA or the DMH are the main candidate areas rather than the PO/AH.

**Conflict of Interests**

The author declare that there is no conflict of interests regarding the publication of this article.

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