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Does Cytochrome C Oxidase Developmentally Condition The Neuron To Ischemia?

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Abstract: Given the possible dynamic existence of axial forms of prototypic ischemic events involving neurons, one might consider the specific concept of selective vulnerability of such neurons to ischemia as a phenomenon arising directly from biologic as well as selective developmental parameters. Indeed, one might consider specific neuronal subsets as simply a characterization, to variable degree, of biologic processes with relevance also to developmental mechanisms in determining ischemia as a pathway of progression or nonprogression. Such a concept of biologic and developmental determination in terms of degree of neuronal susceptibility to ischemia might actually constitute a single axial system that permits possible neuronal recoverability in the context of an induced neuronal injury. Indeed, one might relate defective biologic and developmental recoverability to specific enzymatic systems such as cytochrome C oxidase deficiency arising in a context of either a "normal" or "dysfunctional" neuronal adaptability.

Key words: Ischemia, neuron injury, cytochromec

INTRODUCTION

ESSENTIAL ISCHEMIA AS A BORDERLINE PHENOMENON

An integral phenomenon of ischemic necrosis of cells and tissues would appear to belie the true existence of a complex interplay of processes that paradoxically might at times promote infarction; this is true particularly in relation to compensatory mechanisms or in terms of mechanisms that decrease resistance to ischemic injury as selective vulnerability traits.

Mechanisms of recovery from mild ischemia might, alternatively, enhance progression towards death of cells and tissues in cases of severe ischemia. Progression of perinatal cerebral ischemia might constitute a fundamental phenomenon of neuronal pathology as processes ranging from loss of membrane potential to calcium influx-induced activation of proteases, lipases and endonucleases, and subsequent cytoskeletal injury.

Inflammatory consequences of ischemic neuronal injury might evolve as a developmental system in its own right, directly related to immaturity of the neuron as essential pathways of apoptosis and of imbalance between reactivity and inhibitory neurotransmitter mechanisms[1].

Actively operative factors would biologically arise as cells and tissues effected by ischemia as integrally incorporated mechanisms of progression.

Repeated episodes of ischemia to cells might induce variant physiologic adaptation. The cell would conditionally resist episodes of relative ischemic injury as part of homeostatic systems of potential recovery that, physiologically and biochemically, modify the internal milieu.

An appreciation of the nature of ischemia within a framework of adjustability of cells and tissues as repeated episodes of decreased blood supply would be inherent to life processes and states of potential recovery. Ischemia exerts pathologic effect beyond simple deprivation of oxygen and nutrients or of compensatory reactions on the part of cells and tissues exposed to such ischemia. Heat shock proteins that include HS-70 would play a neuroprotective role in response to oxidative stress and even possibly in the treatment of neurodegenerative disorders[2,3].

Ischemic hypoxia would contribute to the development of Alzheimer-type neurodegeneration via mechanisms arising as oxidative metabolites and inflammatory responses, synaptic membrane- derived lipids and the generation of oxygen-free radicals. Hypoxia might prove an effective biologic inducer of gene activation leading to the production of Nuclear Factor kappaB and hypoxia-inducible factor-alpha that promote inflammation in neurodegeneration[4].

Ischemia, as recognized pathologically and clinically, would evolve as an accentuation of the same set of conditions operating as compensation to and reactive

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progression from injury inflicted on living cells and tissues.

Even within a context of strict homeostatic control of the cellular micro-environment, ischemia would constitute a set of circumstances instrumental in setting in motion successive compensatory mechanisms on the part of cells and also systemically. Hypoxia would promote the development of radial glia in the sub-ventricular and ependymal zones; a subset of such radial glial cells express fibroblast growth factor (FGF) receptor 1 and are in close contact with FGF2-positive cells in the subventricular zone. FGF receptor signaling foster neurogenesis and cell migration; hypoxia-induced FGF signaling in radial glia appear capable of inducing neuroregeneration[5]. Delayed intravenous administration of bFGF improves sensorimotor function as well as reduces infarct size after permanent focal ischemia in rats[6].

Neurogenesis in the subventricular zone of the lateral ventricles and of the subgranular zone of the dentate gyrus would be enhanced in terms of the neural stem cells in cases of brain injury. On the other hand, a neurotrophic factor such as Brain Derived Neurotrophic Factor, that promotes neuronal survival and differentiation during central nervous system (CNS) development, would suppress such insult-induced neurogenesis and would attentuate intrinsic neuroregenerated responses in adult rats[7].

