HBOT 2016 presentation
Pathophysiology of Cerebral and Traumatic Brain Insults:
Similarities and Differences

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TABLE 1. Epidemiology of Stroke and Traumatic Brain Injury (USA statistics).

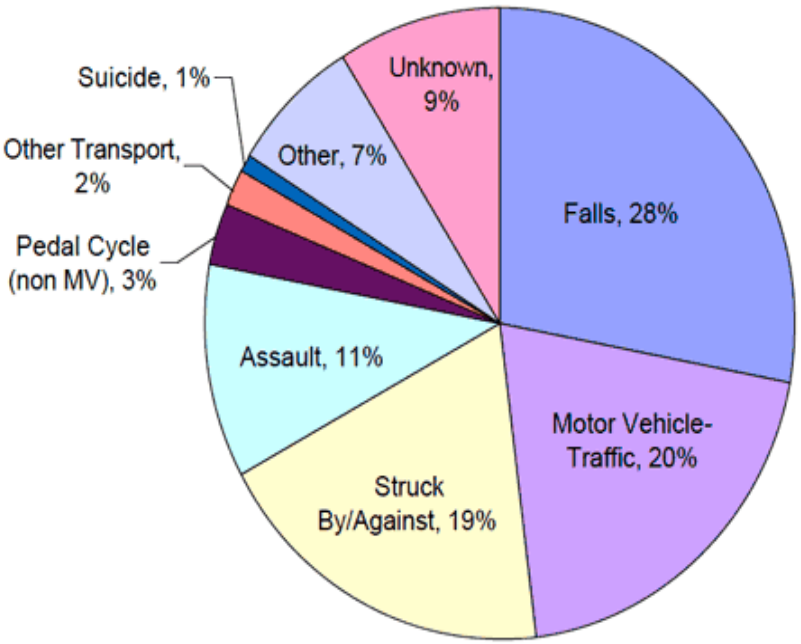
TABLE 1. *Epidemiology of Stroke and Traumatic Brain Injury (USA statistics)*

	Stroke	TBI
Incidence	600,000 new or recurrent strokes annually	1.5 million annually
Gender	In most age groups, more common in men than women although women have a higher incidence of mortality following a stroke	Males are twice as likely to have brain trauma than females
Age	28% under the age of 65	Higher incidence in adolescents, young adults and people over the age of 75
Mortality	167,366 deaths from stroke annually	50,000 annual deaths from brain trauma
Chronic Outcome	1.1 million Americans living with long-term disability from stroke	5.3 million Americans living with permanent disability due to TBI
Costs (Direct and Indirect)	$49.4 billion annually	$48.3 billion annually

Helen M. Bramlett, and W. Dalton Dietrich J Cereb Blood Flow Metab 2004;24:133-150

Civilian TBI experience

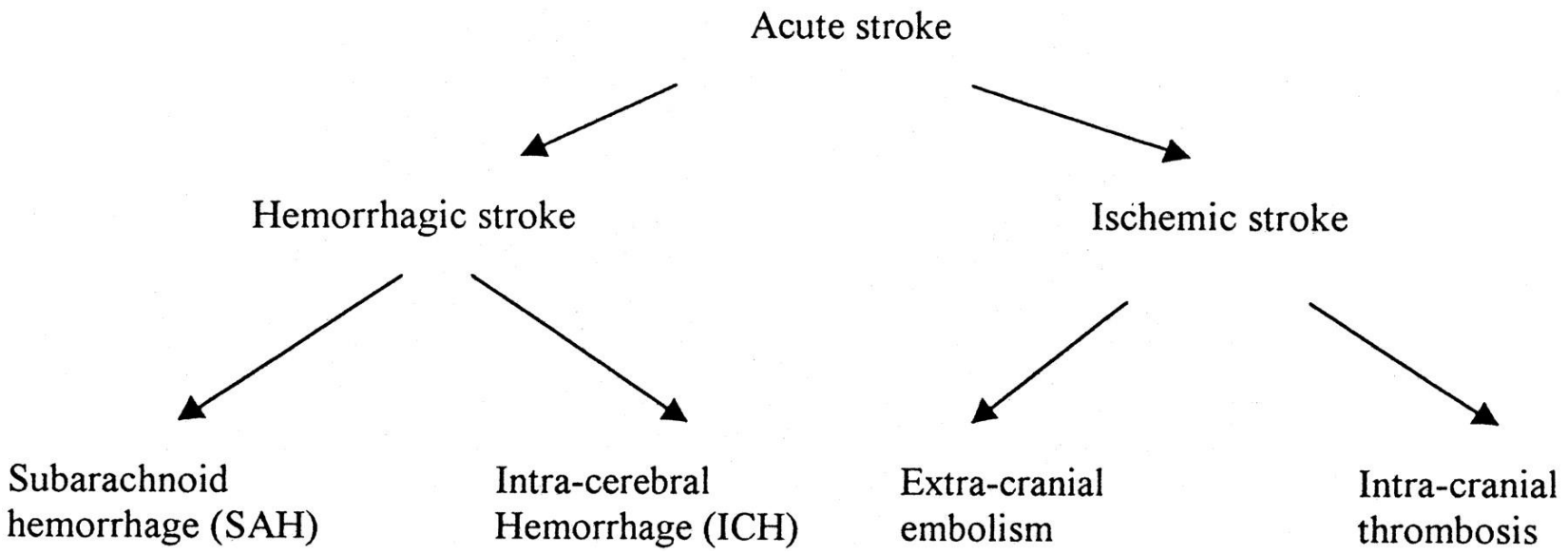
1. Most common cause of disability / death young people
2. 4,563,000 TBIs annually
3. TBI disability in 2% US population; 50,000 deaths
4. 80% mild, 10% moderate, 10% severe
5. $56.3 billion/yr



