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Review

Hibernation-Like Behavior Induced by 2-Methyl-2-Thiazoline and Its Organ-Protective Effects and Mechanisms

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Abstract

Hibernation is a prolonged state of low metabolism that animals enter in response to extreme environmental conditions to enhance their survival in harsh environments. Recent studies have shown that non-hibernating species can also be induced to enter a hibernation-like state. 2-methyl-2-thiazoline (2MT), a potent analog of fox odor, can induce fear-related behavior in mice with low body temperature and low metabolism, and has specific organ-protective effects. A systematic understanding of 2MT-induced hibernation and its underlying mechanisms may aid in expanding its applications in medicine and other fields.

Keywords: 2-methyl-2-thiazoline; hibernation state; organ protection; neural mechanisms; oxidative stress; metabolism

1. Introduction

In extreme conditions such as cold winter or food scarcity, many mammals initiate an adaptive energy-saving survival strategy known as hibernation [1]. During hibernation, the energy consumption of an animal is greatly reduced and it can spontaneously return to an active state when disturbed. The ability of this long-term low metabolic state to prevent organ damage has attracted considerable attention and subsequent discussion. Studies have shown that various methods induce hibernation-like states in non-hibernating species. Among them, 2-methyl-2-thiazoline (2MT) has gradually become a research focus due to its ability to induce a significant decrease in animal body temperature and metabolism, as well as its strong organ-protective effects [2]. Starting from an overview of hibernation and its research significance, this paper comprehensively summarizes the research progress of induced hibernation-like behavior in non-hibernating animals and the organ-protective effects and mechanisms of 2MT-induced hibernation-like behavior. The aim is to provide new ideas for clinical implementation of artificial hibernation.

2. Inspiration and Prospects of Artificial Hibernation

Thermostatic heat-absorbing animals are generally capable of maintaining a constant body temperature over a wide range of ambient temperatures to maintain normal life activities [3,4]. However, when faced with low temperatures or food scarcity, many mammals can lower their body temperature by adjusting their metabolic rate, reducing their core body temperature to a range far below their steady-state set point to conserve energy [5,6]. This state is known as hibernation. Data collected to date indicates that the average minimum body temperature of animals can reach 5.8 °C during hibernation, with the body temperature of many species dropping below 0 °C [7]. Long-term hypothermia can result in irreversible damage to the body, including ischemia and hypoxia of vital organs such as the heart and brain. Nevertheless, hibernating animals can recover their physiological functions and survival abilities completely after awakening from the hibernation states. The enormous clinical potential of artificial hibernation has gradually become a focus of research and significant progress has been made [8]. Existing studies have demonstrated that artificially induced hibernation-like states have a protective effect on irreversible brain damage caused by various diseases [9,10]. According to the recommendations of the National Institutes of Health, artificial hibernation can create enormous therapeutic value in terms of neural protection after traumatic brain injury and stroke [11]. In surgical operations, artificial hibernation also helps improve the preservation of *ex vivo* transplanted organs, increase their survival rate, and reduce organ damage and transplant failure caused by long-term cold storage and local ischemia-reperfusion [12]. In the future, many incurable cancers may also be cured through artificial hibernation.

3. 2-MT and Other Artificial Hibernation Induction Methods

Several studies have indicated that predator odors, fox secretions, and cat collars convey information that induces fearful behavioral responses in mice, resulting in a de-

Table 1. The thermoregulatory properties of 2MT and comparative analysis of related cooling strategies.