Hypoxia and ischemia might, within a "normal" context of physiologic and "homeostatic" operative mechanisms, induce cells and organs to adaptively progress in a responsive manner to ischemia implicating a cellular patterns of dysfunction independent of morphologic injury to cells, tissues or organs. Death-associated protein kinase (DAPK) mRNA levels rise following cerebral ischemia in terms of regulation by calmodulin; it is pro-apoptotic and would appear to play a role in neuronal development or recovery from injury[8].

The very nature of "normal" cellular physiology and biochemistry would constitute induced forms of adaptability based primarily on protecting cells, tissues, organs and the body in the development of significant ischemia.

Concepts of infarction as circumscribed foci of ischemic progression would constitute involvement of otherwise surviving and functionally operative organs in a living organism that implicate supportive integration in fthe face of ischemia of mild, moderate, or severe degree. An essential framework of operative recoverability arising directly from natural biologic properties of cells, tissues, organs and the body would perhaps constitute a basic definition of the nature of ischemia as a simple cyclical reactivity to injury due to oxygen and nutrient deiciency.

Ischemic tolerance might involve suppression of ion channel functions especially by ionotropic glutamate receptors of neurons-this would be achieved by phosphorylation control, interactions between intracellular and extracellular ions, removal of active receptors from the neurolemma and direct sensing of oxygen by Na + and K + channels. Altered C a2 + concentrations and transcriptional events might also constitute molecular forms of adaptation to oxygen deprivation[9].

BIOLOGIC DICHOTOMY BETWEEN HIGH DELIVERY OF BLOOD SUPPLY AND PROTECTIVE EFFECT BY AN EFFECTIVE BLOOD-BRAIN BARRIER

An essential link would operatively exist between the lymphocyte response and the subsequent macrophage reactivity in lesions of ischemic origin as injury to the central nervous system and of peripheral nerves.

In this connection, STAT1 (Signal Transducers and Activators of Transcription) is activated and translocated within ischemic neurons. These would subsequently induce apoptosis via phosphorylation and regulated transcription in a manner related to their crucial role in growth and differentiation in a variety of cell types[10].

The actual development of neuronal cell injury is triggered by transient cerebral ischemia, and would suppress initiation steps of translation in protein synthesis in terms of dephosphorylation of aIF2B epsilon and p70S6K in endoplasmic reticulum[11].

It would seem probable that CD8 + T lymphocytes are specifically linked to CD8 + macrophages in ischemic injury and in the subsequent Wallerian anterograde degeneration involving the peripheral nervous system.
A whole series of responses appear implicated in disruption of the blood brain or blood nerve barrier.

The central nervous system assumes a privileged immune status. The lack of a significant CD8 + macrophage response following ischemic lesions or even intraorbital axotomy of the optic nerve, would reflect such operatively privileged immune status.

Such a scenario might prove fundamental in determining the nature of the regenerative activity of peripheral and central nervous systems in terms especially of axonal sprouting and repair. Blood delivery of a whole host of growth factors and cytokines would constitute centrally determining dynamics of neuro-regeneration and of replacement of injured neural systems.

Pathogenetic mechanisms involved in brain ischemic damage are activated by neurotrauma; such mechanisms would range from excitotoxicity, to overproduction by free

radicals, to inflammation and apoptosis. Also, both ischemia and trauma would trigger protective measures that include heat-shock proteins, anti-inflammatory cytokines and endogenous anti-oxidants[12].

Even in terms of a framework of biologic and of immunologic sequestration of the central nervous system aspects of control or of biologic progression as essential dynamism would further characterize ischemia as specifically variant or "abnormal" cellular, tissue or organ responsiveness.

Any enhanced recovery from an ischemic cerebral lesion would take into account blood delivery to the central nervous system (CNS) in determining not only delivery of essential neurotrophic factors and cytokines but also in ensuring coordination of such effects with each other. The cytokine interleukin-1 would contribute to ischemic brain damage as exerted through the release of inducible nitric oxide[13].

An essential lack of coordination of trophic factors with cytokines involves blood brain barrier dysfunction with lack of lymphocyte and macrophage activation and with limited recoverability of CNS neurons.

A linking up of a whole series of factors would operate at other sites of the body, including especially peripheral nerves, to centrally evolve as blood supply and blood brain barrier reactivity.

The blood brain barrier might possibly be considered a protective series of mechanisms evolving in the essential context of axial blood flow dynamics in homeostatic preservation of the central nervous system.

The blood brain barrier, although presumably fulfilling essential protective requirements in the context of a highly dynamic blood delivery, would induce a limited biologic response to injury of the central nervous system.

