

Physiological Neuroprotective Mechanisms in Natural Genetic Systems: Therapeutic Clues for Hypoxia-Induced Brain Injuries

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1. Introduction

Adaptations, conservation or evolution of physiological systems in human indicates that the physiological system for hypoxia tolerance represents an adaptive character that is present in humans, just like in poikilotherms or endotherms (Hochachka 1993; Hochachka et al. 1996). Precisely, brain metabolic organization capability is thought to represent an adaptive physiological system that is present in humans, but composed of so many neurochemical products and physiological mechanisms that make it difficult to account for its plasticity for manipulation to induce protection (Hochachka 1993; Frappell et al. 2002). Evidence that hypoxia tolerating mammals suppressed metabolic demand in response to hypoxia contributed substantially to the understanding of metabolic regulation as a neuroprotective strategy that can be adapted for the protection of tissue hypoxia in humans. In that case, understanding the physiological mechanisms that are involved in such ability in hypoxia tolerating species may provide a clue for specific mechanisms that could be manipulated in the brain of stroke patients to prevent the death of metabolically vulnerable neurons. In this context, knowledge of the specific role of the central neurotransmitter systems and pathways that control metabolic suppression during hypoxia tolerance is important. This is because the neurochemical-mediators that may defend against hypoxic insults during brain injury act through interconnections within the neural systems that are highly protected in hypoxia tolerating species (Mravec et al. 2006). Exposure of non hypoxia tolerating species to severe hypoxia results in the alteration of the connections within the neural systems because of loss control of local microcirculation of oxygen. This leads to ineffectiveness of membrane potentials to modulate neuronal function (Ackland et al. 2007). If this occurs, there is some hope for effective neuropharmacological intervention through neurotransmitter-mediators. The fact that chemical neurotransmitters are part of normal physiology, whether during development or adulthood, means that specific agonists and

antagonists that restore physiological homeostasis can lead to pharmacological repair of hypoxia-induced neuronal damage in humans.

2. Physiological strategies that protect the brain during ischemic stroke

Hypothermia is one strategy that can decrease hypoxic/ischemic injury under regulated conditions (Rincon 2008; Statler 2008). This is possible because a decline in brain temperature can prevent the death of neurons that are deprived of nutrients. Such a protective strategy has been attributed to the reversible protein phosphorylation that regulates suppression of the rates of multiple ATP-production, ATP-utilization and related cellular processes that allow animals to go through a stable hypometabolic state (Storey and Storey 2007; Storey and Storey 2005). A stable hypometabolic state mechanism is known to protect against pathological effects of cortical neuronal pathology or oxidative stress in stroke patients (Ma et al. 2005). Cumulative evidence from studies of hypometabolism during hibernation in small mammals suggests that hypometabolism is a stable metabolic state that allows timely limited energy regulation during hypoxia (Heldmaier et al. 2004). This is because a stable metabolic state activates defense mechanisms, such as antioxidants, proteins, protease inhibitors that stabilize macromolecules and promote long-term neuronal viability in the stable metabolic state (Zhou et al. 2001; Zhao and Zuo 2005). These adaptations can be manipulated in humans to prevent the death of metabolically vulnerable neurons in stroke patients. Although these adaptations do not fully account for the mechanisms that facilitate the suppression of metabolism during exposure to hypoxia (Nathaniel et al. 2009) or during mammalian hibernation (Drew et al. 2007), it has been proposed that hypoxia itself could facilitate a systematic regulation of metabolism through cooling of core body temperature and stabilization of temperature in the new metabolic rate (Barros et al. 2001). Future studies that explore the mechanisms that switch-off energy demand, when supplies become limited during metabolic suppression could provide clues of how to develop metabolic suppression as novel therapy in the clinical management of stroke.