Epidemiology and scope of the problem of civilian mTBI

- Most information about the incidence and prevalence of mTBI comes from studies of brain injury of all severities.
- Incidence extrapolations for USA for Automobile accidents injury**:** 4,563,000 per year, 380,250 per month, 87,750 per week, 12,501 per day, 520 per hour, 8 per minute
- 1.74 million persons sustain mild TBI requiring an office visit or temporary disability for at least 1 day.
- Most estimates of the percentage of injuries that are mild fall within the 60%-80% range.
- Mild injury occurs about twice as frequently in males, with increased incidence in the 15-24 and over-70 age groups.

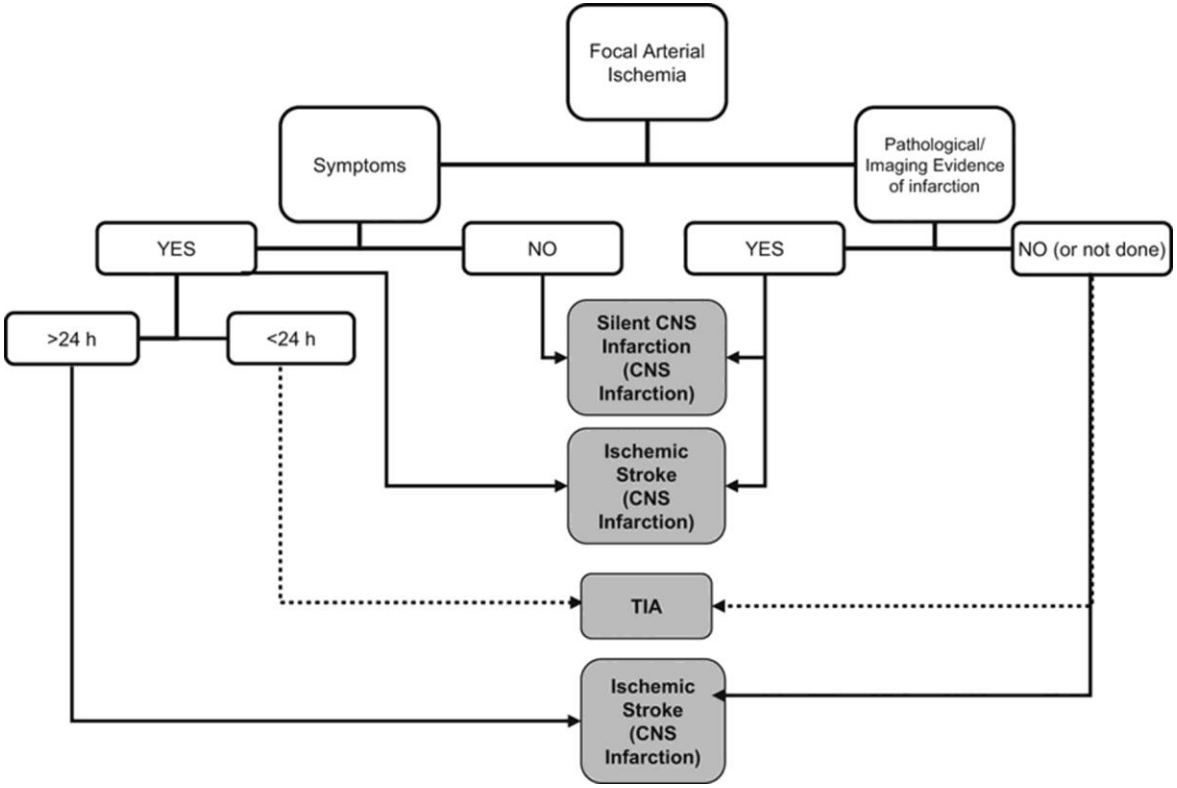
Classification of acute stroke



Yossi Gilgun-Sherki et al. Pharmacol Rev 2002;54:271-284

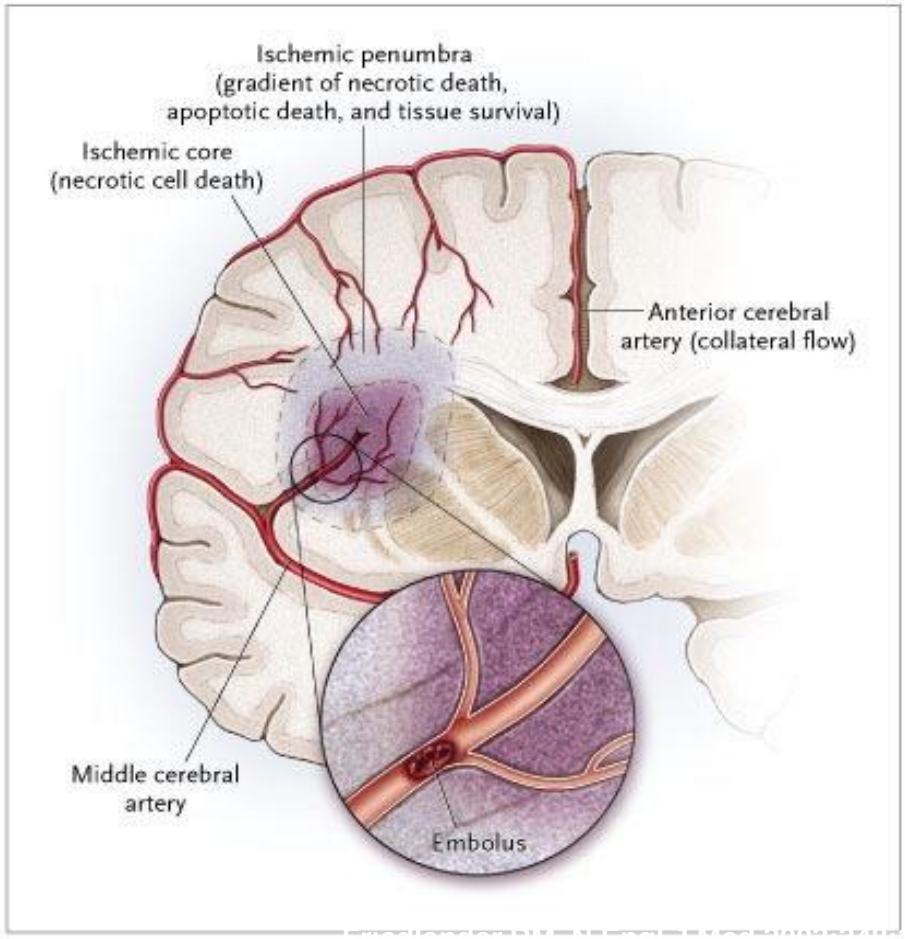
ASPET PHARMACOLOGICAL REVIEWS

Flow chart depicting a proposed decision tree for determination of a cerebrovascular event definition.



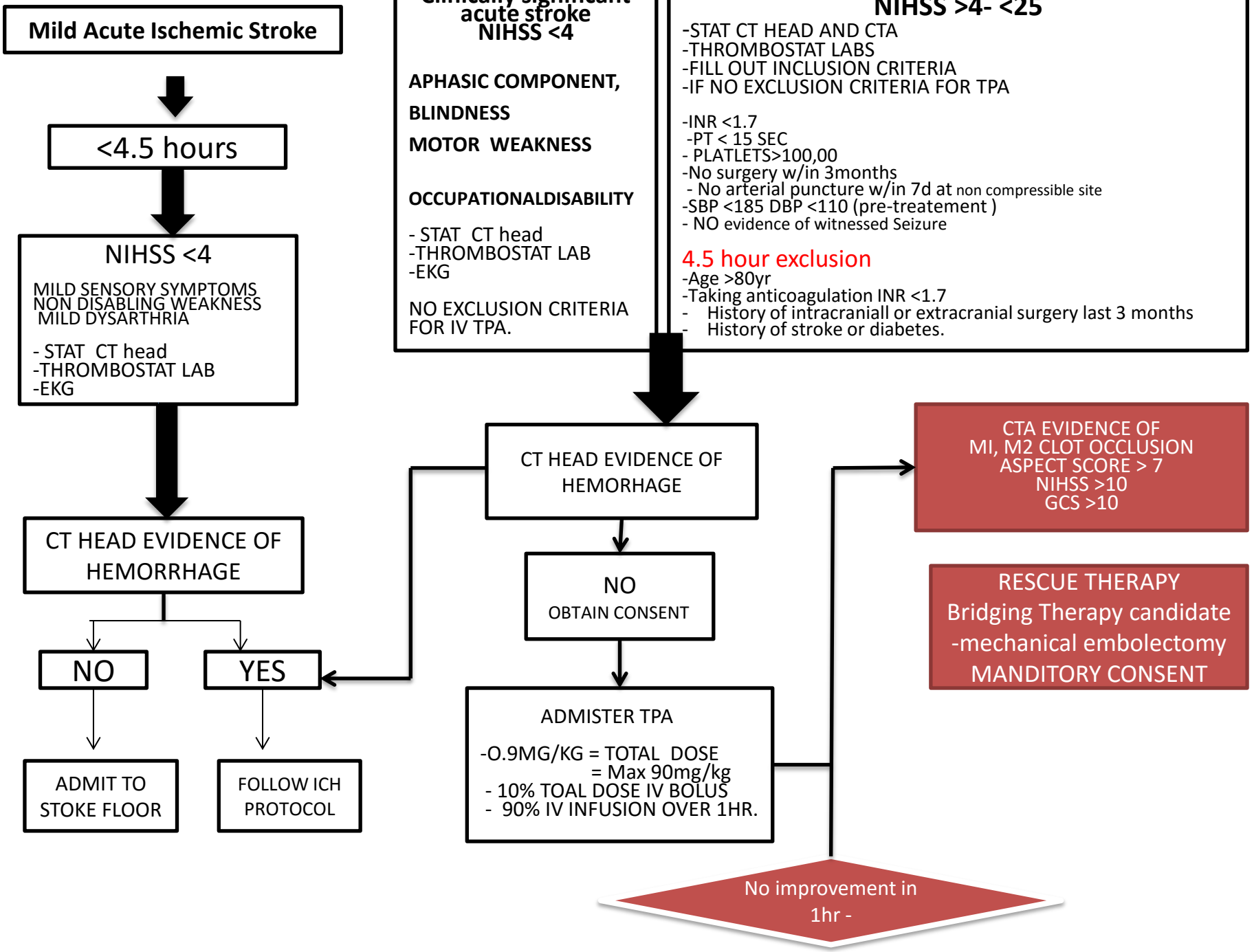
Ralph L. Sacco et al. Stroke. 2013;44:2064-2089