Attempts at improving biologic systems of variable blood supply under stable or "normal" circumstances would involve responsive-type reactivity depending on the particular organ. Ischemia of the CNS as a delicate balance between supply of oxygen and of glucose and as evolving states of biologic variability in responsive adaptation would arise from organ compensatory recovery.

Glial-neuronal interaction would operate to prevent ischemia-reperfusion injury of the retina through increased activity of the mitogen-activated protein kinase (MAPK) signaling pathway of ganglion cells.[14]. In fact, there would develop delayed and differential induction of p38 MAPK isoforms in microglia and astrocytes in transient global brain ischemia[15].

Ubiquitin and protein-disulfide isomerase would exert critical functions as regulatory proteins for CHOP-mediated cell death; their upregulation might confer resistance to ischemic stress in glial cells[16]. Also, gap junction intercellular communication in astrocytes might play a neuroprotective role against glutamate cytotoxicity[17].

Indeed, in cases of injury to the CNS, such a delicate balance, incorporating also or especially functional aspects of the blood brain barrier, might inhibit or impair effective biologic response in terms of regeneration or repair.

Characterization of the biologic sequestration phenomenon related to the central nervous system would perhaps allow a privileged status of high blood delivery to the CNS within a framework of dynamic regenerative phenomena of recoverability of neurons and of neural systems in general. An essential dichotomy of blood supply to an organ such as the CNS in terms of oxygen and glucose utilization would implicate protective compensatory phenomena as variably induced oxidative stress. Unregulated entry of large molecules through the blood-brain barrier and into the organ parenchyma would protect against any circulating micro-organisms and even agonists that injure neurons.

Even with regard to matrix metalloproteinases, tissue inhibitors of metalloproteinase-B would appear associated with neuronal apoptotic death in reperfusion injury[18]. Both apoptotic and necrotic cell death might develop and progress in parallel with focal cerebral ischemia[19,20].

CORRELATION OF CORE TEMPERATURE WITH CEREBRAL BLOOD FLOW IN PATHOPHYSIOLOGY OF CEREBRAL ISCHEMIA

The observed neuroprotective effect of hypothermia after an ischemic episode of the brain attests to the important role of a normal temperature range as a fundamental function of cerebral blood flow. In normal individuals, the core temperature correlates with several parameters affecting blood supply to the brain. In addition to a suggested mechanism for hypothermia-induced neuroprotection via reduction of excessive release of the excitatory amino-acid transmitter glutamate, glycine as another neurotransmitter might also protect in ischemia-induced neuronal injury[21].

Mild hypothermia would induce a neuroprotective effect through a high recovery rate of ATP and PCr (high-energy phosphate) and through the prevention of a secondary decline in high phosphate energy[22].

One may correlate cerebral blood flow with a core temperature in deciding whether that degree of cerebral blood supply adequately maintains normal metabolic and physiologic functions of the cerebrum.

Blood flow and core temperature would integrate as a single pathophysiologic parameter arising from dynamics of cerebral ischemia.

Such integration is reflected in the apparent role of endothelin effecting complex neuron-glial interactions and vascular modulatory activity during ischemia[23]. In terms of neuronal-vascular functionality after cerebral ischemia, hypothermia may fail to protect against neuronal dysfunction during ischemia[24]. In the ischemic penumbra, regeneration of the neuronal network after sustained cerebral ischemia might include GAP-43 (a marker of axonal sprouting), a neurotrophic factor BDNF and a decrease in an adhesion molecular L1[25].

An absolute rate of blood flow to the brain would constitute an accurate assessment of potential damage in cases of brain ischemia that is related to pathophysiologic activation ranging from core temperature to perfusion rates to permeability of blood vessel walls and subsequent potential cerebral edema. With global ischemia to the brain, the core temperature would be altered in terms of the global cerebral ischemia; conversely, hyperthemia would exert deleterious effect arising primarily from ischemia that develops as a result of hemodynamic disturbance.

Such an association of core temperature with cerebral blood flow as an integral pathophysiologic phenomenon ensures normal cerebral function in health but also induces dysfunction in patients with cerebral ischemia. Current concepts of effects of a core temperature in ischemia would perhaps account for the penumbra as a specific attempt at neuronal preservation following ischemic injury to neurons.

Caspase-2 induction and activation are important mediators of delayed neuronal death following transient global ischemia[26]. Also, expression of serine/threonine protein phosphatases in brain regions vulnerable to ischemia would affect cell death after transient forebrain ischemia[27]. Calpain-mediated calcium dependent proteolysis would be involved in the early (induction) and in the late (execution) phases of delayed ischemic neuronal death in the CA1 hippocampus[28].