3. Cellular implications of disruption of brain energy balance when oxygen delivery fails to meet demand

The mammalian brain is a highly oxidative organ that accounts for an inexplicably large percentage of the whole body oxygen consumption that provides the major source of energy during aerobic metabolism (Wang et al. 2002). This implies that structural and functional integrity of brain functions strongly depend on a regular oxygen and glucose supply. Therefore, any disruption of the homeostasis of brain energy demand and supply becomes life threatening. This is because a reduction in oxygen availability due to the abnormality in systemic or local blood circulation cannot be endured for a prolonged period by a non hypoxia tolerant species (Zhou et al. 2001a; Barger et al. 2003). The immediate effect is variation in oxygen partial pressure (PO_2), within the brain that is detected by cellular oxygen sensors. The cellular oxygen sensors, such as hypoxia inducible transcription factors (HIFs), are thought to be available to regulate oxygen homeostasis in the brain. In order for the brain to cope with variations in oxygen partial pressure, these sensors induce adaptive mechanisms to avoid, or at least minimize, brain damage (Nawashiro et al. 1996). Any abnormality in cellular oxygen-sensor response is a reflection of the low partial pressure and

concentrations of oxygen in the brain. The abnormality is primarily because of the inability of a specific oxygen-sensor or target system to tailor adaptive responses according to differences in the cellular oxygen availability in a short or long term. In this context, the arising question is how does low cellular oxygen availability affect neuronal and physiological activities? Major cellular operations in the brain are dependent on the oxygen level in the physiological range (Erecinska et al. 2005). Limitation of oxygen supply to the brain below a critical physiological level blocks oxidative phosphorylation, which drastically decreased cellular ATP leading to a collapse in ion gradients. Consequently, neuronal activity stops. If the process of re-oxygenation is not re-introduced quickly, neurons will die (Nawashiro et al. 1996). In the brain of a stroke patient, early interruption of energy homeostasis when oxygen delivery fails to meet oxygen demand is the first step in a surge of events that leads to cell death of metabolically susceptible neurons. If hypoxia does not set in, availability of glucose will help maintain ATP levels through glycolysis. However, if glucose supply is limited, reduction of high-energy phosphates (e.g. ATP) results in loss of cellular ionic homeostasis (Erecińska and Silver 2001). This is because the disruption of ion homeostasis causes an influx of Na^+ and Cl^- ions, the release of neurotransmitters, opening of voltage-gated Ca^{2+} channels, and anoxic depolarization (Erecinska et al. 2005). This finding suggests that anoxic depolarization is directly associated with hypoxia-induced neuronal loss that leads to irreversible brain damage. An interesting question relevant to this idea is how does anoxic depolarization trigger neuronal death during hypoxia? This question has been investigated in the context of the mechanism of anoxic depolarization. For instance, concurrent changes in $(\text{K}^+)_{\text{out}}$ that lead to failure of $(\text{Na}^+, \text{K}^+) \text{ATPase}$ occur during hypoxia due to ATP depletion (Balestrino et al. 1989). In support of this idea, electrophysiological evidence reveals that failure of ATPase causes anoxic depolarization through some intermediate event, such as Na^+ -induced cell swelling (Rufini et al. 2009). To clarify the direct relationship between anoxic depolarization and ATP levels, synaptic transmission analysis in rat hippocampus revealed that first, Na^+ influx plays a relatively larger role in ATP consumption during hypoxia than Ca^{2+} influx; second, anoxic depolarization imposes a large and rapid drop in ATP levels (Fowler et al. 1999). Taken together, it then implies that depolarization and increased sodium concentration during hypoxia seem to account for a significant portion of the neuronal damage induced by hypoxia that eventually leads to both necrotic and apoptotic processes (Reshef et al. 2000; Gonchar and Mankovskaya 2009).

4. Stimulation of glutamate, activation of NMDA and AMPA receptors regulate calcium influx and promote neuronal damage

Although increased sodium concentration during hypoxia seems to account for a major part of neuronal damage during hypoxia, additional structural damages develop hours or days later because Ca^{2+} influx into neurons is stimulated by glutamate (He et al. 2009), and amplified by activation of NMDA and AMPA receptors (Zamalloa et al. 2009). Glutamate is one of the most widespread excitatory neurotransmitters in the brain. In small amounts, it is indispensable for neuronal function, while in excessive amounts it is a neuronal poison (excitotoxin) that stimulates Ca^{2+} influx into neurons (Liljequist et al. 1995; Bonde et al. 2005). If the excessive extracellular release of glutamate is not regulated, it could lead to brain damage (Robinson 2006). This idea is strengthened by the observation that overstimulation of glutamate receptors promotes neuronal death (Sheldon and Robinson

