19

Clinical Neuroprotection Against Tissue Hypoxia During Brain Injuries; The Challenges and the Targets

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1. Introduction

1.1 Understanding hypoxia tolerance and the challenge of clinical neuroprotection

Most of the existing research on brain hypoxia mainly focused mainly on understanding the mechanisms of neuronal death as the means of identifying targets for therapy. This approach has not been helpful in understanding how the brain of humans can be made to resist tissue hypoxia. This is a major factor that leads to neuronal death during stroke, for example. Hypoxia tolerance is a robust fundamental adaptation to low oxygen supply and represents a novel neuroscience problem with significance to mammalian physiology as well as human health. Physiological and molecular changes during hypoxia are critical to the prevention, management, and treatment of many important health conditions, such as stroke and cardiac arrest. However, the initiation and maintenance of physiological changes during hypoxia tolerance can be very difficult, and even those interventions that succeed in laboratory animals and controlled clinical trials do not always translate into clinical therapy. Transformative advances in the science of mammalian physiology, especially those that can connect mammalian physiological, molecular changes and diseases are urgently needed. In this review, we discussed major molecular and physiological adaptations during hypoxia tolerance that can be developed for the induction of clinical neuroprotection to tissue hypoxia during brain injuries.

2. Convergence between a specific neurotransmitter system and physiological mechanisms maybe critical for tissue hypoxia during brain injuries

Comparative studies of adaptive physiology demonstrated that hypoxia tolerant animal species represent potential sources of new strategies in our search for brain protection. This

is because studies on the neurons of these animals repeatedly reminded us that we are closer to understand how cells and tissues develop resistance to hypoxia. Hypoxia tolerant species are very valuable models for understanding oxygen signaling processes simply because the responses to hypoxia are well developed. The possibility of separating adaptive signaling or defense responses from injury is a major benefit of studying hypoxia tolerant cells. They also serve as models for the slow adaptation of tissues to hypoxia, which humans are clearly capable of, and which might be enhanced to improve adaptation to diseases involving oxygen deficits.

Studies on the pathophysiology of shock-induced disturbances in tissue homeostasis reveal that tissue hypoxia is a consequence of distressed microcirculation that worsens the diffusion geometry, such that tissue hypoxia induced significant physiological changes in brain cells. Measuring the targets that detect tissue hypoxia is known to reveal the immediate effect of the distressed microcirculation. Recent studies on hypoxia neurobiology research have advanced a considerable body of evidence supporting the hypothesis that convergence between neurotransmitter systems and physiological mechanisms is protective in hypoxia tolerant species. Establishing this protective phenotype in response to hypoxic stress depends on a convergence response at the genomic, molecular, and cellular and tissue levels (Singer, 2004, Jeffrey, 2006). At the cellular level, studies in mammalian hibernation that explore hypoxia tolerance capability reveal evidence of ion channel arrest, regulation of inhibitory neurotransmission and suppression of substrate oxidation as cellular physiological adaptations (Gentile et al., 1996, Wang et al., 2002). Furthermore, extracellular levels of GABA decline in the striatum during hibernation, while extracellular glutamate remains unchanged during steady-state torpor of hibernation when compared with euthermic animals (Zhou et al., 2001). A decrease in the tissue-specific depression of substrate oxidation is also thought to decrease oxygen consumption, and consequently attenuate cytotoxic events that lead to cell death (Barger et al., 2003). This effect was attributed to a decrease in ATP demand resulting in the maintenance of homeostasis of brain energy demand and supply. The central mechanism that underlies hypoxia preconditioning-induced tolerance, which maintains the homeostasis of brain energy demand and supply, remains unclear. Interestingly, a number of potential neurochemical induction pathways have been proposed to control hypoxia tolerance in natural genetic systems of hypoxia tolerance. Such pathways include neuroactive cytokines (Nawashiro et al., 1996), glutamate receptors (Ravid et al., 2007, Sivakumar et al., 2009), adenosine receptors (Perez-Pinzon et al., 2005), the ATP-sensitive potassium Channel (Reshef et al., 2000), nitric oxide (Gonzalez-Zulueta et al., 2000) and oxidative stress (Dalen et al., 2009).

