Hypothalamic or Extrahypothalamic Modulation and Targeted Temperature Management After Brain Injury

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Targeted temperature management (TTM) has been recognized to protect tissue function and positively influence neurological outcomes after brain injury. While shivering during hypothermia nullifies the beneficial effect of TTM, traditionally, antishivering drugs or paralyzing agents have been used to reduce the shivering. The hypothalamic area of the brain helps in controlling cerebral temperature and body temperature through interactions between different brain areas. Thus, modulation of different brain areas either pharmacologically or by electrical stimulation may contribute in TTM; although, very few studies have shown that TTM might be achieved by activation and inhibition of neurons in the hypothalamic region. Recent studies have investigated potential pharmacological methods of inducing hypothermia for TTM by aiming to maintain the TTM and reduce the shivering effect without using antiparalytic drugs. Better survival and neurological outcome after brain injury have been reported after pharmacologically induced TTM. This review discusses the mechanisms and modulation of the hypothalamus with other brain areas that are involved in inducing hypothermia through which TTM may be achieved and provides therapeutic strategies for TTM after brain injury.

Keywords: therapeutic hypothermia, targeted temperature management, hypothalamus, pharmacological-induced hypothermia, electrical stimulation, brain injury

Introduction

CLINICAL AND ANIMAL STUDIES have shown that survival and neurological outcomes after brain injury can be significantly improved with the rapid administration of therapeutic hypothermia (TH) or targeted temperature management (TTM) (Huang *et al.*, 2015). Selecting and maintaining a constant temperature between 32°C and 36°C during TTM in comatose adult survivors after return of spontaneous circulation from cardiac arrest (CA) has been recommended by American Heart Association guidelines as a neuroprotective method (Callaway *et al.*, 2015). The effects of hypothermia after CA are complex and not fully understood (Schmutzhard *et al.*, 2012). A recent TTM study showed that TH at 33°C did not demonstrate additional benefit over TH at 35°C after CA, although equivalence between the two interventions was not concluded (Nielsen *et al.*, 2013). However, both study groups were targeted for fever avoidance and subjected to active cooling devices. Despite controversial opinions in interpreting the results from the aforementioned TTM study (Lu *et al.*, 2014; Nordberg *et al.*, 2014; Perchiazzi *et al.*, 2014; Stub 2014; Taccone and Dell'Anna, 2014; Varon and Polderman, 2014; Golan, 2015; Polderman and Varon, 2015), TTM has been extensively applied in post-CA patients (Arrich *et al.*, 2016;

Srivilaithon and Muengtaweepongsa, 2016). TTM has also been shown to improve outcomes after neonatal hypoxic-ischemic encephalopathy (Perman *et al.*, 2014), traumatic brain injury (TBI) (Suehiro *et al.*, 2014), refractory status epilepticus (Niquet *et al.*, 2015), and spinal cord injury (Saito *et al.*, 2013).

During TTM induction, ice packs or cold intravenous fluids are used to reduce the patient's core body temperature (BT) (Vaity *et al.*, 2015), but these methods cause forced hypothermia that may interrupt the normal physiological function of the brain and cause shivering (Logan *et al.*, 2011; Testori *et al.*, 2011), which is one of the most common side effects during TTM. Certain pharmacological agents, such as paralytics, narcotics, sedatives, or a combination of these agents, have been used to control shivering (Logan *et al.*, 2011; Testori *et al.*, 2011). To overcome such problems, research has been developed toward nonphysical induction of TTM such as pharmacological induction with different drugs (Jinka *et al.*, 2011; Katz *et al.*, 2012; Katz *et al.*, 2012; Knapp *et al.*, 2014; Katz *et al.*, 2015). Studies have suggested that TTM can be induced by activating (Osaka, 2010; Jeong *et al.*, 2015) or inhibiting (Nikolov and Yakimova, 2010; Cerri *et al.*, 2013) hypothalamic or other brain nuclei. Such modulation may interfere less with normal physiological conditions, but the detailed mechanisms still remain to be elucidated (Weng *et al.*, 2011; Katz *et al.*, 2012).