In acute ischemic injury, core temperature-related parameters might involve a predisposition to greater or lesser degrees of injury to neurons via threshold settings involving metabolic activity, synaptic and neuronal excitability, neurotoxicity from released neurotransmitters as glutamate and probably several other excitatory /inhibitory neurotransmitters in the brain. Hyperbaric oxygenation administered during cerebral ischemia would offer significant neuroprotection, through reduced extracellular dopamine[29].

Both core temperature and cerebral blood flow parameters might determine an overall potential for homeostatic recovery on the part of neurons that allows for manipulative control enhancing neuronal viability.

Circumstances prove highly variable in terms of core temperature or of hemodynamic disturbance influencing ischemic effects and subsequent dynamics of progression or of nonprogression of neuronal ischemic injury.

Preconditioning adaptation induced by transient ischemia might increase brain tolerance to oxidative stress; such mechanisms might involve a role for nitric oxide, cGMP and new protein expression such as thioredoxin[30]. There would develop selective proteasomal dysfunction in the hippocampal CA1 region after transient forebrain ischemia underlying delayed neuronal death[31].

Tolerance to global cerebral ischemia in Huntington's disease transgenic mice would be analogous to ischemic preconditioning in a manner independent of short-term expression of endogenous neuroprotective proteins[32].

Oxidative stress phenomena might simply reflect a vast range of neuronal injury without specific reference to the precise cause of the injury as exemplified by Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis[3]. Transient oxidant exposure as in reperfusion of embryonal cortical neurons would cause a biphasic energy depletion followed by apoptosis as in asphyxiated brains[33]. Both oxygen lack and oxygen excess might constitute pathologic effects that are determined by biologic development characterizing neuronal subsets. Fundamental differences would exist between immature and adult neurons in the downstream involvement of GABA receptors during metabolic insult, particularly in acute and chronic energy inhibition as in stroke/ischemia[34].

CEREBRAL ISCHEMIA ARISING AS FUNCTIONAL BIOLOGY OF CYTOCHROME C OXIDASE OF THE CELLS AFFECTED

Prominent involvement of both brain and skeletal muscle in disorders characterized by deficiency of cytochrome C oxidase (COX) deficiency reflect lesions as seen with involvement of inferior medullary olive or of other neuronal groups in cytochrome C oxidase deficiency in brain-specific regions.

The capricious distribution pattern of cytochrome oxidase deficiency as a dual genetic relationship operating between nuclear and mitochondrial genomes involves the production of various assembly elements essential in the complex construction of the COX apparatus as an integral mitochondrial consequence.

The multiplicity of nuclear genes, mitochondrial genes and COX assembly genes would ensure a normal cytochrome C oxidase complement in tissues as one

component in a whole electron transfer respiratory chain involved in oxidative generation of adenosine triphosphate (ATP).

Iinterference with the ATP excitatory system of extracellular ATP induced transmission in the CNS would provide neuroprotection from brain ischemia. This might relate to stimulation by ATP of ionotropic ligand-gated ion channel purinoceptors with increased intracellular calcium levels and with a process of excitotoxic neuronal injury in stroke[35].

The oxidative enzyme apparatus of the cell is reflected in the development of the cells concerned in actual identification of cell groups constituting a direct reflection of fundamental dynamics of evolving ischemic effect.

Such conditions might actually belie the concept of a simple "cytochrome C oxidase deficiency". A deficiency might be inseparable from cellular dynamics of potential recovery from ischemia.

Analyzing specific neuronal groups in the central nervous system might account for patterns of evolution incorporated within a possibly defective developmental process.

The latter would also be potentially affected by cytochrome C oxidase deficiency in ways indicated by defective neuronal development. The dual genetic control constituted by nuclear and mitochondrial genomes and by a highly complex assembly of the COX would emphasize the centrality of this particular enzyme in determining developmental viability of the cell and also in determining biologic identity of the cell

Cytochrome C oxidase would determine development of survival systems of the ischemic cell as a biologic entity, as related, in turn, to other neurons in the CNS.

Degree of susceptibility to various pathogenic agents might reflect systems of biologic and pathobiologic nature as in cytochrome C oxidase conditioning of ischemic cells.

Perhaps, it is essentially the actual biologic impact of both the efficiency of cytochrome C oxidase and the effect of this on development of the neurons that would determine, to an important extent, specific cellular outcome in cases of cerebral ischemia.

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