	Animal	Inducion Method	Minimum Temperature	Duration
2MT	Mouse	Inhale 10 mg/kg	24 °C	>12 h
		SC 50 mg/kg	34 °C	8 h
TMT	Mouse	Exposed to 20 µL 30 min	Drop by 1.7 °C	3 h
5′-AMP	Mouse	IP 10.0 mmol/g	24 °C	12 h
2-DG	Hamster	IP 2500 mg/kg	25 °C	5 h
H_2S	Mouse	Inhale 80 mg/kg	15 °C	3 h
Fasting	Mouse	Food-restricted for 24 h	24 °C	10 h
Hypoxia	Mouse	7% O_2 exposure 120 min	13 °C	2 h
Qrfp neuron	Mouse	Chemogenetic activation	25 °C	>7 d
avMLPA^{Vglut2} and avMLPA^{Adcyap1}	Mouse	Chemogenetic activation	Drop by 5.9 °C and 6.3 °C	>14 h

2MT, 2-methyl-2-thiazoline; TMT, 2,4,5-trimethyl-3-thiazoline; 5′-AMP, adenosine-5′-monophosphate; 2-DG, 2-deoxy-D-glucose; Qrfp, pyroglutamylated RFamide peptide; avMLPA, Medial and lateral preoptic area; Vglut2, vesicle glutamate transporter 2; SC, Subcutaneous injection; IP, Intraperitoneal injection; Adcyap1, adenylate cyclase activating polypeptide 1.

crease in body temperature and metabolism [13,14]. Early behavioral studies have shown that this fearful behavior in mice can be induced by artificial overstimulation [13]. The development of 2MT optimized from 2,4,5-trimethyl-3-thiazoline (TMT) in fox secretions induces the strongest fearful behavioral response in mice, with activity more than 10 times greater than that of other fear odors [2,15]. Matsuo *et al.* (2021) [16] found that inhalation of 2MT caused a 10 °C drop in body temperature of mice within five hours, which decreased to a minimum of 24 °C over the following seven hours. After discontinuing the inhalation of 2MT for one week, mouse body temperature and behavior returned to normal.

Other methods also induce artificial hibernation, each with its own characteristics (Table 1). Dawe *et al.* (1969) [17] conducted an experiment in which they extracted serum from squirrels that had not awakened from hibernation and injected it into other squirrels. Results showed that injected squirrels immediately entered a state of hibernation. However, it was necessary to ensure that the hibernating animals were not awakened during the blood extraction process. After analyzing blood components in the serum of hibernating animals, small and large molecules were found that were respectively capable of either inducing or inhibiting hibernation. The relative concentration changes of these two molecules in the blood controlled the entire hibernation cycle [18]. This experiment was the first to induce hibernation in animals and demonstrated the possibility of artificially induction. Mice cannot hibernate in their natural environment, but can induce torpor bouts and a short-term decrease in body temperature through fasting, which may be related to a decrease in glucose supply [8]. However, exposure to TMT blunts the daily torpor of calorically restricted mice [19]. Mice receiving adenosine-5′-monophosphate (5′-AMP) can lower their body temperature, and decrease blood glucose levels while increase fatty acid levels [20]. To determine the metabolic signals that induce a decrease in body temperature in mice, Dark *et al.* [21] used 2-deoxy-D-glucose (2-DG) and mercaptoacetate (MA) to respectively inhibit glycolysis and lipid oxidation in hamsters. Results showed that 2-DG induced a fall in the core body temperature of hamsters to below 30 °C, while MA had no effect [21]. Blackstone *et al.* [22] found that the average body temperature of mice could be lowered by up to 15 °C after inhaling hydrogen sulfide gas. Additionally, repeated hypoxia can also cause severe hypothermia in mice which may have a protective effect on brain ischemia and hypoxia [4]. Further, it has now been found that direct manipulation of neurons in the brain also induces hibernation-like behavior. After using the DREADDs (design receptors specifically activated by design drugs) system to stimulate neurons expressing pyroglutamylated RFamide peptide (Qrfp), mice also enter an extremely long-lasting state of regulated hypometabolism, Qrfp neurons were found in the anteroventral periventricular nucleus (AVPe), medial preoptic area (MPA), and periventricular nucleus [23]. Additionally, further investigations using optogenetic approaches have revealed that Q-neurons act to induce artificial hibernation primarily by projecting to the dorsomedial hypothalamic nucleus (DMH) [23]. Hrvatin *et al.* [8] analyzed the neurons in the medial and lateral preoptic area (avMLPA) and used single-cell RNA sequencing to ultimately identify a subset of hibernation-driving neurons marked by the gene for vesicle glutamate transporter 2 (*Vglut2*) and the peptide for adenylate cyclase activating polypeptide 1 (*Adcyap1*). Simultaneously, the neural circuit regulating hunger, temperature, and energy balance was also activated. These studies were the first to reveal the neural pathway regulating hibernation-like states and laid the foundation for exploration of the neural circuit mechanisms regulating extreme low temperature and metabolism states.