2007a). Since excessive glutamate is harmful to the brain, how exactly can excess amounts of glutamate be regulated in the brain cells? It is possible that such regulation could be achieved by controlling a specific effector system that modulates the activities of glutamate. In support of this idea, studies by Pellegrini-Giampietro et al.(1999), Sheldon and Robinson (2007a) suggest that the mechanism that regulates glutamate transporter activity within minutes is a major redistributor of proteins in the plasma. This idea is further strengthened by the finding that glutamate transporters are regulated by the mechanism that redistributes proteins to or from the plasma membrane(Savolainen et al. 1995; Noda et al. 2000; Sheldon and Robinson 2007b). Findings from these studies indicate that longer-term activation of protein kinase C (PKC) decreased the activity and cell surface expression of the predominant forebrain glutamate Glu-1 transporter that is being redistributed from the plasma membrane to an intracellular compartment. Taken together, the existing studies reveal that the cellular machinery required for redistribution is via lysosomal degradation and not proteosomal degradation. Since longer-term activation of PKC results in degradation of GLT-1 that can be blocked by inhibitors of lysosomal but not proteosomal degradation, we speculate that regulation of total GLT-1 levels during hypoxia could play a significant role in hypoxia neuroprotection. Since the stimulative effect of glutamate (Noda et al. 2000) and activation of NMDA and AMPA receptors (Sobczyk et al. 2005) led to calcium overload (Mulvey and Renshaw 2009), our interest in this review to determine whether the different roles of glutamate, NMDA and AMPA receptors are the sole means of extracellular accumulation of calcium following hypoxic insults. By analyzing the influence of a specific ion channel inhibitor on the rise of cytosolic free calcium (Ca^{2+}) during hypoxia in a rat's cerebrocortical brain slices, Bickler (1998) found that the cytosolic calcium changes during hypoxia are due to multiple mechanisms. The changes are incompletely inhibited by a combined ion channel blockade. They are associated with the disruption of the cell membrane integrity. There is evidence that other factors may be at work as well. One factor is oxidative stress that is associated with the activation of microglia. Activation of microglia in turn, releases inflammatory cytokines, nitric oxide and extracellular accumulation of calcium, resulting in stress and neuronal death. Another factor is an increase in reactive oxygen species production. This alters cellular components including calcium levels and contributes to cytotoxic events that lead to cell death.

5. Cellular responses in brain neural systems can help in understanding hypoxia-induced hypometabolism and neuroprotection

In the previous section, we described how the stimulation of glutamate, activation of NMDA and AMPA receptors can regulate calcium influx and promote neuronal damage. It is now important to discuss how cellular responses in brain neural systems can help in understanding hypoxia-induced hypometabolism to initiate neuroprotection. Obviously, this proposal needs an explanation on how the cellular responses in any brain neural network would be a major factor for understanding hypoxia-induced hypometabolism and functional integrity. Indeed, a correlative neurophysiological observation tells us that understanding hypometabolism during neuroprotection should be in the context of functional integrity, because hypoxic response of each neuron can be unexpectedly heterogeneous, even within the same brain region(Boutilier 2001). The heterogeneity might be due to the fact that hypoxia itself leads to considerable downregulation of ion channels inside the brain neuronal systems, such that hypoxic reaction of individual neurons vary

(Pena and Ramirez 2005). The variation, in turn, may help in maintaining functional integrity. The idea is supported by the observation that ion channel arrest does not lead to the shutdown of entire networks, nor can networks operate by all cellular components entering a general hypometabolic-neuroprotective state (Ramirez et al. 2007). For instance, a general shutdown of NMDA or Ca^{2+} dependent processes would not be beneficiary to a hypoxia tolerating animal in a hypometabolic state. This is because such a shutdown would severely compromise higher-brain functions. Therefore, hypoxia research should focus on understanding mechanisms of hypometabolism during neuroprotection in the context of functional integrity, and as expressed by hypoxia tolerating species. This disconnect may explain why the protection against tissue hypoxia during stroke is still a main medical problem. There is no doubt that activation of NMDA receptors or intracellular Ca^{2+} may lead to necrosis and apoptosis. However, restraining these mechanisms is not very helpful because they also affect neuroprotection. Taken together, understanding how hypoxia-tolerant neurons sense changes in oxygen dynamics and create signals that have instant and long-term effects on neuronal survival will be significant in developing new strategies for neuroprotection. Studies of how metabolism is regulated at cellular levels during which energy-producing and energy-consuming processes are balanced, facilitated by neurotransmitters-mediated mechanism would be of considerable interest. Since many of the existing studies support the idea that adenosine induces neuroprotection during hypoxia, we will now focus on the different physiological and molecular mechanisms used by adenosine in inducing protection in natural systems of hypoxia tolerance.

