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Review article

Hibernation-like neuroprotection in stroke by attenuating brain metabolic dysfunction

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ABSTRACT

Many mammalian species naturally undergo hibernation, a process that is associated with drastic changes in metabolism and systemic physiology. Their ability to retain an undamaged central nervous system during severely reduced cerebral blood flow has been studied for possible therapeutic application in human ischemic stroke. By inducing a less extreme 'hibernation-like' state, it has been hypothesized that similar neuroprotective effects reduce ischemia-mediated tissue damage in stroke patients. This manuscript includes reviews and evaluations of: (1) true hibernation, (2) hibernation-like state and its neuroprotective characteristics, (3) the preclinical and clinical methods for induction of artificial hibernation (i.e., therapeutic hypothermia, phenothiazine drugs, and ethanol), and (4) the mechanisms by which cerebral ischemia leads to tissue damage and how the above-mentioned induction methods function to inhibit those processes.

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Contents

Abbreviations: AQP, aquaporin; AQP-4, aquaporin 4; AQP-9, aquaporin 9; ASIC, acid sensing ion channel; BBB, blood-brain barrier; ETC, electron transport chain; GLUT, glucose transporter; GLUT1, glucose transporter 1; GLUT3, glucose transporter 3; HIE, hypoxic-ischemic encephalopathy; ICSI, intracarotid cold saline infusion; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MCA, middle cerebral artery; MCAO, middle cerebral artery occlusion; MMP, matrix metallopeptidase; MMP-2, matrix metallopeptidase 2; MMP-9, matrix metallopeptidase 9; NADPH, nicotinamide adenine dinucleotide phosphate; NMDA, *N*-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOX, nicotinamide adenine dinucleotide phosphate oxidase; PFK, phosphofructokinase; ROS, reactive oxygen species; SBC, selective brain cooling; t-PA, tissue plasminogen activator; TNF-α, tumor necrosis factor alpha; TRP, transient receptor potential.

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1. Introduction

1.1. What is hibernation?

Hibernation is an altered physiological state seen in a number of mammals. It is a survival tool utilized by a variety of species to endure the harsh seasons when resources are scarce. Ordinarily, mammals can maintain a constant body temperature of about 37 °C regardless of ambient temperatures due to their high metabolic rate generating heat in their bodies (Geiser, 2013; Heldmaier et al., 2004). Animals that are capable of heat generation and maintenance are called tachymetabolic endotherms. However, heat generation comes at a large cost. An immense amount of energy is required for endotherms to maintain their ideal body temperature; therefore, food is crucial. There are periods of time when tachymetabolic endotherms undergo hypometabolism. This hypometabolism, also termed torpor, can be separated into two categories in mammals. The first, shallow daily torpor, follows circadian rhythm of activity and rest (Geiser, 2013; Geiser and Ruf, 1995; Ruf and Geiser, 2014). A 0.5–2 °C decrease in body temperature is observed during resting phase in mammals and this is associated with a 20% decrease in metabolic rate (Geiser, 2013; Heldmaier et al., 2004; Storey and Storey, 2010). The second category, hibernation, is characterized by a much larger decrease in both body temperature and metabolic rate, lasting several days or weeks (Drew et al., 2009; Geiser and Ruf, 1995; Ruf and Geiser, 2014; Storey and Storey, 2010). During hibernation, body temperature can be as low as −2.9 °C; spontaneous arousals occur regularly and mammals return to active core temperature of about 37 °C from their minimal body temperature (Carey et al., 2003; Drew et al., 2007). Hibernators rely heavily on metabolic inhibition, such that their metabolic rate during prolonged torpor can be reduced to as low as 1% of active state basal metabolic rate (Carey et al., 2003; Drew et al., 2007; Geiser, 2004; Storey and Storey, 2010). Decreased rates of gas exchange are also observed in hibernators, accompanied by severely depressed ventilation rates (Milsom and Jackson, 2011). They may only breathe episodically or even exclusively by passive diffusion through their skin and airways. This is achieved partially through the low body temperature increasing hemoglobin's affinity for oxygen. Additionally, hibernators experience significantly decreased cardiovascular parameters, such as heart rate and blood pressure (Horwitz et al., 2013).

Hibernation is an incredible phenomenon that still leaves us with many unanswered questions. In addition to surviving immense temperature drops and metabolic rate decreases, hibernators in deep torpor also withstand drastic fluctuations in cerebral blood flow without causing brain damage (Dave et al., 2012; Drew et al., 2009; Zhou et al., 2001). Cerebral ischemia, a common result of cerebral trauma, stroke, and heart failure, can lead to brain damage within seconds and permanent brain dysfunction or death within minutes if not treated in time (Dave et al., 2012; Frerichs et al., 1994). While humans and other mammals suffer from cerebral ischemia, animals that hibernate tolerate the extensive decrease in cerebral blood supply without experiencing devastating damages to the brain. In this systematic review, we aim to provide information on the background of hibernation as a natural neuroprotective mechanism for cerebral ischemia, summarize possible methods for induction of a hibernation-like state, and discuss the mechanisms by which they are thought to be neuroprotective.

1.2. Hibernation as a natural neuroprotectant

Hibernation is a natural survival mechanism during times of food shortage and is characterized by drastic decreases in both body temperature and metabolic rate (Dave et al., 2012; Drew et al., 2009, 2007, 2001). Animals typically enter a deep torpor state with depressed body temperature and metabolism; intermittently, animals wake and return to their euthermic body temperature by endogenous heat production for about one day before returning to deep torpor. This cycle of deep torpor and wake is called a hibernation bout (Geiser, 2004; Geiser and Ruf, 1995; Heldmaier et al., 2004; Ruf and Geiser, 2014). Hibernators actively regulate the characteristics of deep torpor and the rhythm of hibernation bouts (Drew et al., 2007).

Studies suggest that hibernation is neuroprotective. In a paper by Zhou et al. (2001), histological slides of traumatic brain injury in both hibernating and non-hibernating arctic ground squirrels showed that there was less cell death and phagocytosis in the slides of the hibernating tissue. In another study, Frerichs (1999) demonstrated that during hibernation, the weighted average cerebral blood flow dropped to less than 10% of active state levels and that glucose utilization was decreased by approximately 98%. Along with core body temperature, the central nervous system also has a significant decrease in temperature during hibernation. This temperature depression has even been associated with functional changes in the hippocampus, most notably, the addition of control over hibernation bout (Arant et al., 2011). Furthermore, hippocampal slices from hibernating animals showed a higher tolerance for in vitro hypoxia/aglycemia (Frerichs, 1999), presumably due to the down regulation of cellular metabolism in hibernating brain tissue (Carey et al., 2003).

Another area of research is exploring a number of methods to induce a 'hibernation-like' state in non-hibernators and studying the neuroprotective effects of the altered physiology. Several physiological changes during hibernation are suggested as potential neuroprotective mechanisms, such as hypothermia, metabolism depression, inflammatory response suppression, and increased resistance to oxidative stress. These have been artificially

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