Taken together, findings from the aforementioned studies indicate that neuroprotective mechanisms against hypoxic insults in natural genetic systems of hypoxia or ischemic tolerance maybe be hinged on the convergence between a specific neurotransmitter system and physiological mechanisms. Although only few of the existing studies have been demonstrated in humans, one of these few studies indicates that elucidation of the central neurochemical mechanism of hypoxia tolerance is in this area of interest because the tolerance has been experimentally induced by clinically approved drugs (Konstantin et al., 2003). In another human study, it was found that adenosine plasma levels strikingly increased, such that the adenosine flow lasted days after transient ischemic or hypoxia attack and weeks after stroke (Moncayo et al., 2000, Pasini et al., 2000). Our view openly acknowledges the existence of hypoxia tolerance capacity in human brains and a possible

central endogenous neuroprotective mechanism for hypoxia brain injuries in humans. In this context, considering the roles of adenosine as a molecule, it is possible that adenosine might represent a potential central neurotransmitter system that modulates physiological mechanisms during hypoxia protection. It is also important to emphasize that hypoxia itself could be the driving force for the convergence between a specific neurotransmitter system such as adenosine and physiological mechanisms during protection in hypoxia tolerant species. Since extensive studies have been done on adenosine system in the context of hypoxia protection over the past twenty years, we will now summarize the existing knowledge of specific roles of adenosine (A1) receptor in inducing survival during hypoxia.

3. Specific roles of A1 receptor during hypoxia tolerance

Survival in a severe hypoxic stress during which arterial oxyhemoglobin saturation is equal to 35% or less is connected with the ability of the brain to adapt to low oxygen supply and demand, and is thought to be regulated by a specific neurotransmitter system, such as adenosine (Blood et al., 2002). Studies in young sheep and adult rats indicate that intracerebral A1 concentrations increased during hypoxia. The specific role of A1 was linked to its ability to inhibit neuronal activity (Fowler et al., 1999). In vitro studies on hippocampal slices indicate that elevation of A1 receptors is associated with hypoxia (Jin and Fredholm, 1997), and severe asphyxia *in vivo* (Hunter et al., 2003c), following inhibition of neuronal activity. Studies in the fetal sheep further revealed that breathing movements can be inhibited by hypoxia and that such adaptation could be abolished by adenosine-receptor blockade at the level of the thalamus due to the inhibition of thalamic neurons (Chau and Koos, 1999). In a mouse knocked-out of A1 receptor, there is a significant decrease in tolerance to hypoxia (Johansson et al., 2001). Involvement of adenosine or adenosine triphosphate-sensitive potassium (K_{ATP}) channels in the development of tolerance has been suggested in global ischemia and hypoxia models (Kumral et al., 2010), cross-tolerance models (Xu et al., 2002) and *in vitro* studies (Perez-Pinzon et al., 2005). Activation of A1 receptors directly accelerate neuritogenesis in the primary neuronal precursor cells of rats(Canals et al., 2005). This finding suggests that A1 receptors may play an important role in myelinization and neuronal differentiation with the potential for clinical management of neuronal repair in hypoxic-induced brain injury.

By evaluating the action of hypoxia on synaptic transmission in hippocampal slices Sebastião and Ribeiro (2001) revealed that γ-aminobutyric acid (GABA), acetylcholine, and even glutamate may also have a neuroprotective role; however their action is evident only when activation of adenosine A_1 receptors is impaired. This finding indicates that adenosine A_1 receptors have a pivotal role of neuromodulating during hypoxia, though other substances can enhance adenosine actions when the nucleoside is not operative. A_1 receptors fine tuning neuromodulation is a very restrained change, similar to what *e.g.,* a pianist does, modulating a tune through introduction of another tune to modify the characteristics of the previous tune. A_1 receptors have specificity of interacting with receptors of other neurotransmitters and neuromodulators as well as with adenosine transport systems. A_1 receptors and other cellular elements involved in brain insults act via interconnections between the cellular elements and their secretions, such as the immune system(Ribeiro, 2005). In this manner, the nervous system can be highly regulated in normal physiology to induce neuroprotection against hypoxia. The fact that chemical

neuromodulators such as A1 receptors are already part of normal physiology, either during embryonic development or adulthood, implies that their activity can be modified by specific pharmacological agonists and antagonists to restore homeostasis or to promote the safe pathways that can lead to tissue hypoxia protection.