6. Adenosine induces neuroprotection by mediating ion signaling during response to chronic hypoxia

Several lines of evidence indicate that reduced ion leakage is an important mechanism for energy conservation during extreme hypoxia, and adenosine has been implicated in ion channel activity. Precisely, it has been shown that A1 receptor stimulation inhibits the brain's electrical activity through K^+ channel activation (direct coupling *via* G-proteins to ion channels) and/or by inhibiting the high-voltage-activated Ca^{2+} channels (Fowler et al. 1999; Reshef et al. 2000). Extracellular adenosine plays a role in the reduction of K^+ influx (channel arrest) that occurs in a brain that was subjected to chronic hypoxia (Reshef et al. 2000). Monitoring of the changes in extracellular K^+ concentration (K^+)_o in the in-situ brain of the turtle (*Trachemys scripta*), following inhibition of Na^+/K^+ -ATPase with ouabain revealed that the time to reach full depolarization (K^+)_o plateau was 3 times more in the chronic hypoxic brain than in normoxic controls (Pék and Lutz 1997). The initial rate of K^+ leakage was reduced by approximately 70%. Following superfusing the brain, before the onset of chronic hypoxia with the non selective adenosine receptor blocker, theophylline, or the specific adenosine A1 receptor blocker, 8-cyclopentyltheophylline, there was a significant reduction in the time to full depolarization in the ouabain-challenged hypoxic-brain and an increase in the rate of K^+ efflux (Pék and Lutz 1997). The results indicate that A1 receptors are involved in the expression of chronic hypoxia-induced ion channel arrest in the brain. This finding is supported by other studies that indicated that in a chronic hypoxic tolerant specie, the basic strategy for hypoxia survival is the maintenance of ion gradients to avoid anoxic depolarization (Lutz et al. 1996; Perez-Pinzon and Born 1999). To this extent, an important question that re-occurred in many of the most recent theoretical papers is how does hypoxia tolerant species respond to anoxia? In our physiological perspective of

hypoxia neuroprotection, adaption to anoxia (an extreme form of hypoxia) is mainly controlled by hypoxia/ischemic conditioning mechanism(Liu et al. 1991). In addition, the different physiological adaptations for extreme hypoxia have been well described in turtles, one of the species with a unique ability to tolerate extreme hypoxia. In humans, an extreme hypoxia condition causes major histopathological events to the brain. However, in turtles that have the ability to resist extreme form of hypoxia, tolerance is seen when a sublethal ischemic/anoxia insult is induced sometime before a lethal ischemic/anoxia insult is induced(Liu et al. 1991). The mechanisms involved are not well understood. Therefore, a better understanding of the mechanisms that induce extreme tolerance to hypoxia in turtles may provide novel therapeutic interventions that may aide human brain to resist the ravages of extreme hypoxia.

6.1 Adenosine facilitates hypoxia neuroprotection by mediating intracellular signaling pathways

Several lines of evidence indicate that severe hypoxia can cause an imbalance between oxygen supply and consumption. This is usually accompanied by transportation of adenosine down its concentration gradient from the cell via nucleoside transporters, such as ENT1 and the ENT2. These transporters are equilibrative nucleoside transporters that are expressed in the CNS (Chaudary et al. 2004b; Chaudary et al. 2004a), to promote the extracellular accumulation of adenosine. In this context, adenosine seems to act as an autocrine signal that indicates the disproportion between cellular oxygen availability and oxygen usage. Since adenosine is also an essential component of ATP synthesis, adenosine pools need to be vigilantly sustained in metabolically active cells in the brain. This could be done by minimizing extracellular release of adenosine, first by down-regulation of ENT activity. This would aid the restoration of ATP pools once the hypoxic stress has been removed. It is also important to point out that an ENT activity could lead to reuptake of extracellular adenosine to terminate receptor activation, as uniquely done by the neurotransmitter transporters to help restore intracellular pools of adenosine. The precise nature of the relationship between adenosine transporters, adenosine receptors and intracellular signaling pathways is not well known. Hypoxia is known to regulate the adenosine transporter mENT1 (inhibitor-sensitive), and protein kinase c q (PKCq) is involved in regulation of mENT1(Chaudary et al. 2004a), suggesting that chronic hypoxia regulates ENT1, both in terms of protein and overall reactivity through PKC-mediated hypoxia preconditioning.