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Hypothalamus and Temperature Regulation

The hypothalamic region of the brain is well known to be involved in controlling BT through interactions between hypothalamic and other brain regions (Morrison, 2016). Apart from the hypothalamic area, there are different effector areas that are responsible for specific thermoregulatory responses. These effector areas are located throughout the brain stem and the spinal cord (Morrison, 2016). The activation or inhibition of different brain areas may help in inducing TH.

Role of Hypothalamus and Its Different Nuclei in Temperature Regulation

The regulation of BT is mainly under the control of the hypothalamus. The preoptic area (POA), a part of the anterior hypothalamus, is one of the major neuronal structures involved in controlling BT. It receives afferent input from peripheral thermoreceptors and performs temperature regulation (Morrison, 2016). Hypothalamic slice recordings suggest that the POA possesses different temperature-sensitive neurons like warm-sensitive (WS), cold-sensitive (CS), and temperature-insensitive neurons, with the majority being WS (Morrison and Nakamura, 2011). Different temperature-sensitive neurons in the POA are involved in activation of thermoregulatory effect (Morrison and Nakamura, 2011). For example, the median preoptic area (MnPO), a subregion in the POA (Nakamura, 2011), receives thermosensory signals (Nakamura and Morrison, 2008) from both warm and cool sensors in the skin through lamina I of the spinal cord and subsequently through the lateral parabrachial nucleus (Tanaka *et al.*, 2011; Jo, 2012). The MnPO then projects inhibitory thermosensory signals to the rostral medullary raphe (RMR) (Nakamura, 2011; Morrison, 2016). Activation of RMR increases heat production by activating sympathetic nerve activity to the interscapular

brown adipose tissue (iBAT) (Morrison, 2016). Thus, activation of MnPO neurons further inhibits RMR activity and causes heat loss (Nakamura and Morrison, 2008) (Fig. 1).

Activation of neurons in the dorsomedial hypothalamic nucleus (DMH) has been shown to elicit hyperthermia (Kataoka *et al.*, 2014), whereas inhibition decreases iBAT temperature (Morrison, 2016). Activation of neurons in the DMH activates glutamate receptors in the rostral raphe pallidus (rRPa), triggering sympathoexcitation and thermogenesis (Kataoka *et al.*, 2014), whereas gamma-aminobutyric acid (GABA)-ergic neurons in the POA appear to provide a key source of the tonic inhibitory input to sympathetic nerve fibers in the DMH to decrease iBAT temperature (Morrison, 2016). In a normothermic environment, GABAergic neurons in the POA tonically inhibit the DMH. However in a cold environment, signals from somatosensory nerves in the skin activate GABAergic neurons suppressing the tonic firing of the DMH neurons; in turn, neurons in the rRPa controlling BAT sympathetic tone are stimulated, which results in stimulating thermogenesis, and vice versa for reverse thermogenesis in warm conditions (Contreras *et al.*, 2015).

Electrophysiological Pattern of the Hypothalamus During Hypothermia

Hypothalamic neurons possess different types of neurons such as WS, CS, and temperature-insensitive neurons. The activities of these different hypothalamic neurons vary with changes in BT. Firing rates of CS neurons in the POA by the intracellular recordings progressively decrease as BT increases from 32.4°C to 34.5°C and are completely inhibited at a temperature of 37.2°C (Curras *et al.*, 1991). The firing rates of WS neurons increase concomitantly with increases in BT. This shows a significant difference in the firing rates of

FIG. 1. Showing the cold defense signal from skin to the higher neural center. The cold signal from the skin travels through lamina 1 of spinal cord to the LPB, which further sends excitatory input to the MnPO. The MnPO then inhibits the medial preoptic nucleus located in MPO. Inhibition of the MPO withdraws the inhibitory input to the DMH and this withdrawal excites the rRP. The rRP excitation sends excitatory sympathetic input to BAT and thus finally causes thermogenesis. MnPO, median preoptic area; MPO, hypothalamus.

