International Journal of Molecular Medicine and Advance Sciences 2 (1) : 84-89, 2006

Interactive Dynamics of the Penumbral Zone in Neuronal Ischemia and Prosurvival

Lawrence, M.Agius
Department of Pathology St. Luke's Hospital, Gwardamangia,
University of Malta Medical School, Msida, Malta, Europe

Abstract: In terms of a purely neuronal concept of evolving susceptibility to ischemia or hypoxia, the penumbral phenomenon around a focus of infarction might determine how the cerebral tissues either provoke further progressive neuronal injury or else promote neuronal recovery. Such tissue participation would thus develop as interstitial/vasogenic edema or even as intracellular cytotoxic effect. Integral tissue involvement would promote vascular and hemodynamic factors in determining neuronal outcome. Vascular blood supply and mechanisms linked to cellular energy stores might indicate the participation of neuronal pathways of potential susceptibility or of recoverability that are fully dependent on strict evolving effect. Neuronal ischemia would constitute a phenomenon of tissue evolution as reflected in the penumbra around a focus of already established infarction. The presence of a core of ischemic necrosis in cerebral tissues would determine evolving mechanisms in the penumbral zone determining pathologic and clinical characterization of progressive neuronal ischemia/hypoxia. The individual neuron would constitute one expression of many in a vascular occlusive series of phenomena associated with progression or nonprogression of such neuronal injury. Active tissue participation might develop in directly and indirectly induced cell injury and cell death as either necrosis or apoptosis. Indeed, a central role for tissue vascularity might perhaps determine either cell apoptosis or necrosis in ischemic events of progression or nonprogression.

Key words: Neuronal ischemia, penumbral zone, cell injury

INTRODUCTION

THE PENUMBRA INVOLVES EITHER EXTENSION OF ISCHEMIC NECROSIS OR LIMITS NECROSIS OR APOPTOSIS OF NEURONS

Biologic implications of the apoptotic mechanisms of programmed cell death are particularly important in terms of neurodegeneration and even in the whole general context of cell death including its characterized relationships with cell necrosis as seen in brain ischemia and inflammation[1]. This aspect of cell death dynamics would tend to be compounded by the considerable heterogeneity of stroke pathophysiology in the general population ranging from hypertensive, to embolic and diabetic predisposition to neuronal ischemia[2]. Indeed, for example, in diabetic patients, activation of apoptotic cell death pathways might constitute a possible mechanism for progression of ischemic injury[3].

The distinction of a directly applied form of injury would apply strictly to both active apoptosis and consequential cell necrosis. As such, neurodegeneration as a generic cellular phenomenon would constitute precipitated cascades of events as induced by extrinsic factors, irrespective of any contributing genetic or inherently acquired properties of the cells concerned. As such, genetic elements linked intrinsically to a neurodegenerative state might not be directly implicated in inducing neuronal cell death. Indeed, a highly complex series of phenomena of neuronal ischemic effect would be operative particularly in the region of cerebral penumbral development and progression[4,5]. Also, the mitochondrial apoptosis pathway would be activated by multiple mechanisms during focal cerebral ischemia[6].

Genetically determined neurodegenerative disorders might evolve as cell constitutional factors that permit the development of one of a potentially wide array of forms of cell death via potentially diverse mechanisms as induced by different injurious agents.

For example, phosphorylated PTEN as a suppressor gene would play an important role in cell survival after ischemia as an upstream regulator of P13K-Akt[7].

The programmed execution of apoptotic cell death may be more properly considered as essentially staged series of phenomena once the initial nuclear form of irreversible injury has taken place; this would apply

Corresponding Author: Lawrence, M. Agius, 27 Guzeppi Caruana Street Tal-Virtu, Rabat, RBT 09 Malta, Europe

beyond any possible outcome of subsequent death of the cell as viewed pathobiologically. A molecular definition of the penumbra as gene expression patterns might help clarify such dynamics[8].

Brain ischemia would constitute cell necrosis that is clearly defined and rapidly evolving in terms of neuronal dissolution. Apoptotic cell death in the penumbral region of an ischemic focus might evolve as a phenomenon that may progress to fully developed zonal necrosis.