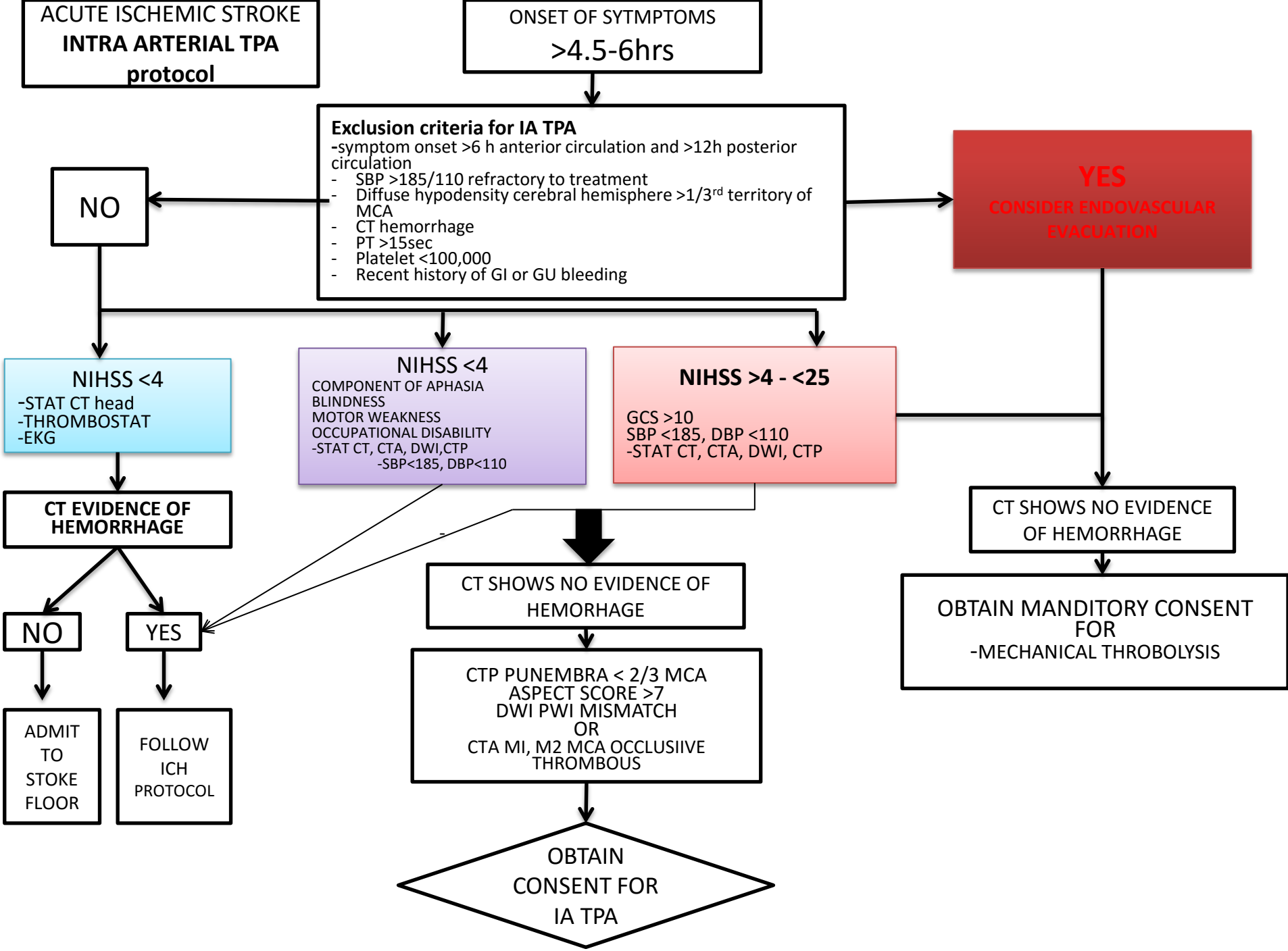
Time window in the acute stroke



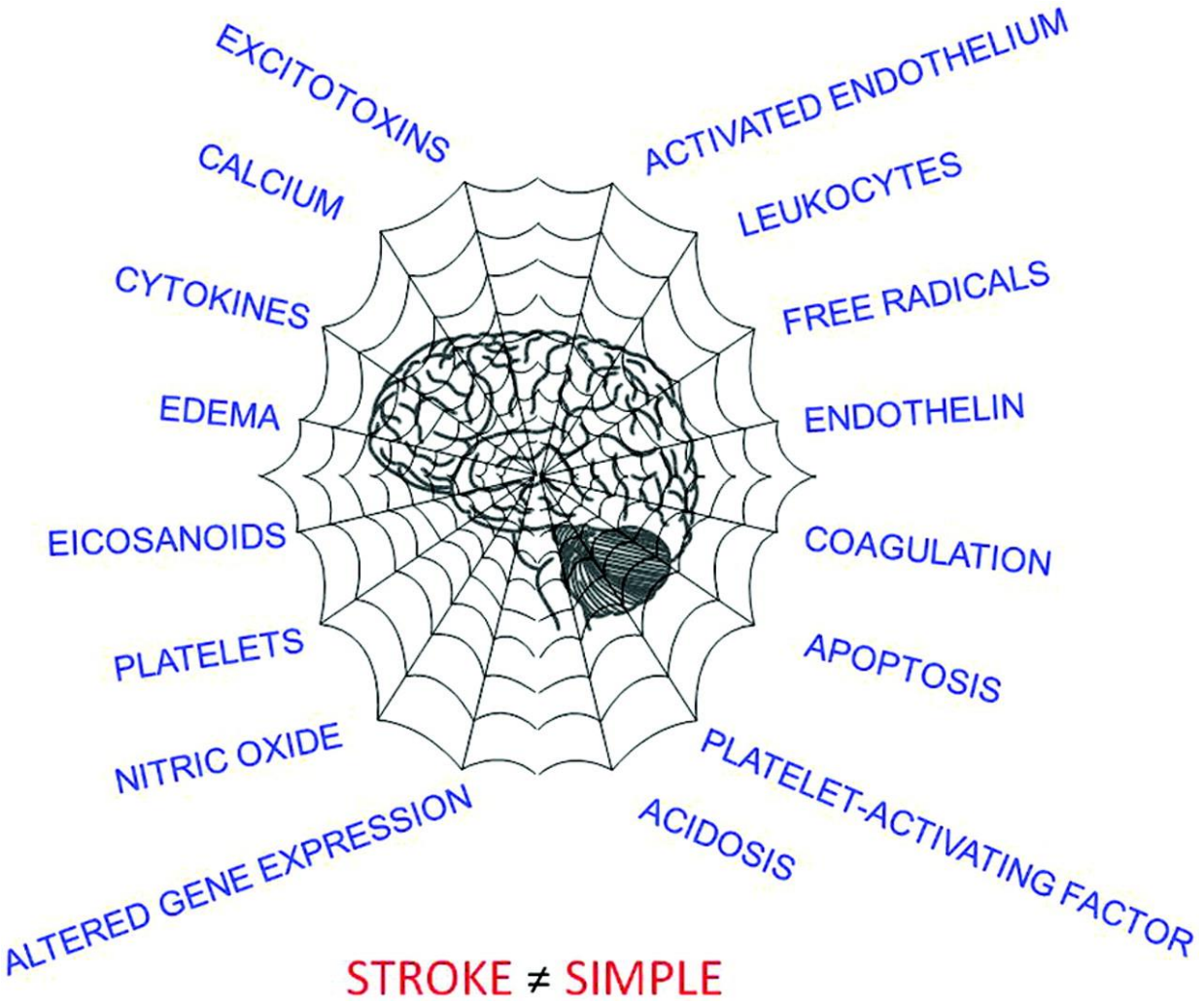
Penumbra

The territory perfused by this artery and areas with little or no collateral flow are subjected to extreme hypoxia and necrotic cell death. In the penumbra, where there is some degree of collateral blood flow, a gradient of tissue perfusion establishes a threshold among necrotic cell death, apoptotic cell death, and tissue survival.


Mild Acute Ischemic Stroke
<4.5 hours
NIHSS <4
MILD SENSORY SYMPTOMS
NON DISABLING WEAKNESS
MILD DYSARTHRIA
- STAT CT head
-THROMBOSTAT LAB
-EKG
CT HEAD EVIDENCE OF HEMORRHAGE
NO
YES
ADMIT TO STOKE FLOOR
FOLLOW ICH PROTOCOL
Clinically significant acute stroke NIHSS <4
APHASIC COMPONENT,
BLINDNESS
MOTOR WEAKNESS
OCCUPATIONALDISABILITY
- STAT CT head
-THROMBOSTAT LAB
-EKG