CS and WS neurons between 32°C and 36°C (Griffin *et al.*, 1996). The firing rates of CS cells are most likely inhibited by WS neurons with increases in BT, while the frequency of inhibitory postsynaptic potentials of WS neurons decreases while cooling the hypothalamic area (Boulant, 2006).

Intracellular electrophysiological activity was recorded from temperature-sensitive and temperature-insensitive neurons in rat POA tissue slices using a whole-cell patch clamp perfused with either arginine vasopressin (AVP) or vasopressin receptor-1 antagonist (V_{1a}). AVP increased the spontaneous firing rate in 65% of WS neurons and decreased nearly 50% of CS and temperature-insensitive neurons. Perfusion of V_{1a} resulted in the opposite effect of AVP. Since excited WS neurons or inhibited CS and temperature-insensitive neurons promote heat loss or suppress heat production and retention, it was suggested that AVP excites WS neurons and inhibits CS in the POA through vasopressin receptors (Tang *et al.*, 2012) and produces hypothermia.

Activation and/or Inhibition of Hypothalamic Neurons for TTM

Hypothalamic nuclei help in maintaining BT, and with the advancement of knowledge of different hypothalamic nuclei and their role in temperature regulation, various studies have started to focus on inducing hypothermia by activating and

inhibiting different hypothalamic nuclei through pharmacological drug stimulation, receptor activation, or electrical stimulation (Table 1).

Pharmacological activation of hypothalamic neurons for TTM

Attempts have been made to activate different hypothalamic regions to induce hypothermia. Microinjection of nor-adrenaline (NA) into the POA induces hypothermia (Mallick and Alam, 1992; Vetrivelan *et al.*, 2006) by activating α_1 -adrenoceptors (Mallick *et al.*, 2002; Vetrivelan *et al.*, 2006; Jha and Mallick, 2009) and α_2 -adrenoceptors (Quan *et al.*, 1992; Romanovsky *et al.*, 1993). Activation of α_1 -adrenoceptors activates WS neurons in the POA and inhibits CS neurons, thus producing hypothermia (Jha and Mallick, 2009; Osaka, 2009). NA-induced hypothermic and antipyretic effects were mediated through nitric oxide (NO) in the POA, as demonstrated by prior microinjection of NO synthase inhibitor N^G-monomethyl-L-arginine (5 nmol), which attenuated the hypothermic effect induced by NA (Osaka, 2010). In a different study, when cholinergic stimulation was performed in the POA with neostigmine (an acetylcholine esterase inhibitor), a fall in rectal temperature and an increase in Fos-immunoreactivity (Fos-IR) were seen in the paraventricular nucleus, supraoptic nucleus, and the MnPO. An increase in Fos-IR suggests the