The degree of ischemic insult would constitute pathways promoting necrosis and neuronal apoptosis. Reperfusion might contribute substantially to caspase-2 activation in inducing penumbral apoptosis but also in the necrotic core[9].

The penumbra as an essential zonal extension of ischemic injury would arise with strict reference to a severely induced central zone of initial necrosis, a phenomenon perhaps distinct from active cell death execution. The penumbral region around a focus of ischemic necrosis would constitute an important dysfunctional consequence of the actual necrotizing process in infarction.

Such a process might implicate mechanisms that normally operate to actively limit extension of any focus of tissue or cellular necrosis in the brain.

Apoptosis affecting the penumbral region of ischemia would perhaps develop as cell death promoting or preventing extension of the necrotic core. Sequential cascade-type events might evolve as cell death of either apoptotic or necrotic type that is dependent on dynamic inter-relations of vascular and hemodynamic mechanisms of evolution and effect. Penumbral zone development would strictly relate to an occluded vessel in the central zone of necrosis. Cerebral tissue necrosis immediately encircling an occluded arterial vessel of supply would be distinct in terms of its evolution to apoptosis or to necrosis affecting the penumbra. In terms of cellular damage derived from ischemia or hypoxia, therefore, a phenomenon based on fundamental dynamics of tissue participation around vascular hemodynamic involvement as dysfunctional elements would go beyond individual cellular concepts of end-target ischemia.

ISCHEMIA/HYPOXIA ACTIVELY ENHANCES TRANSITION TO NORMALITY BEYOND THE PENUMBRA

The term "caspase-dependent cell death" would imply provoked over-activity of involved neurons. A state of excessive overactivity may induce or prevent neuronal cerebral injury. Such an induced crisis of programmed overactivity would perhaps be operative or not operative within a scheme that increases oxygen insufficiency or ischemia. Indeed, neuronal overactivity would tend to further accentuate a state of hypoxia and of insufficient substrates in these neurons.

The neuron as a major target for apoptosis, as seen for example in pontosubicular necrosis, would implicate oxygen insufficiency in terms of an active system of further induced oxygen lack. This would specifically provoke a series of executive steps leading to injury of individual cells and tissues.

The creation of further effective lack of oxygen might precipitate dysfunctional ion channel activity across mitochondrial membranes inducing a stereotyped program of cellular injury evolving in a tissue context. Active participation by neuronal cells and neural tissue in hypoxic and ischemic injury affecting selective neuronal cell groups in hippocampus and ventral pons[10] would perhaps constitute apoptosis as active vascular and hemodynamic mechanisms. Indeed, systems counter-analogous to homeostatic maintenance or to compensatory adaptation[11] by the internal milieu might effectively damage regional tissue fields as integral to restricted tissue and cellular necrosis. The penumbra might allow participation of systems around a core of ischemic neuronal necrosis that constitutes transition from central necrosis to a penumbra of apoptosis arising from vascular occlusion or from hemodynamic dysfunction. A critical transition between the penumbra of neuronal apoptosis to normal neuronal populations beyond the penumbra would evolve specifically in terms of disturbed cellular homeostasis.

NONAVAILABILITY OF ENERGY AS PROGRESSIVELY PERSISTENT CELL/NEURONAL INJURY

PARP-1 activation as a powerful utilizer of NAD and ATP in ongoing DNA repair might constitute a system progressing relative to inducible no (nitric oxide) and glutamate production[12]. Reperfusion injury and superoxide-mediated forms of cell damage might constitute DNA injury mainly significant as energy depletion of cells in attempted recovery from such neuronal injury.

Whether in fact PARP-1 activation constitutes an effective sensor of irreversible neuronal injury would relate to the utilization versus over-utilization of energy stores of the cell concerned. Glutamate-induced neurotoxicity as in focal ischemia might perhaps constitute neuronal over-excitation in a context particularly of previously injured neurons[13].