The PKC-mediated hypoxia protection occurs when extracellular adenosine interacts with adenosine receptors (A_{1} , A_{2A} , A_{2B} , and/or A_{3}), and activation of adenosine receptors stimulate signaling pathways that "resist" the stress caused by hypoxia (David et al. 2002). It then implies that the onset of hypoxia leads to a decrease in cellular ATP stores and subsequent generation of adenosine, which is then released extracellularly. An increase in adenosine levels, in addition to bradykinin and opioids, initiate a series of intracellular signaling events via G-protein-coupled receptor signaling leading to activation of PKC activation (Di-Capua et al. 2003). Several studies have shown that injections of adenosine could protect neuronal cells against hypoxic-type injury via a PKC-mediated mechanism (Dave et al. 2009). A series of intracellular signaling that leads to the adenosine-mediated PKC-induced mechanism of hypoxia protection include; i) adenosine stimulates G-protein-coupled receptors, such as the A_{1}/A_{3} adenosine receptors which activate phospholipases (phospholipase C; PLC) via G-proteins ($G_{i/o}$). ii) Other preconditioning stimulus, such as

extracellular glutamate stimulates NMDARs, leading to increased cytosolic calcium and PLC activation. iii) ϵ PKC is activated by PLC, and it increases di-acylglycerol (DAG) production, which in turn activates PKC isozymes including ϵ PKC. Finally, the ϵ PKC activation of extracellular signal-regulated kinase (ERK) promotes survival. Neuronal survival occurs because PKC may induce the opening of K^+ (ATP) channels in the mitochondria (K_{ATP}) to regulate ATP production, and reduce generation of ROS. Interestingly, mitochondria are ideally located to serve as the cellular oxygen signal and mediator of protective mechanisms, such as ion channel arrest. Thus, regulation of mitochondria based mechanism of ion channel arrest involving ATP-sensitive mitochondrial K^+ channels, cytosolic calcium and ROS concentrations could contribute to neuronal survival.

It is also very important to point out that adenosine-mediated ϵ PKC signaling is mediated in part through ERK, a mitogen-activated protein kinase (MAPK) family member that has been implicated in antiapoptotic signaling (Lange-Asschenfeldt et al. 2004). ERK maintains mitochondrial function by inhibiting deleterious Bcl-2 associated death domain protein BAD activity (Qiu et al. 2001). Taken together, adenosine-mediated ϵ PKC signaling seems to activate ERK. This activation is involved in antiapoptotic signaling and cell survival during the induction of hypoxia preconditioning state, in order to salvage 'at-risk-tissue' with residual energy levels. The role of adenosine-mediated ϵ PKC signaling in altering the expression or activity of calcium/calmodulin-dependent protein kinase II, MAPK family members, c-Jun N-terminal kinase, ERK, protein kinase B and PKC indicates that multiple kinases participate in the response of the tissue to counteract the effect of hypoxia (Obexer et al. 2006). This is important because PKC activity has been implicated in cell injury in the cerebral brain (Bright et al. 2008) indicating that it could be involved in a conserved hypoxia response pathway. ϵ PKC activation delays the collapse of ion homeostasis during ischemia in arctic ground squirrels (Dave et al. 2009). This finding suggests that ϵ PKC mediates 26 collapse of ion homeostasis in Arctic Ground Squirrels. This is possible because ϵ PKC inhibits both 27 Na^+/K^+ -ATPase and voltage-gated sodium channels, which are primary mediators of 28 the collapse of ion homeostasis during ischemia in Arctic Ground Squirrel (Perez-Pinzon et al. 2005). For this reason, the specific role of ϵ PKC in mediating hypoxia/ischemia-induced brain injury following the onset of stroke will be an interesting area of attention. Even more interesting is that the controversy over whether PKC mediates or is simply activated during hypoxia/ischemia-induced cell injury has been resolved to an extent by studies in ischemic models that suggest that PKC activity occurs via ϵ PKC that mediates adenosine-induced preconditioning via K^+ _{ATP} function (Chaudary et al. 2004b; Bright et al. 2008).