TABLE 1. COMPARISON OF DIFFERENT DRUGS AND THEIR EFFECT ON MODULATION OF BODY TEMPERATURE

<i>Drug</i>	<i>Administration site</i>	<i>Mode of action</i>	<i>Studied by</i>	<i>Comment</i>
CCK Octapeptide	Intravenous	Possibly due to activation of CCK-B (central type) receptors located in the hypothalamus. Skin vasodilation and blood pressure reduction	Weng <i>et al.</i> (2011)	Induces hypothermia and improves neurological outcome after ventricular fibrillation
CHA	Subcutaneous	Activation of A1ARs in the CNS	Jinka <i>et al.</i> (2015)	Induces hypothermia and improves neurological outcome after CA
ADAC	Substantially	Activation of A1ARs in the CNS	Bischofberger <i>et al.</i> (1997)	Induces hypothermia and induces neuroprotection after ischemic brain injury
Muscimol	Periaqueductal gray	By inhibiting sympathetic nerve activity to interscapular brown adipose tissue	de Menezes <i>et al.</i> (2006)	Decreased body temperature
DHC	Subcutaneous	By activating TRPV1	Cao <i>et al.</i> (2014)	Induces hypothermia
2-DG	Intravenous	By inhibiting the activity of raphe pallidus by increasing activity of GABA _A receptor	Osaka (2015)	Induces hypothermia
L-glutamate	LPO	By inhibiting heat producing area	Osaka (2012)	Decreases rectal temperature
Senktide	MnPO	Activates the NK ₃ R in MnPO and causes heat dissipation	Dacks <i>et al.</i> (2011)	Decreases core body temperature
Neuropeptide Y	Intracerebral ventricular	By inhibiting sympathetic nerve activity to interscapular brown adipose tissue	Billington <i>et al.</i> (1991)	Induces hypothermia
NTR agonist HPI201	Bolus and intraperitoneal	Activation of NTRs in brain	Gu <i>et al.</i> (2015); Wei <i>et al.</i> (2013)	Induces hypothermia and improves neurological outcome after TBI and stroke

2-DG, 2-deoxy-D-glucose; A1ARs, activation of adenosine A1 receptors; ADAC, adenosine amine congener; CA, cardiac arrest; CCK, cholecystokinin; CHA, ⁶N-cyclohexyladenosine; CNS, central nervous system; DHC, dihydrocapsaicin; GABA_A, gamma-aminobutyric acid(A); NTR, neurotensin receptor; TBI, traumatic brain injury; TRPV1, transient receptor potential vanilloid channel 1.

roles of different cholinergic neurons located in the hypothalamus, which act through activation of muscarinic receptors and cause hypothermia (Takahashi *et al.*, 2001). L-glutamate microinjection into the lateral preoptic area also decreases BT by tonic inhibition of heat production and vasodilation (Osaka, 2012). These studies suggest that hypothermia may be induced by pharmacological activation of certain hypothalamic nuclei, which may help in inducing TTM.

Pharmacological inhibition of hypothalamic neurons for TTM

Experimental evidence supports the involvement of inhibitory GABAergic systems in thermoregulation (Jha *et al.*, 2001; Frosini *et al.*, 2003a, 2003b). GABA_A agonists and GABA itself act on presynaptic GABA_A heteroreceptors and help in releasing NA, which excites WS neurons, then increases heat dissipation, and generates hypothermia (Jha *et al.*, 2001).

Microinjection of muscimol (a GABA agonist) into the DMH has also been shown to decrease body core temperatures, whereas prior microinjection of muscimol into the DMH attenuated the hyperthermic effect produced by 3,4-methylenedioxymethamphetamine (MDMA) in the DMH. MDMA increases heat production by activating sympathetic nervous activity to brown adipose tissue (BAT) (Blessing *et al.*, 2006) and constricting cutaneous blood vessels, thus reducing dissipation of body heat (Pedersen and Blessing, 2001). Inhibiting neurons in the DMH with muscimol prevents MDMA-evoked hyperthermia and shows that DMH neurons play an important role in controlling heat generation in iBAT and possibly cutaneous blood flow (Zhang and Bi, 2015). Activation of neurons in the DMH increases sympathetic outflow, which in turn increases heat production (Zhang and Bi, 2015). This is due to the efferent connections from the DMH to the medullary raphe pallidus (RPa) where sympathetic premotor neurons controlling metabolic activity to iBAT are located (Cao *et al.*, 2004). Therefore, inhibiting the DMH may suppress MDMA-evoked hyperthermia by preventing iBAT thermogenesis and cutaneous vasoconstriction (Rusyniak *et al.*, 2008). Pharmacological inhibition of certain hypothalamic nuclei may induce hypothermia.