Over-utilization of neuronal energy stores would constitute irreversible neuronal injury related specifically to DNA breakage. DNA injury would determine recoverability of neuronal injury in terms of essential loss of neuronal viability. It is indeed in this sense, perhaps, that the very concept of neuronal viability would translate mainly as degrees of utilization of energy determining recoverability of the neuron from damage that goes beyond simple distinction of apoptosis from necrosis. Neurodegeneration as attempted neuronal recovery is influenced by DNA damage that provokes further injury and further energy depletion.

Once initiated, neuronal injury might transform to an ongoing cascade of events that continually self-reinforces irreversibility in terms of mechanisms stemming from the actual cause of ischemia.

Synaptic transmission may become impaired after cerebral ischemia, with involvement of phosphorylation of presynaptic proteins contributing to such injury[14].

In a sense, perhaps, PARP-1 and energy over-utilization are mechanistic pathways that allow progression as cell injury and as a progressive irreversibility of an early stage of neuronal injury.

The infliction of such neuronal injury would implicate variable availability of energy as related to ATP[15] and NAD stores but especially as immediately available forms of cell energy. Early ischemia and hypoxia would induce cell injury as potential transformation impairing recoverability of neurons. Attenuation of the post-reperfusion increase in neuronal cytosolic Cytochrome C would decrease neuronal phosphorylated-Akt in preventing an increase in infarct area[16].

Reperfusion injury in superoxide or oxidant injury might constitute a main cause of persistent neuronal injury that impairs recoverability in the added context of nonavailability of cellular energy stores and of evolving neuronal injury.

INTRANEURONAL ACIDOSIS/REBOUND ALKALINIZATION CYCLES AS SELECTIVE VULNERABILITY OF HIPPOCAMPAL NEURONS TO ISCHEMIA AND HYPOXIA

Intracellular acidosis followed by rebound alkalinization would specifically implicate not only excessive glutamate release from neurons but also neuronal injury resulting from such glutamate release. This particular susceptibility of neurons might involve more than just induced release of glutamate.

A strict acidosis followed by a rebound alkalinization sequence intra-neuronally might constitute basic circumstances rendering the neuron selectively vulnerable to potentially varied injury including further excessive glutamate release.

Such selective vulnerability of neurons in terms of sharp acidification/rebound alkalinization cycles would render an exquisite susceptibility of neurons that involves hippocampal ischemia and hypoxia. These latter lesions would relate to reperfusion injury or to re-exposure to excess oxygen within a context both of vascular hemodynamic disturbance and also of impaired energy store dynamics of transfer and utilization. In this sense, the no reflow perfusion phenomenon would contribute actively in developing neuronal damage in the ischemic penumbral region[17].

Even states of seizure activity with their often dynamically induced phases of disturbed oxygen supply to neurons might promote selective vulnerability of groups of neurons to alternating cycles of intra-neuronal acidosis and rebound alkalinization.

HYPOXIA BEYOND CELL INJURY OR CELL ADAPTATION AND AS A PATHWAY OF STIMULATED CELL BIOLOGIC MECHANISMS

Hypoxic resistance incorporates not simply resistance to chemotherapy and radiotherapy in the case of tumors but also evolutionary pathways that integrate in complex fashion much of the cell biologic and biochemical processes in cell survival after oxygen lack[18]. In a sense, hypoxia would activate pathways such as c-jun expression and binding of the activator-protein 1 (AP-1) element in a manner that would transform the cell. This would operate not simply from a predominantly aerobic to a less aerobic mode of pathway mechanisms but to operative cascade-type events actively combating hypoxic injury.

In this manner, for example, Vascular Endothelial Growth Factor (VEGF)[19] as a system pathway of induced angiogenesis would not simply constitute a response to hypoxia of tumor cells but a virtual mechanism that utilizes hypoxia-driven pathways towards realized endothelial hyperplasia and angiogenesis.

Hypoxia and ischemia regulate the expression of several important genes at the level of transcription and of mRNA stability including the differential expression of poly(C)-binding protein isoforms[20]. Hypoxic conditions appear an essential series of mechanistic pathways virtually inherent to cell biology, whether this specifically implicates stress-induced injury to the cell or not[21].