It is clear that there are various substances and methods available for inducing a hypothermic state, but the degree and duration of hypothermia induced by different methods are not entirely consistent. It is not known whether there is a unified mechanism mediating the generation of hibernation-like behavior. This remains a subject for investigation. Compared to other methods, subcutaneous in-

Table 2. The key findings of 2MT in organ protective research.

Reference	Year	Animal	Model	Route of administration and dosage of 2MT	2MT function
Matsuo *et al*. [16]	2021	Mouse	Hypoxia (4 % O_2 condition) Cutaneous I/R injury Cerebral I/R injury	Inhale 10 mg/kg 30 min Exposed to 100 µL 30 min IP 1% 2MT (100 µL)	Enhance hypoxia resistance ability Reduce the level of I/R injury
Matsuo *et al*. [25]	2020	Mouse	Lethal endotoxic shock (LPS-induced)	IP 1% 2MT (200 µL)	Suppresses excessive inflammation Potentiates cellular immunity
Onoe *et al*. [26]	2022	Rabbit	Endotoxin shock (LPS-induced)	IV 80 mg/kg	Improves circulatory dynamics
Nishi *et al*. [24]	2022	Mouse	Cardiac I/R injury	SC 50 mg/kg	Cardiac protective effect

I/R, ischaemia/reperfusion; LPS, lipopolysaccharide; IV, intravenous injection.

jection of 2MT at a dose of 50 mg/kg lowers mouse body temperature to a minimum of 34 °C [24]. Other methods achieve lower temperatures and it is important to clarify how this cooling both protects animals and enables them to recover without damage. Such knowledge may contribute to the ability to use lower temperatures for better and longer organ protection in future clinical practice.

4. Organ Protective Effects of 2MT-Mediated Hibernation-Like Behavior

2MT significantly reduces body temperature, heart rate, respiratory rate, and whole-body oxygen consumption in mice in a short period of time. After establishing hypoxia and tissue ischaemia/reperfusion (I/R) injury models, Matsuo *et al*. (2021) [16] found that 2MT induces strong hypothermia, anaerobic metabolism, and an anti-hypoxia response in mice, thereby prolonging their survival time under lethal hypoxic conditions (Table 2, Ref. [16,24–26]). Furthermore, 2MT exhibited therapeutic effects on skin and brain I/R injury models, significantly reducing skin ulcers and cortical infarct size, Notably, the anti-hypoxic activity induced by 2MT can be controlled independently from temperature suppression. However, the experiment did not observe the systemic effects of 2MT on mice. Matsuo *et al*. (2021) [16] also first described administration of 2MT in a lipopolysaccharide (LPS) induced lethal endotoxic shock mouse model. After simultaneously administering LPS and 2MT, they used Bio-Plex to analyze the serum cytokine profile. Results showed that 2MT achieves anti-inflammatory effects by suppression of the release of multiple cytokines in the serum, while enhancing cellular immunity [25]. Based on this experiment, Onoe *et al*. [26] monitored the mean arterial pressure, superior mesenteric venous blood flow, and jejunal mucosal tissue blood flow before and after administering 2MT. Results indicated that 2MT maintains intestinal circulation in the rabbit endotoxic shock model and improves systemic hemodynamics [26]. To further confirm the role of 2MT in cardiovascular disease, Nishi *et al*. [24] revealed that a single subcutaneous administration of 2MT ameliorates oxidative stress, reduces infarct size, and preserves left ventricle contractility through metabolic energy modulation and hypothermia in the mouse cardiac I/R injury model. The experiment was the first to confirm the therapeutic effect on the heart of 2MT-induced hypothermia before reperfusion. 2MT-induced hypothermia may be a future adjunctive measure for percutaneous coronary intervention of ischemic heart disease. However, currently, no report has directly evaluated the effect of 2MT on cardiac function. Further research could elucidate its cardiac protective effect based on 2MT-induced hypothermia to translate the drug's cardiac protective effect into clinical practice.