Receptor activation of hypothalamic neurons for TTM

Specific receptor activation in hypothalamic regions induces hypothermia. Focal microinfusion of neurokinin-3 receptor (NK₃R) agonist Senktide into the MnPO has been reported to decrease core temperature (Dacks *et al.*, 2011). Senktide activates the NK₃R present in the MnPO and causes heat dissipation from the body (Nakamura and Morrison, 2010).

The role of vasopressin receptor has been studied in inducing hypothermia. Infusion of AVP or V_{1a} receptor agonist excites WS neurons, inhibits CS and temperature-insensitive neurons, and ultimately induces hypothermia (Tang *et al.*, 2012). Since the V_{1a} antagonist does the opposite of AVP, this study shows that AVP modulates the activity of temperature-sensitive and temperature-insensitive neurons in the POA through the V_{1a} receptor.

Extrahypothalamic Pharmacological Injection and TTM

In addition to hypothalamic modulations, decrease in BT can be induced by intravenous (i.v.), intraperitoneal (i.p.),

and intracerebroventricular (i.c.v.) injection of drugs such as GABA (Nikolov and Yakimova, 2010), cholecystokinin octapeptide (Weng *et al.*, 2011), cannabinoid receptor agonists (Rawls *et al.*, 2002), and anabolic neuropeptides like neuropeptide Y (Bi *et al.*, 2012; Bi, 2013). Intravenous administration of 2-deoxy-D-glucose (2-DG) (200 mg/mL per kg) decreases BAT temperature ($-1.1 \pm 0.2^\circ\text{C}$) (Madden, 2012).

i.c.v. injection of GABA, GABA_A, and GABA_B agonists causes decrease in rectal temperature by decreasing or inhibiting gross motor behavior, as well as inhibiting muscle tone (Frosini *et al.*, 2004). Cholecystokinin causes activation of cholecystokinin B (CCK-B) receptors located in the hypothalamus and causes hypothermia (Szelenyi, 2001). Injection of cannabinoid agonists causes activation of cannabinoid receptors (CB₁) located in the POA, lateral hypothalamic area (Tsou *et al.*, 1998; Moldrich and Wenger, 2000), ventromedial hypothalamus, as well as other hypothalamic regions involved in BT regulation (Azad *et al.*, 2001). Activation of CB₁ leads to inhibition of potassium-evoked neuronal NO synthase and decreases NO, which is responsible for maintaining normal BT, and thus decreases BT (Hillard *et al.*, 1999). Central administration of neuropeptide Y suppresses the sympathetic nerve activity to iBAT and decreases thermogenesis (Bi *et al.*, 2012; Bi, 2013). 2-DG (250 mg/mL, i.v.) inhibits the activity of RPa in rat by increasing the activity of GABA receptors and induces hypothermia (0.4°C decrease) (Osaka, 2015).

Electrical stimulation

Apart from pharmacological induction and receptor modulation to induce hypothermia, some studies reported that electrical stimulation of certain hypothalamic brain regions induced hypothermia. Mild electrical stimulation (monophasic square-wave pulses: 15 Hz, 7.0 μA , 0.5 ms) to the ventromedial hypothalamic area has been reported to reduce iBAT (net decrease = 0.2°C) and colonic temperature (net decrease = 0.07°C) (Woods and Stock, 1994). One possible explanation from the authors is that, at a lower frequency, inhibitory neurons are more active. These inhibitory neurons might have inhibited the sympathetic activity to iBAT. Thus, effects, including a decrease in iBAT and colonic temperature, were observed.