Several lines of evidence suggest that ϵ PKC can confer cerebral protection partly by maintaining mitochondrial function via ERK activity and by modulating adenosine-induced mK^+ _{ATP} channel function. It is also possible that ϵ PKC activity inside the mitochondria may facilitate the regulation of mK^+ _{ATP} channels, which is important for defending mitochondrial membrane potential and robust maintenance of ionic homeostasis. Recently, the role of ϵ PKC as a key mediator of neuroprotection was investigated (Teshima et al. 2003). Finding from this study indicates that epsilonPKC inhibits both Na^+/K^+ -ATPase and voltage-gated sodium channels, which are primary mediators of the collapse of ion homeostasis during ischemia in Arctic Ground Squirrel. Their results support the hypothesis that ϵ PKC activation is neuroprotective by delaying the collapse of ion homeostasis during ischemia or

hypoxia. This probably involves robust maintenance of ion homeostasis, which leads to the conservation of energy by plummeting calcium influx during metabolic challenges. In summary, studies exploring the specific signaling pathways in which PKC participates, including different downstream effectors in different phases of stroke injury will be significant to develop an adenosine-mediated ϵ PKC signaling therapeutic strategy for the clinical management of stroke patients. It is also important to emphasize that continuous cerebral blood flow, maintenance of cerebral oxygen tension and normal mitochondrial function are vital for the maintenance of brain function and tissue viability in the face of chronic hypoxia. The maintenance of normal brain functions require many parameters to work together and contribute to the homeostasis of brain energy demand and supply. Such a combination of parameters that could, in turn, lead to hypoxia protection include regulation of levels of inducible nitric oxide synthase (Thompson and Dong 2005; Thompson et al. 2009) and expression of HIF-1 α (Trollmann and Gassmann 2009). Other parameters include the activation of extracellular-signal-regulated kinase (Osorio-Fuentealba et al. 2009; Wilkerson and Mitchell 2009) and c-Jun N-terminal kinase/stress-activated protein kinases (Comerford et al. 2004). Understanding the central mechanism that regulates the combination of the parameters is necessary when developing new approaches to remedying hypoxia-induced brain injuries. This is because there is the possibility that a single central cellular mechanism could invoke a combination of parameters that could lead to the remarkable tolerance to hypoxia as seen in natural genetic models of hypoxia-tolerance.

7. Conclusion

Physiological mechanisms of hypoxia neuroprotection in natural systems of hypoxia tolerance represent the core of our understanding of how the brain of a stroke patient can be made to resist hypoxic insults. Our understanding of physiological adaptations associated with hypoxia tolerance in natural systems, and the diverse cellular implications of disrupting brain energy balance when oxygen delivery fails to meet demand provide the insights of how the human brain can be made tolerant to hypoxia. In this review, we suggest that the physiological mechanisms used 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.

8. References

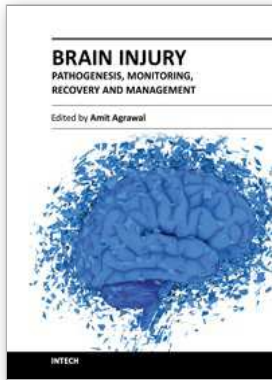
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The present two volume book "Brain Injury" is distinctive in its presentation and includes a wealth of updated information on many aspects in the field of brain injury. The Book is devoted to the pathogenesis of brain injury, concepts in cerebral blood flow and metabolism, investigative approaches and monitoring of brain injured, different protective mechanisms and recovery and management approach to these individuals, functional and endocrine aspects of brain injuries, approaches to rehabilitation of brain injured and preventive aspects of traumatic brain injuries. The collective contribution from experts in brain injury research area would be successfully conveyed to the readers and readers will find this book to be a valuable guide to further develop their understanding about brain injury.

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