5. Mechanisms Underlying the Organ-Protective Effects of 2MT Induced Hibernation-Like Behavior

5.1 Neural Pathway that Mediates 2MT-Induced Hibernation-Like Behavior

Fear behavior responses are induced by innate and acquired stimuli involving different mechanisms. TMT mainly induces innate fear behavior response in mice through the olfactory pathway [27]. Saito *et al*. [28] used optogenetics and found that TMT activates glomeruli in many regions of the olfactory bulb, thereby activating the olfactory cortex, amygdala, and bed nucleus of the stria terminalis (BNST) to induce strong fear behavior responses in mice [28]. The BNST is a higher-order sensory center for olfactory signals and mice show significant activity experiencing predatory danger [29]. The BNST plays an important role in regulating the emotional state and behavioral responses of mice under crisis conditions, mediating the formation of fear behavior responses when in potential danger [30]. Bruzsik *et al*. [31] employed chemical genetic techniques to suppress specific neurons in the BNST and discovered that neurons that secrete somatostatin (SST) and corticotropin-releasing hormone (CRH) are capable of bidirectionally regulating innate fear behavior in mice in a complementary manner. Specifically, BNST SST neurons promote the occurrence of fear behavior in mice, while BNST CRH neurons facilitate the extinction of fear behavior [31]. A positive genetic screening revealed that neurons expressing the transient receptor potential ankyrin 1 (TRPA1) in the