4. Cellular mechanisms that promote neuronal death can be manipulated to promote neuronal survival

It is well known that neuronal death or apoptosis may result from continued activation of damaging molecular processes or pathways set in motion by a series of hypoxic insults, with the ultimate breakdown of the cell as a unit. According to Lipton (1999) such neuronal death is a morphological one, during which the cell cannot recover to perform its anatomical function. The idea is that the study of molecular processes of neuronal death at this point provides an understanding of what leads to these drastic structural changes and what needs to be done to promote neuronal survival. An interesting question in this regard is how can the molecular mechanisms or pathways that promote hypoxia-induced neuronal death be manipulated to promote neuronal survival? By targeting the disruption of the mouse caspase 8 genes, it has been shown that caspase 8 can regulate the activities of death promoting receptor signaling within the TNFR superfamily. For example, the deletion of caspase 8 gene completely abrogated TNFR12 and Fas receptor-induced apoptosis that was enacted via generation of reactive oxygen species during hypoxia (Cobelens et al., 2007). In other studies that explore the mechanisms of hypoxia-induced cell death in primary cortical neurons, it was found that TNFalpha was responsible for inducing cell death in the cortical neurons of cultured rats (Reimann-Philipp et al., 2001). These investigations established that TNF receptors are responsible for neuronal apoptosis because of the formation of an intracellular protein complex induced by hypoxia.

Although TNFalpha is directly implicated in neuronal apoptosis, TNFalpha-induced neuronal death can be inhibited by nerve growth factors (Haviv and Stein, 1999). This finding indicates that that hypoxia-associated apoptotic effects of TNFalpha can be converted by trophic factors (NGFs), and that the survival-promoting effect of NGF is mediated by a specific pathway not shared by all tyrosine kinase receptors. This implies that the manipulation of caspases and NGFs during hypoxia-induced activation of TNFalpha in the cortical neurons can prevent apoptotic effect of TNFalpha during hypoxia. Phosphorylation networks regulating JNK activity have evolved to enable swift and accurate responses, even in the face of hypoxia-induced cellular perturbations (Bakal et al., 2008). The JNK signaling network is thought to maintain cell and tissue integrity during hypoxia-induced cellular stress that involves stress-activated protein kinases (SAPKs), also known as JUN NH_2-terminal kinases (JNKs). Hypoxia-induced activation of JNK is an early response to hypoxic stress (Antoniou et al., 2009). When treated with CEP-1347, which inhibits JNK activation, the increase of cellular JNK activity was blocked, such that sympathetic and cortical neurons were saved from hypoxia-induced stress (Qi et al., 2009). Hypoxia-induced cell death can be averted by inhibiting JNK activation(Wardle, 2009). The explanation for this is that C-jun, a transcription factor that controls genes involved in cell death, is a constituent of another transcription factor called AP-1, and when phosphorylated by JNK, c-jun becomes activated and induces apoptosis, by withdrawing survival signals but when inactivated, metabolically vulnerable neurons can be saved from apoptosis.

Apart from JNK, there are other molecular systems that are able to induce apoptosis or neuronal death when in an active form, yet in an inactive form fail to do so. Molecular factors such as CREN, NF-kB (238) and FKHRL1 (Obexer et al., 2006), must be in its inactive form in order to refrain from inducing the expression of death genes in cerebellar granule neurons during hypoxia. These factors (CREN, NF-kB and FKHRL1) can be activated by Akt (Akt is a protein family of the kinases B (PKB) that is involved in cellular signaling to support their continued existence in brain cells to promote apoptosis (Park et al., 2007). Akt can also inhibit the cellular machinery that functions in killing cells. This is possible by phosphorylation at sites both upstream (BAD) and downstream (Caspase 9) of mitochondrial cytochrome c release (Dashniani et al., 2009). Such phosphorylation has been previously suggested to regulate glucose metabolism, thus, helping cells to live rather than die following hypoxic insults (Zhou et al., 2001). In summary, most of the aforementioned studies have been done in rats, exploring similar studies in hypoxia tolerating species will provide an in-depth-understanding of the activities of these molecular mechanisms or pathways during neuronal survival in hypoxia tolerating conditions.