Other than the electrical stimulation of hypothalamic neurons, electrical stimulation (square wave pulses of 10 second duration, 50 Hz and 100 μA) to pars compacta of the substantia nigra compacta (SNC) located in middle brain region has also been shown to induce hypothermia (net decrease = 0.6°C) in rats when maintained at lower temperature (Below 22°C) (Lin *et al.*, 1992). Electrical stimulation to SNC releases striatal dopamine through nigrostriatal region and induces hypothermia by dopaminergic pathway (Lin *et al.*, 1992). Electrical stimulation (0.1 ms, 1 mA, 10 Hz) of the lower midbrain around retrorubral field has been shown to decrease the temperatures of brown fat ($0.33 \pm 0.03^\circ\text{C}$) and the rectum ($0.10 \pm 0.01^\circ\text{C}$) in anesthetized Wistar rats and hamsters (Hashimoto, 1999). Electrical stimulation to the midbrain region activates the raphe nucleus, which in turn activates WS neurons located in the thalamus. This results in tonic inhibition of BAT thermogenesis and decreases rectum temperature (Hashimoto, 1999). Electrical stimulation (500 ms stimulation trains, $25 \times 300 \mu\text{A}$ square wave cathodal pulses of 100 μs duration) to the zona incerta (horizontally elongated region of gray matter cells in the subthalamus below the thalamus) also decreases temperature in

brown fat (0.2–0.8°C) possibly by inhibiting the sympathetic supply to the intercostal nerves and cooling the blood entering the BAT due to an induced thermodilatory effect in the tail of the rat (Kelly and Bielajew, 1996). Although these preclinical studies reported that electrical stimulation led to decrease in BT, there is a lack of recent studies verifying these techniques and applying them for TTM in animal models after brain injury since these techniques have been reported before the era of TTM.

Hypothermia and Torpor-Like State

Some mammals naturally induce a torpor-like state to decrease their metabolic energy requirements by decreasing their BT in harsh conditions such as food scarcity or exposure to cold temperatures (Andrews *et al.*, 2011). The neural mechanism leading to hypothermic torpid state is not clear. It has been shown that central activation of the adenosine A1 receptor (A1AR) induces hypothermia and generates a torpor-like state (Jinka *et al.*, 2011; Iliff and Swoap, 2012) in both rats (Tupone *et al.*, 2013) and mice (Muzzi *et al.*, 2013). Injection of ⁶N-cyclohexyladenosine (CHA), an A1AR agonist, has also been shown to induce hibernation (Jinka *et al.*, 2011; Jinka *et al.*, 2015). Central activation of the A1AR inhibits thermogenesis through activation of the BAT sympathoinhibitory pathway. Furthermore, A1ARs are mainly inhibitory receptors and their synaptic activation causes inhibition of neurotransmitter release (Wetherington and Lambert, 2002). A1AR also causes inhibition of GABA release (Ulrich and Huguenard, 1995; Pickel *et al.*, 2006) onto inhibitory nucleus tractus solitarius (iNTS) neurons (Cao *et al.*, 2010). Activation of inhibitory iNTS neurons causes inhibition of BAT and shivering thermogenesis. A1AR-mediated inhibition of BAT and shivering thermogenesis arises from the inhibition of the sympathetic neurons, which are located in rRPA and control the cold defense thermal effect (Nakamura and Morrison, 2011; Morrison *et al.*, 2012).

Pharmacological-Induced Hypothermia for TTM After Brain Injury

Since TTM can be achieved by pharmacological administration of drugs, various studies have been performed to evaluate the effect of pharmacologically induced hypothermia after CA on survival and neurological outcomes. Shivering is one of the most common side effects in TTM (Presciutti *et al.*, 2012), and it abolishes the effect of hypothermia in CA patients (Zgavc *et al.*, 2011). However, controlling the shivering is very difficult, especially in conscious patients (Testori *et al.*, 2011). The pharmacological studies showed the advantage of pharmacologically induced hypothermia over forced hypothermia in the way that it reduced or abolished the shivering effect normally caused during forced hypothermia (Katz *et al.*, 2012; Jinka *et al.*, 2015).