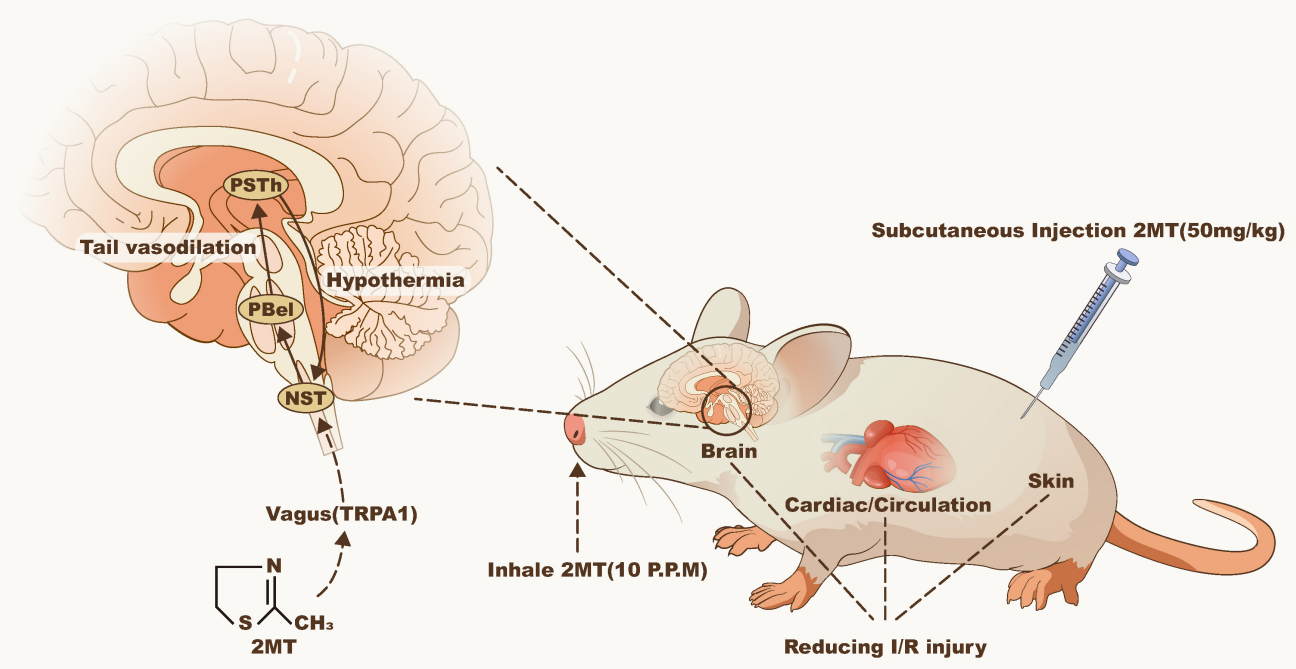

Fig. 1. Schematic diagram of organ protection and neural mechanism of 2MT-induced hibernation-like behavior. PSTh, posterior subthalamic nucleus; PBel, external lateral parabrachial subnucleus; NST, nucleus of the solitary tract; TRPA1, transient receptor potential ankyrin 1.

trigeminal ganglion play a crucial role in the 2MT-induced hypothermia and low metabolic state [32]. TRPA1 receptors are mainly expressed in the olfactory bulb and piriform cortex, can serve as a potential new chemical sensor to detect harmful chemicals in the environment, and mediate fear behavior induced by thiazole compounds [33]. Furthermore, the trigeminal TRPA1 gene regulates 2MT-induced avoidance behavior [32]. Using whole brain mapping and chemical activation experiments, Matsuo *et al.* [16] found that 2MT binds to TRPA1 in both the trigeminal and vagus nerves, activating the TRPA1-positive sensory pathway that projects to the spinal trigeminal nucleus (Sp5) and nucleus of the solitary tract (NST). This pathway, from the brainstem to the periaqueductal gray of the midbrain, coordinates the crisis response pattern and induces a decrease in body temperature in mice. Optogenetic and chemogenetic techniques have been used to discover that 2MT stimulation activates a large number of neurons in the posterior subthalamic nucleus (PSTh), the external lateral parabrachial subnucleus (PBel), and NST in mice (Fig. 1). Deleting TRPA1 from neurons in these brain regions reduces their activation, revealing the mechanism of the PBel-PSTh neural circuitry in 2MT-induced hypothermia [34]. As a central hub connected to both PBel and NST, PSTh mediates 2MT-induced body temperature reduction and tail vasodilation. Specifically, the PSTh-NST pathway plays a major role in mediating the low temperature induced by 2MT in mice, while the PBel-PSTh pathway plays a major role in tail vasodilation [34]. Contrary to the decrease in tail temperature caused by electric shock in mice, 2MT induced an increase in tail temperature. This may be due to 2MT being an indirect fear message that lowers core body temperature by relaxing the blood vessels in the tail of mice [15,34]. Vascular movements are controlled by sympathetic preganglionic neurons in the spinal cord through sympathetic ganglia in the brainstem, which may also be related to the low body temperature and low metabolic state induced by 2MT [35]. Future studies should clarify which vascular control nucleus downstream of the PBel-PSTh-NST pathway may mediate 2MT-induced tail vasodilation. In summary, the low-temperature and low-metabolic state induced by 2MT may be mediated by multiple coordinated neural pathways.