NO EXCLUSION CRITERIA FOR IV TPA.
NIHSS >4- <25
-STAT CT HEAD AND CTA
-THROMBOSTAT LABS
-FILL OUT INCLUSION CRITERIA
-IF NO EXCLUSION CRITERIA FOR TPA
-INR <1.7
-PT < 15 SEC
- PLATLETS>100,00
-No surgery w/in 3months
- No arterial puncture w/in 7d at non compressible site
-SBP <185 DBP <110 (pre-treatement)
- NO evidence of witnessed Seizure
4.5 hour exclusion
-Age >80yr
-Taking anticoagulation INR <1.7
- History of intracraniall or extracranial surgery last 3 months
- History of stroke or diabetes.
CT HEAD EVIDENCE OF HEMORHAGE
NO
OBTAIN CONSENT
ADMISTER TPA
-O.9MG/KG = TOTAL DOSE
= Max 90mg/kg
- 10% TOAL DOSE IV BOLUS
- 90% IV INFUSION OVER 1HR.
CTA EVIDENCE OF MI, M2 CLOT OCCLUSION
ASPECT SCORE > 7
NIHSS >10
GCS >10
RESCUE THERAPY
Bridging Therapy candidate
-mechanical embolectomy
MANDITORY CONSENT
No improvement in 1hr -