Actively operative pathways in the cell would relate to hypoxia as a series of mechanisms that are specifically driven. Cells would effectively utilize hypoxia as a stimulus as well as a source of progressive pathobiology.

Such considerations might be significant also with respect to prosurvival cell signaling that is actively initiated before onset of cell death pathways in neuronal ischemia[22].

NEURONAL ISCHEMIA BEYOND A SIMPLE CONCEPT OF DIRECTLY APPLIED NEURONAL INJURY

Actual neuronal ischemia might implicate the establishment of criteria, pathophysiologically and pathologically, that would go especially beyond phosphorylated ERK and cytochrome C[23]. Such criteria might incorporate the neuron and the neuronal network with its supporting blood supply and glial framework as systems of response and compensation and as a real potential for recovery from ischemia. Indeed, the essentially dynamic nature of the pathobiology of ischemia might constitute potential progressiveness with strict reference to contextual neural tissue involvement.

Ischemia, as a clinical and pathologic event, might constitute insufficient delivery of oxygenated blood to neurons especially as a mechanistic pathway characterized by incorporated patterns of upregulation and downregulation of cellular adaptability to such cell injury.

Variable but clinically significant neuronal ischemia might constitute evolving neuronal exposure in terms of integrally acute and chronic lack of oxygen. Impaired delivery of oxygenated blood would specifically determine cellular injury developing essentially in a tissue and organ context.

Neuronal ischemia clinically leading to neuronal death as necrosis or apoptosis might implicate variable availability of neurotrophic factors and even of intracellular calcium as highly dynamic parameters promoting cellular cascade-type pathways.

Incorporation of both neuroprotective and neurodegenerative cellular processes might be analogous to apoptotic mechanisms whereby ischemia is itself an activation pathway either of effective neuro-protective mechanisms or of precipitated cascade-type events. Initial steps in neuronal injury would evolve in a context of pathobiologic attempts at cell and integral tissue recovery.

Also anti-apoptotic transgenes as for bcl-2 protein would theoretically be useful in alleviating post-ischemic injury[24]. Ischemia might actually promote operative compensatory mechanisms of recoverability on the part of the neuron as an integral neural tissue of response. In fact, one might, perhaps, better consider the neuron as only one component within a full system of failed blood supply to tissues as evolving pathways of either injury or compensation in the ischemia/hypoxia.

Acute neuronal susceptibility would progressively increase resistance to ischemia as homeostatic pathways of responsive participation in tissue hemodynamics.

In a sense, neuronal response and injury, after an episode of ischemia of lesser or greater degree, might evolve as a reactivity of neurons that are highly dependent on a constant supply of oxygen to neurons or to neural tissues.

Selective vulnerability of neuronal systems to ischemia might indicate an intrinsic reactivity of the neuron incorporating responsive adaptation and also expenditure of mitochondrial energy.

Voltage-gated ion channels in the neuronal membrane and activation or suppressed activation of whole cascades of proteases or caspases might constitute pathways of apoptotic or necrotic neuronal cell injury specifically centered on vascular hemodynamics. Partial or total vascular occlusion within a context of tissue participation would evolve in terms of cytotoxicity[25] versus vasogenic edema. These would constitute interactive pathways of possible progressiveness in cases of neuronal and neural tissue injury in ischemia/hypoxia. Inducible nitric oxide synthase as expressed in the ischemic penumbra might be involved in the recruitment of penumbra into infarction, with subsequent increase in infarct size[26].

A concept of cellular adaptation to hypoxic conditions[27] might implicate integral utilization of available oxygen in a manner that would allow its optimal utilization also as growth factor availability[28,29] or even as erythropoietin[30] utilization. In this manner, perhaps, metabolic utilization of oxygen and of glucose might operate in response to hypoxia, via a system of facilitated receptivity to trophic effect. In this sense, perhaps, cells would indeed be structured in a manner that allows hypoxia to selectively induce or suppress cellular and tissue pathways integrally coupling modes of utilization with metabolic rate control.

In this sense, VEGF as a system of angiogenesis might induce a response to autonomous tumor cell apoptosis/antiapoptosis phenomena in cases of tumor evolution.