Hormones are chemical substances produced by specialized glands with the primary function of regulating cellular activity. Levels of hormones in the brain demonstrate unique secretory characteristics that are linked to hypoxia. Leptin is a protein hormone with important effects in regulating metabolism functions. Most recent evidence has implicated leptin, the product of the obese gene derived from fat cells and placenta known to regulate body weight and food intake (Otukonyong et al., 2005), and synaptic plasticity during hypoxia neuroprotection (Shanley et al., 2001). More recently, the neuroprotective effects of leptin against tissue hypoxia have been explored (Perez-Pinzon and Born, 1999). This study revealed that leptin receptors are expressed in neurons of the hypothalamus. Another study (Guo et al., 2008),revealed the expression of leptin in the hippocampus and cerebral cortex. Endogenous synthesis and release of leptin by the brain may explain how localized leptin could protect neurons during hypoxia. For instance, cumulative evidence indicate that leptin could exert its neuroprotective effects to enhance neuronal survival both in vitro and in vivo by a mechanism involving stimulation of the Janus kinase (JAK)-signal transducers and activator of transcription (STAT) pathways. It has been shown that leptin protects neurons from neurotoxic 1-methyl-4-pyridinium (MPP+)-induced cell death in a dose dependent manner by activating the phosphatidylinositol 3-kinase (PI3-K)/Akt pathway; Jingnan et al., 2006). In mice model, systemic administration of leptin was shown to decrease infarct volume induced by focal cerebral hypoxia ischemia (Zhang et al., 2007). Apoptosis resulting from hypoxia or global ischemia is involved in the pathology of cerebral infarction and neuronal death. Leptin has been reported to inhibit apoptosis by removing growth factor from neuroblastoma cells utilizing JAK2-STAT3 and P13K/AKT signaling pathways (Guo et al., 2008). In seizures and epilepsy related hypoxia, leptin has been shown to protect hippocampal neurons against excitotoxicity in leptin deficient ob/ob mice, which are more prone to seizures (Erbayat-Atlay et al., 2006). Leptin has been reported as a hypoxic response gene whose transcription is induced by transcription factor HIF-1. Understanding the specific role of leptin in hypoxia conditioning can add leptin to the list of potential molecules for the treatment of hypoxia-associated brain injury.

Ghrelin is another peptide hormone that has been implicated in regulating glucose homeostasis (Andrews, 2011). The discovery of ghrelin was based on its ability to stimulate

growth hormone (GH) release by activating the GH secretagogue receptor (GHSR1a) widely distributed in the hypothalamus and the pituitary gland. The neuroprotective effect of ghrelin has been demonstrated in many animal models of hypoxic-induced brain injury and stroke (Donnan et al., 2008). Injection of ghrelin intraperitonealy or intravenously in rats (both in vivo and in vitro) neuroprotects the forebrain by reducing infarct volume and cell death (Liu et al., 2009). Ghrelin has also been shown to attenuate CAI and CA3 hippocampal neuronal loss by inhibiting casp 3 activation in the pilocarpine-model of epilepsy (Xu et al., 2009). It is also important to point out that the crosstalk in leptin and ghrelin secreting sites to contribute to neuroprotection during the period of hibernation. Precisely, during the winter months hibernating mammals, such as the Arctic ground squirrel undergo physiological and behavioral changes to cope with seasonal periods of food scarcity and high energy demand. Before going into hibernation, the Arctic ground squirrel eat a lot and accumulate body fat, such that leptin level increases resulting in the development of leptin resistance without which the process of adipose mass deposition will fail, and hibernation which is also characterized with hypoxia tolerance will be in jeopardy. When hibernating, the Arctic ground squirrels do not eat because food is scarce, body metabolism decreases and hypothermia sets in. Since ghrelin stimulates appetite, and the animals are able to eat after hibernation is over. Leptin resistance is known to allow fat to be stored in anticipation of another season. Therefore, we propose that the understanding of the interconnections between the leptin and ghrelin with the metabolic networks could open new windows on the treatment that identifies the role of leptin and ghrelin in the preservation of metabolically vulnerable neurons during tissue hypoxia following the onset of stroke.

5. Conclusion

Analysis of brain mechanisms that control hypoxia tolerance in natural systems indicate that the physiological and molecular mechanisms of hypoxia neuroprotection represent the core of our understanding of how the brain can be made to resist tissue hypoxic insults. Studies of mammalian hypoxia physiology revealed that hypoxia tolerating models have an intrinsic ability to resist hypoxia. The physiological and intracellular mechanisms underlying such protection are not fully understood. Transformative advances in the science of mammalian physiology, especially those that can connect mammalian physiological and molecular changes and diseases, such as stroke and cardiac arrest, are urgently needed. In this review, we suggest that the protective physiological and molecular mechanisms employed by hypoxia-tolerant species offer clues on strategies to adapt for the clinical management of brain injuries where oxygen demand fails to match the supply.

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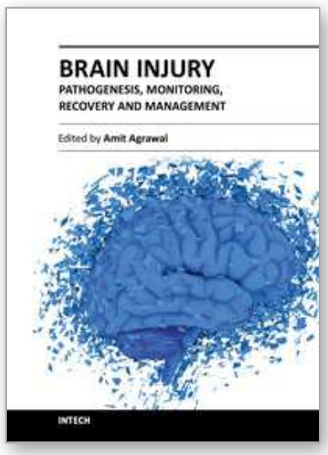

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