ACUTE ISCHEMIC STROKE
INTRA ARTERIAL TPA protocol
ONSET OF SYTMPTOMS
>4.5-6hrs
Exclusion criteria for IA TPA
-symptom onset >6 h anterior circulation and >12h posterior circulation
- SBP >185/110 refractory to treatment
- Diffuse hypodensity cerebral hemisphere >1/3rd territory of MCA
- CT hemorrhage
- PT >15sec
- Platelet <100,000
- Recent history of GI or GU bleeding
NO
YES
CONSIDER ENDOVASCULAR EVACUATION
NIHSS <4
-STAT CT head
-THROMBOSTAT
-EKG
NIHSS <4
COMPONENT OF APHASIA
BLINDNESS
MOTOR WEAKNESS
OCCUPATIONAL DISABILITY
-STAT CT, CTA, DWI,CTP
-SBP<185, DBP<110
NIHSS >4 - <25
GCS >10
SBP <185, DBP <110
-STAT CT, CTA, DWI, CTP
CT EVIDENCE OF HEMORRHAGE
NO
YES
ADMIT TO STOKE FLOOR
FOLLOW ICH PROTOCOL
CT SHOWS NO EVIDENCE OF HEMORHAGE
CTP PUNEMBRA < 2/3 MCA
ASPECT SCORE >7
DWI PWI MISMATCH
OR
CTA MI, M2 MCA OCCLUSIIVE THROMBOUS
OBTAIN CONSENT FOR IA TPA
CT SHOWS NO EVIDENCE OF HEMORRHAGE
OBTAIN MANDITORY CONSENT FOR
-MECHANICAL THROBOLYSIS

Stroke is not simple.



John M. Hallenbeck Stroke. 2012;43:585-590

American Heart Association.

Neurodegeneration after ischemic stroke

Complex mechanisms of ischemic brain injury involve:

- Energy failure
- Excitotoxicity
- The accumulation of reactive oxygen species (ROS), programmed cell death
- Inflammatory processes
- Microvascular unit
- Brain injury-induced immunodeficiency
- Reversible phosphorylation
- Protein kinases and phosphatases are becoming the focus of stroke research, as reversible phosphorylation has a crucial role in the fine-tuning of many biochemical pathways, including cell death and survival signaling

Carsten Culmsee, Josef Krieglstein EMBO Rep. 2007 Feb; 8(2): 129–133.