Apoptosis of tumor cells might even develop as an autonomous series of mechanisms of autocrine loop operability whereby hypoxia determines the threshold levels of such intra-loop autocrine operability. Tumor cell hypoxia may evolve as a main determinant of threshold levels of operability of autocrine loops. These might participate to directly allow neuronal integration when a cerebral artery of supply is occluded (as detected

especially by functional or perfusion-computed tomography)[31] or where ischemic/hypoxic injurious events develop as progressive apoptosis or necrosis. Indeed, the penumbra might actually constitute a tendency for neuronal ischemic/hypoxic injury that progresses or does not progress in neural tissue and as vascular components of ischemia or hypoxia. Vascular endothelial growth factor might be important in repair of damaged neuronal DNA that develops after transient cerebral ischemia[19].

REFERENCES

1. Siao, C.J. and S.E. Tsirka, 2002. Extracellular proteases and neuronal cell death, Cell Mol. Biol. (Noisy-le grand), 48: 151-161.
2. Muir, K.W., 2002. Heterogeneity of stroke pathophysiology and neuroprotective clinical trial design. Stroke, 33: 1545-1550.
3. Muranyi, M., M. Fujioka, Q. He, A. Han, G. Yong, K. Csiszar and P.A. Li, 2003. Diabetes activates cell death pathway after transient focal cerebral ischemia, Diabetes, 52: 481-486.
5. Pestalozza, I.F., S. Di Legge, M. Calebresi and G.L. Lenzi, 2002. Ischaemic penumbra: Highlights. Clin. Exp. Hypertens, 24: 517-529.
6. Yin, X.M., Y. Luo, G. Cao, L. Bai and W. Pei, *et al*., 2002. Bid-mediated mitochondrial pathway is critical to ischemic neuronal apoptosis and focal cerebral ischemia. J. Biol. Chem., 277: 42074-42081.
7. Omori, N., G. Jin, F. Li, W.R. Zhang, S.J. Wang and Y. Hamakawa, *et al*., 2002. Enhanced phosphorylation of PTEN in rat brain after transient middle cerebral artery occlusion. Brain Res., 954: 317-322.
8. Chuquet, J., K. Benchenange, G. Liot and M. Fernandez-Monreal, *et al*., 2002. Matching gene expression with hypometabolism after cerebral ischemia in the nonhuman primate. J. Cereb Blood Flow Metab, 22: 1165-1169.
9. Manabat, C., B.H. Hau, M. Wendland and N. Derugin, *et al*., 2003. Reperfusion differentially induces caspase-3 activation in ischemic core and penumbra after stroke in immature brain. Stroke, 34: 207-213.
10. Stadelmann, C. *et al*., 2001. Expression of cell-death-associated proteins in neuronal apoptosis associated with Pontosubicular neuron necrosis. Brain Pathology, 11: 273-281.
11. Fisher, M. and R. Ratan, 2003. New perspectives on developing acute stroke therapy. Ann. Neurol., 53: 10-20.
12. Ha, H. and S.H. Snyder, 2000. Poly (ADP-ribose) Polymerase-1 in the nervous system, Neurobiol. Dis., 7: 224-239.
13. Wu, A. and D.G. Fujikawa, 2002. Effects of AMPA-receptor and voltage-sensitive sodium channel blockade on high potassium-induced glutamate release and neuronal death *In vivo*. Brain Res., 946: 119-129.
14. Bolay, H., Y. Gursoy-Ozdemir, Y. Sara, R. Omar, A. Can and T. Dalkara, 2002. Persistent defect in transmitter release and synpsin phosphorylation in cerebral cortex after transient moderate ischemic injury. Stroke. 33: 1369-75
15. Lust, W.D., C. Taylor, S. Punkik, W.R. Selman and R.A. Ratcheson, 2002. Ischemic cell death: Dynamics of delayed secondary energy failure during reperfusion following focal ischemia, Metab Brain Dis., 17: 113-121.
16. Yoshimoto, T., P. Kanakaraj, J. Ying Ma and M. Cheng, *et al*., 2002. NXY-159 maintains Akt activation and inhibits release of cytochrome C after focal cerebral ischemia. Brain Res., 947: 191-198.
17. Liu, S., J. Connor, S. Peterson, C.W. Shuttleworth and K.J. Liu, 2002. Direct visualization of trapped erythrocytes in rat brain after focal ischemia and reperfusion. J. Cereb Blood Flow Metab, 22: 1222-1230.
18. Vasilevskava, I.A. and P.J. O'Dwyer, 1999. Effects of geldanamycin on signaling through activator-protein 1 in hypoxic HT29 human colon adenocarcinoma cells. Cancer Res. 59: 3935-3940.
19. Yang, Z.J, W.L. Bao, M.H. Qiu and L.M. Zhang, *et al*., 2002. Role of vascular endothelial growth factor in neuronal DNA damage and repair in rat brain following a transient cerebral ischemia. J. Neurosci. Res., 70:140-149.
20. Zhu, Y., Y. Sun, X.O. Mao, K.L. Jin and D.A. Greenberg, 2002. Expression of poly (C)-binding proteins is differentially regulated by hypoxia and ischemia in cortical neurons. Neuroscience, 110: 191-198.
21. Kokubo, Y., G.B. Matson, J. Liu, A. Mancuso and T. Kayama, *et al*., 2002. Correlation between changes in apparent diffusion coefficient and induction of heat shock protein, cell-specific injury marker expression, and protein synthesis reduction on diffusion-weighted magnetic resonance images after temporal focal cerebral ischemia in rats. J. Neurosurg, 96: 1084-1093.
22. Shibata, M., T. Yamawaki, T. Sasaki and H. Hattori *et al*., 2002. Upregulation of Akt phosphorylation at the early stage of middle cerebral artery occlusion in mice. Brain Res., 942: 1-10.
23. Li, F., N. Omori, K. Sato, G. Jin, I. Nagano, M. Shoji and K. Abe, 2002. Coordinate expression of survival p-ERK and proapoptotic cytochrome C signals in rat brain neurons after transient MCAO, Brain Res, 958: 93-98.