5.2 Metabolic Adaptation and Oxidative Stress Mechanisms that Mediate 2MT-Induced Hibernation-Like Behavior

Before entering hibernation, mammals significantly increase their body fat and shift their energy metabolism from glucose to fat to provide energy during hibernation [36]. Storey *et al.* [37] analyzed metabolites extracted from active and hibernating squirrel brain tissue and found that during hibernation, there was a significant decrease in glucose-6-phosphate and fructose-6-phosphate, indicating that during this stage glucose uptake activity is significantly inhibited to save energy. In contrast, during the 2MT-induced crisis response mode, brain glucose uptake activity accelerates and lactate levels increase, which is enhanced probably to protect the brain from crisis [38]. Lactate level is generally considered an indicator of anaerobic

metabolism during peripheral circulatory failure. However, for the previously mentioned rabbit shock model, 2MT reduces circulating lactate levels and improves hemodynamic [26]. There is also a metabolic similarity between hibernation and the 2MT-induced crisis response mode. During hibernation, the activity of pyruvate dehydrogenase (PDH) in brain cells is reduced and although 2MT stimulation does not reduce PDH protein levels, it does inhibit PDH activity by increasing two PDH phosphorylation sites, thereby inhibiting the tricarboxylic acid (TCA) cycle [16,39]. In summary, the metabolic state of mice after 2MT stimulation shifts towards a crisis response mode characterized by promoting glycolysis and inhibiting the TCA cycle. 2MT stimulation leads to a decrease in TCA cycle activity, a decrease in mitochondrial respiratory chain activity, a significant decrease in reactive oxygen species levels, and a downregulation of the lipid peroxidation marker 4-hydroxy-2-nonenal level, resulting in a decrease in oxidative stress levels [16].

6. Application Limitations and Outlook

The hibernation-like behavior induced by 2MT is primarily triggered by the activation of innate fear pathways in animals. Although it may exhibit certain differences from true hibernation, such as the elevation of tail temperature, increased levels of steroid hormones, and upregulated glucose uptake [16,19], both conditions share similarities in terms of low metabolism and reduced body temperature. Furthermore, this hibernation-like phenomenon induced by 2MT demonstrates distinct organ protective effects. It possesses adaptive functions in both cognitive and behavioral responses and is directly associated with the organism's ability to ensure survival in crisis situations [16,40], which inspired the hypothesis that the survival state induced by 2MT may outperform passive therapeutic hypothermia.

Currently, several studies have confirmed that the hibernation-like state induced by 2MT exhibits significant organ-protective effects at the animal level and mediates activation of the vagus nerve to produce an anti-inflammatory effect and maintain immune response homeostasis. Based on these effects, this molecule may hold a significant potential for life-saving clinical applications, such as in cases of trauma, heart attack, stroke, traumatic brain injury, and major surgeries [34,35]. Konkoly *et al*. [33] conducted *in vitro* experiments using TRPA1-overexpressing Chinese Hamster Ovary (CHO) cell lines. Results showed that after the injection of 2-MT, the intracellular calcium influx levels increased in both mouse and human TRPA1-overexpressing CHO Cells, with no significant difference observed between the two. However, these findings are limited to *in vitro* situations and there is currently no research at the *in vivo* level to show whether 2MT induces similar hibernation-like behavior in humans or large mammals.

However, despite the challenges, 2MT or similar thiazolidine compounds still hold significant potential, warranting further investigation for any possible systemic protective effects in humans. Subsequent studies may need to explore their molecular targets at a more comprehensive *ex vivo* level while also elucidating their impact in large mammalian models *in vivo*. Additionally, conducting a thorough comparative analysis between the protective effects of active-induced hypothermia and traditional physical cooling is essential. If the discovery of non-toxic thiazolidine compounds with similar effects eventually finds applications in clinical practice to induce life-protective states in humans, it would be highly beneficial, and the field would have a significant impact. However, even if the drug may not ultimately exhibit its protective effects in humans, the research on the low-temperature neural pathways and metabolic adaptive effects that mediate this phenomenon can still inspire the application of related technologies in future medicine.

Author Contributions

FM and CR conducted literature research and authored the paper. FM and TL reviewed and revised the paper. TL and GH were involved in paper topic selection, reviewing and editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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