Common mechanisms of the ischemic and traumatic insults

Issue is in the tissue

Pathophysiology
Neuropathological Evidence

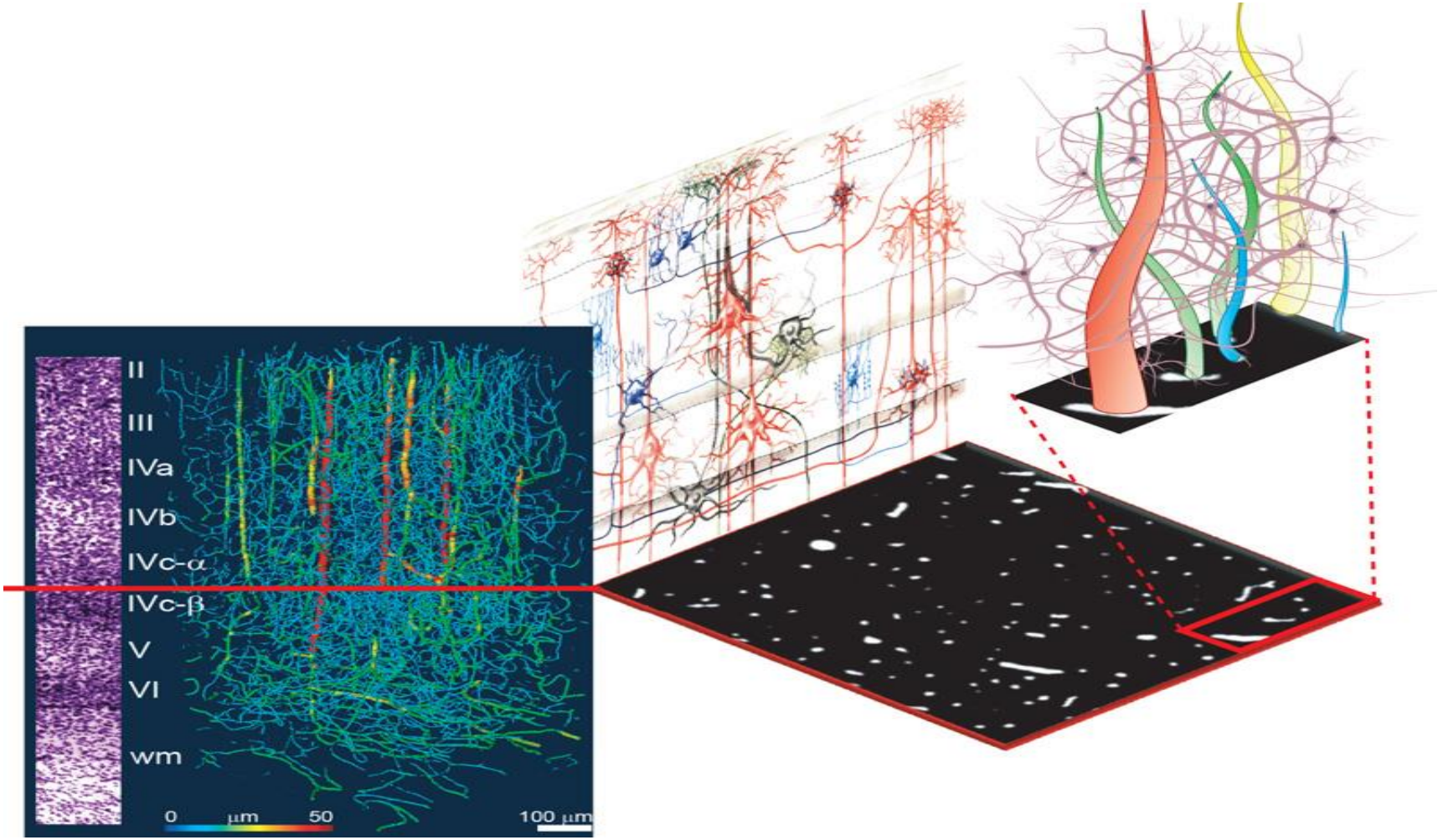
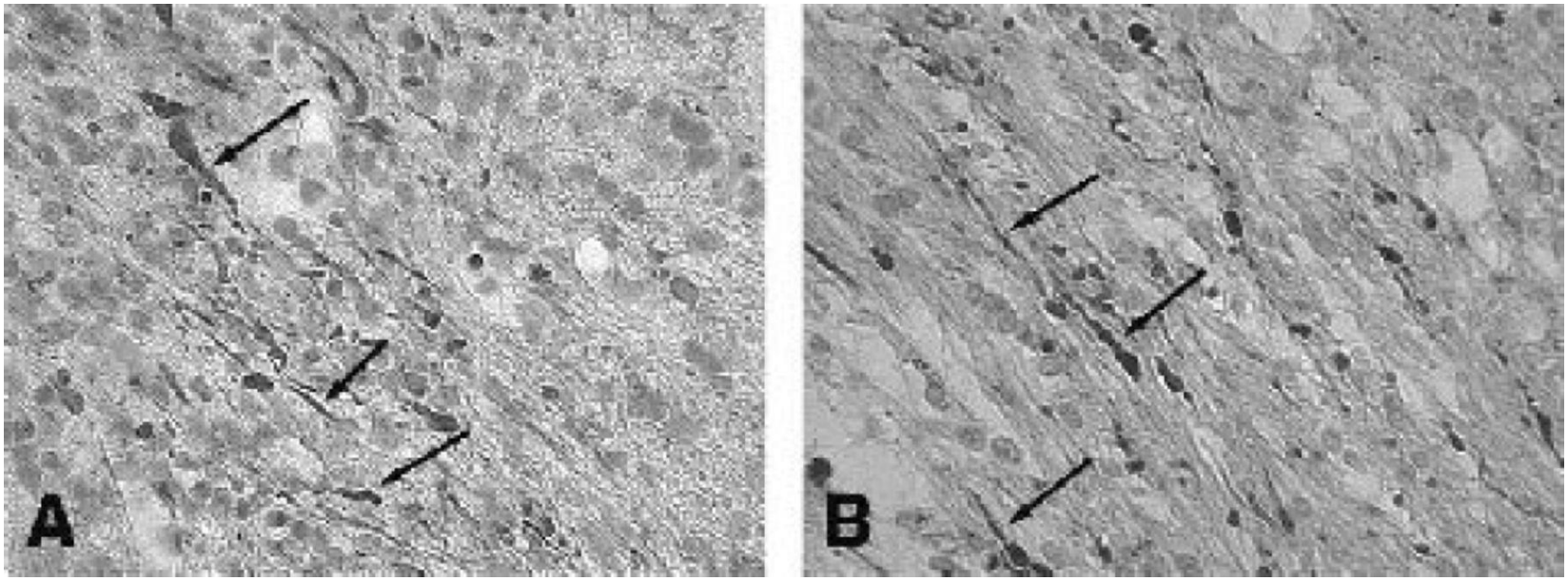


Fig. 1. Both cerebral ischemia and traumatic injury lead to white matter vulnerability.



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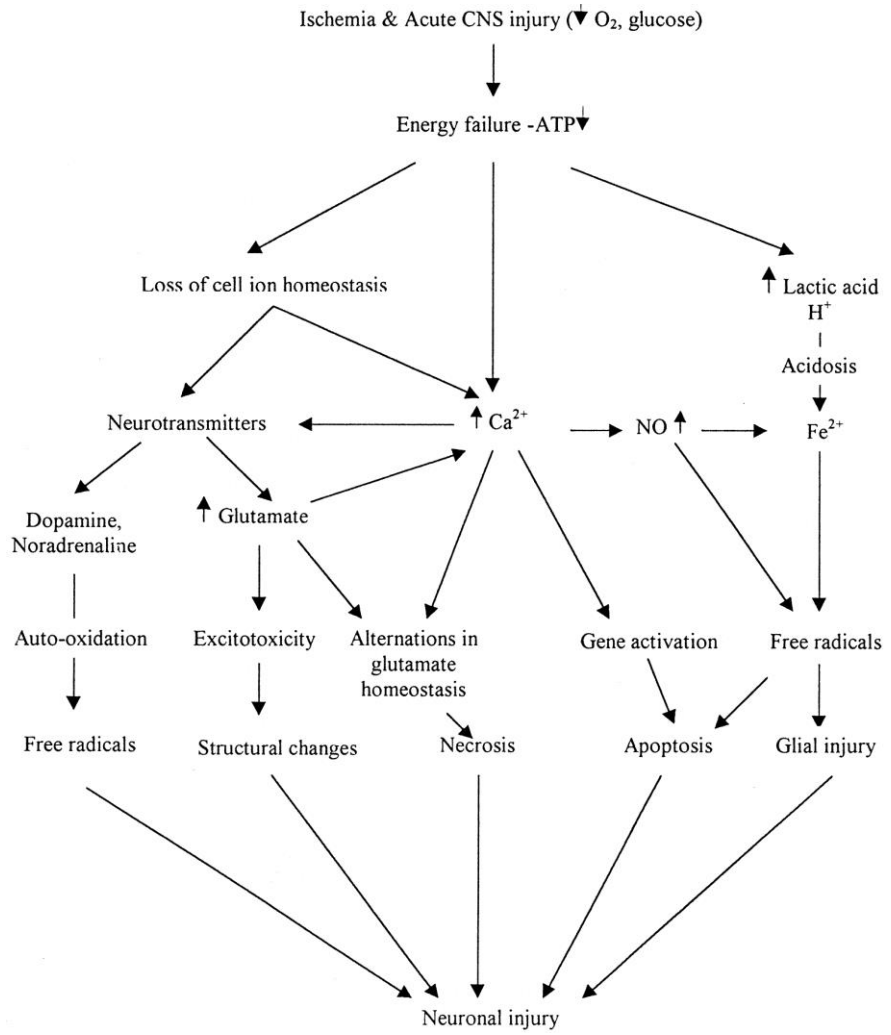
JCBFM