24. Cao, Y.J., T. Shibata and N.G. Ranov, 2002. Liposome-mediated transfer of the bcl-2 gene results in neuroprotection after *In vivo* transient focal cerebral ischemia in an animal model. Gene. Ther., 9: 415-419.
25. Li, W., X.M. Yuam, S. Ivanova, K.J. Tracey, J.W. Eaton and W.T. Brunk, 2003. 3-Aminopropanol, formed during cerebral ischemia, is a potent lysosomotropic neurotoxin, Biochem. J., Pt(epub ahead of print).
26. Zhu, D.Y., Q. Deng, H.H. Yao, D.C. Wang, Y. Deng and G.Q. Liu, 2002. Inducible nitric oxide synthase expression in the ischemic core and penumbra after transient focal cerebral ischemia in mice. Life Sci., 81:1985-1996.
27. Nakajima, T., S. Iwabuchi, H. Miyazaki and Y. Okuma, *et al*., 2002. Relationship between the activation of cyclic AMP responsive element binding proteins and ischemic tolerance in the penumbra region of rat cerebral cortex. Neurosci. Lett., 331: 13-16.
28. Feldser, D. *et al*., 1999. Reciprocal positive regulation of hypoxia-inducible factor 1-alpha and insulin-like growth factor 2. Cancer Res., 59: 3915-3918.
29. Dillon-Arter, O., R.E. Johnston, C.V. Borlongan, M.E. Truckenmiller, M. Coggiano and W.J. Freed, 2002. T155g-immortalized kidney cells produce growth factors and reduce sequelae of cerebral ischemia, Cell Transplant, 11: 251-259.
30. Brines, M., 2002. What evidence supports use of erythropoietin as a novel neurotherapeutic, Oncology (Huntingt), 16: 79-89.
31. Wintermark, M. and J. Bogousslavisky, 2003. Imaging of acute ischemic brain injury: The return of computed tomography. Curr. Opin. Neurol., 16: 59-63.