Cholecystokinin (CCK) is found as sulfated octapeptide (CCK-8S) in the central nervous system (Bowers *et al.*, 2012). CCK mediates its action by activating CCK receptors, which are located throughout the nervous system. Intravenously administered cholecystokinin octapeptide (200 µg/kg in 0.3 mL saline) has been used to induce mild hypothermia in rats. CCK attenuated postresuscitation myocardial dysfunction and improved neurologic outcomes and duration of survival following cardiopulmonary resuscitation (Weng *et al.*, 2011). Although the mechanisms remain to be well established and

controversy exists regarding the blood–brain barrier (BBB) permeability after CA (Tress *et al.*, 2014), an infusion of CCK may cross the BBB and impair permeability to smaller molecules after cerebral ischemia (Dobbin *et al.*, 1989) and activate CCK-B (central type) receptors located in the hypothalamus (Weng *et al.*, 2011).

HBN-1 (30 mL/kg bolus of premixed solution (1.89 g/kg of ethanol, 0.08 U/kg of vasopressin, and 2 mg/kg of lidocaine) over 30 minutes followed by 3 mL/(kg · h) infusion for 12 hours (2.27 g/kg of ethanol, 0.096 U/kg of vasopressin, and 2.4 mg/kg of lidocaine)) was developed as a pharmacological alternative to physical methods to induce a regulated state of TH and lower core temperature from 37.5°C to 34°C in rats. Core temperature was maintained between 33°C and 34°C without resulting in shivering for more than 13 hours in an environmental temperature of 19°C (Katz *et al.*, 2012). Ethanol has been reported to cause heat dissipation by peripheral vasodilation and sweating (Yoda *et al.*, 2005), and a combination of ethanol with vasopressin and lidocaine helps in facilitating effect of ethanol for longer by reducing the tolerance of the body to ethanol-induced hypothermia (Daikoku *et al.*, 2007). HBN-1 was shown to reduce the surrogate biomarkers (Serum and cerebral spinal fluid neuron-specific enolase activity) of brain injury in rats compared to forced hypothermia (Katz *et al.*, 2012). HBN-1 (ethanol 3.03 g/kg, vasopressin 0.13 U/kg, and lidocaine 3.2 mg/kg) intravenous injection pharmacologically induced hypothermia in rats, which improved survival and neurological outcomes after CA (Katz *et al.*, 2015). The time required to induce hypothermia after CA could be reduced by nearly 50% with the use of HBN-1 alone compared to the forced hypothermia method, by surface cooling or intravenous cooling in rats (Katz *et al.*, 2015). The mechanism involved in lowering the BT remains unclear, although it was suggested that it might be due to suppression of the heat producing area or stimulation of the heat losing area located in hypothalamus (Katz *et al.*, 2012). The use of HBN-1 in clinical studies still requires further investigation.

Recently, a new method was developed to maintain BT between 29°C and 31°C in rats by keeping them to an ambient temperature of 16°C with the combination injection of two drugs at a 4-hour interval: A1AR agonist CHA (1 mg/kg, intraperitoneally) with 8-(p-sulfophenyl) theophylline (8-SPT (25 mg/kg, intraperitoneally) (Jinka *et al.*, 2015), a nonspecific adenosine receptor antagonist which cannot easily cross the BBB (Jinka *et al.*, 2015). Activation of adenosine-1 receptors with CHA caused a hypothermic and torpor-like condition (Jinka *et al.*, 2011; Iliff and Swoap, 2012; Tupone *et al.*, 2013) and inhibited shivering, as well as nonshivering thermogenesis (Tupone *et al.*, 2013). Administration of CHA causes bradycardia, whereas prior injection of 8-SPT reverses the bradycardia produced by CHA without affecting BT. Authors suggested that with CHA treatment, the animals having CA survived better and showed less neuronal cell death compared to normothermic animals. Despite a low ambient temperature, central activation of A1AR in combination with a thermal gradient might be a way for pharmacologically induced TTM. Adenosine receptors are widespread and ubiquitously present throughout the body and influence various physiological and pathophysiological functions of the body (Fredholm *et al.*, 2005); thus the effects of adenosine receptor activation or inhibition may not be sufficient to suggest that delivery of adenosine is clinically effective and safe (Chen *et al.*, 2013).

Dihydrocapsaicin (DHC) (1.25 mg/kg, subcutaneous in C57BL mice), which is transient receptor potential vanilloid channel 1 (TRPV1), has been shown to induce hypothermia. TRPV1 is activated by heat, as well as its agonist, and expresses in WS nerve fibers (Yang *et al.*, 2010). TRPV1 has a very significant role in thermoregulation, but the exact mechanism has not been discovered (Moran *et al.*, 2011; Nilius, 2013). Infusion of DHC induced hypothermia and had a neuroprotective effect in stroke, as well as ischemic reperfused mice (1.25 mg/(kg·h)) (Cao *et al.*, 2014) and rats after CA (0.75 mg/(kg·h)) (He *et al.*, 2016), but further more animal and clinical studies are needed.

Neurotensin receptor (NTR) agonist HPI201 (also known as ABS201) has been reported to pharmacologically induce TTM, reduce shivering, and attenuate TBI in the developing rat brain (i.p. 2 mg/kg) (Gu *et al.*, 2015). When administered (first bolus 2 mg/kg, and followed by 1 mg/kg, intraperitoneal injection) HPI201 induced overall 2–3°C dose-dependent reduction of body and brain temperature, reduced neuronal and BBB damage, attenuated inflammatory response, and promoted functional recovery after stroke in mice (Wei *et al.*, 2013). NTR is present on serotonin neurons located in the nucleus raphe magnus and dorsal raphe in brain and increases the firing of serotonergic neurons. It also affects other functions modulated by the serotonergic system, which includes antinociception, sleep wake cycle, and stress (Boules *et al.*, 2013). These preclinical studies require more investigations before moving to future clinical translation.

Medical Gas-Induced TTM and the Effect After Brain Injury

Gases like NO (Almeida and Branco, 2001) and hydrogen sulfide (H₂S) (Mooyaart *et al.*, 2016) have been used to induce hypothermia. NO induces hypothermia through opioid receptors (Benamar, Geller *et al.*, 2002). Hydrogen sulfide binds to cytochrome oxidase and, thereby, prevents oxygen from binding, which leads to the dramatic slowdown of metabolism and thus regulates BT (Roth and Nystul, 2005). Hydrogen sulfide serves as an endothelium-derived relaxing factor (EDRF), endothelium-derived hyperpolarizing factor (EDHF), and vasodilator (Lefer, 2007; Paul and Snyder, 2012). Although H₂S has been shown to induce hypothermia in mice (Volpato *et al.*, 2008) and rats (Lou *et al.*, 2008), this methodology remains controversial as it fails to induce hypothermia in larger animals (Li *et al.*, 2008; Drabek *et al.*, 2011).

H₂S has been shown to improve outcome after CA (Minamishima *et al.*, 2011; Kida *et al.*, 2014). The neuroprotection may be due to hypothermia itself (Mooyaart *et al.*, 2016) or attenuation of Caspase 3 that causes cell death in the brain (Minamishima *et al.*, 2009). More future studies are needed to confirm these findings.

Conclusion

The hypothalamus is one of the major regulatory centers of BT with the POA as one of the major regulatory subareas. Modulating hypothalamic regions through pharmacological and electrical stimulation methods might contribute to TTM. Hypothalamic activation induces hypothermia by vasodilation, whereas pharmacological inhibition of certain brain areas, like DMH with GABA, results in hypothermia in preclinical animal models. Pharmacological drugs like CCK, GABA, neuropeptide

Y, 2-DG, CHA, HBN-1, and DHC have been reported to induce hypothermia or TTM in preclinical studies generally as single or small series reports from single laboratories. Further large investigation is needed to verify these techniques and evaluate their effect on TTM after brain injury toward clinical translation.

Acknowledgments

This work was supported by R01HL118084 from National Institutes of Health (to X.J.). R.C. Choudhary and X. Jia were supported by NIH R01HL118084.

Author Disclosure Statement

No competing financial interests exist.

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