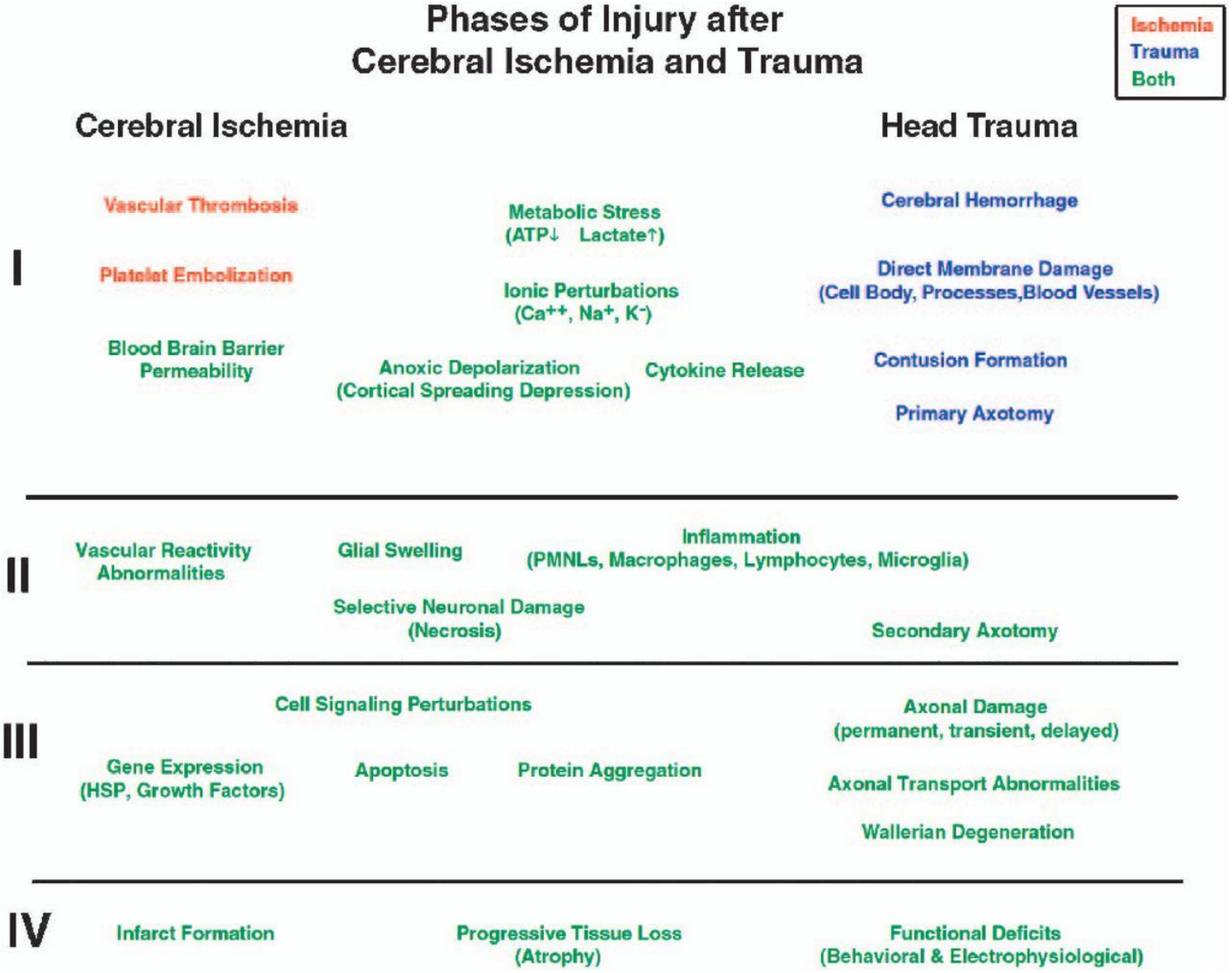
Cellular mechanisms that may be involved in acute ischemia and CNS injury.



Yossi Gilgun-Sherki et al. Pharmacol Rev 2002;54:271-284

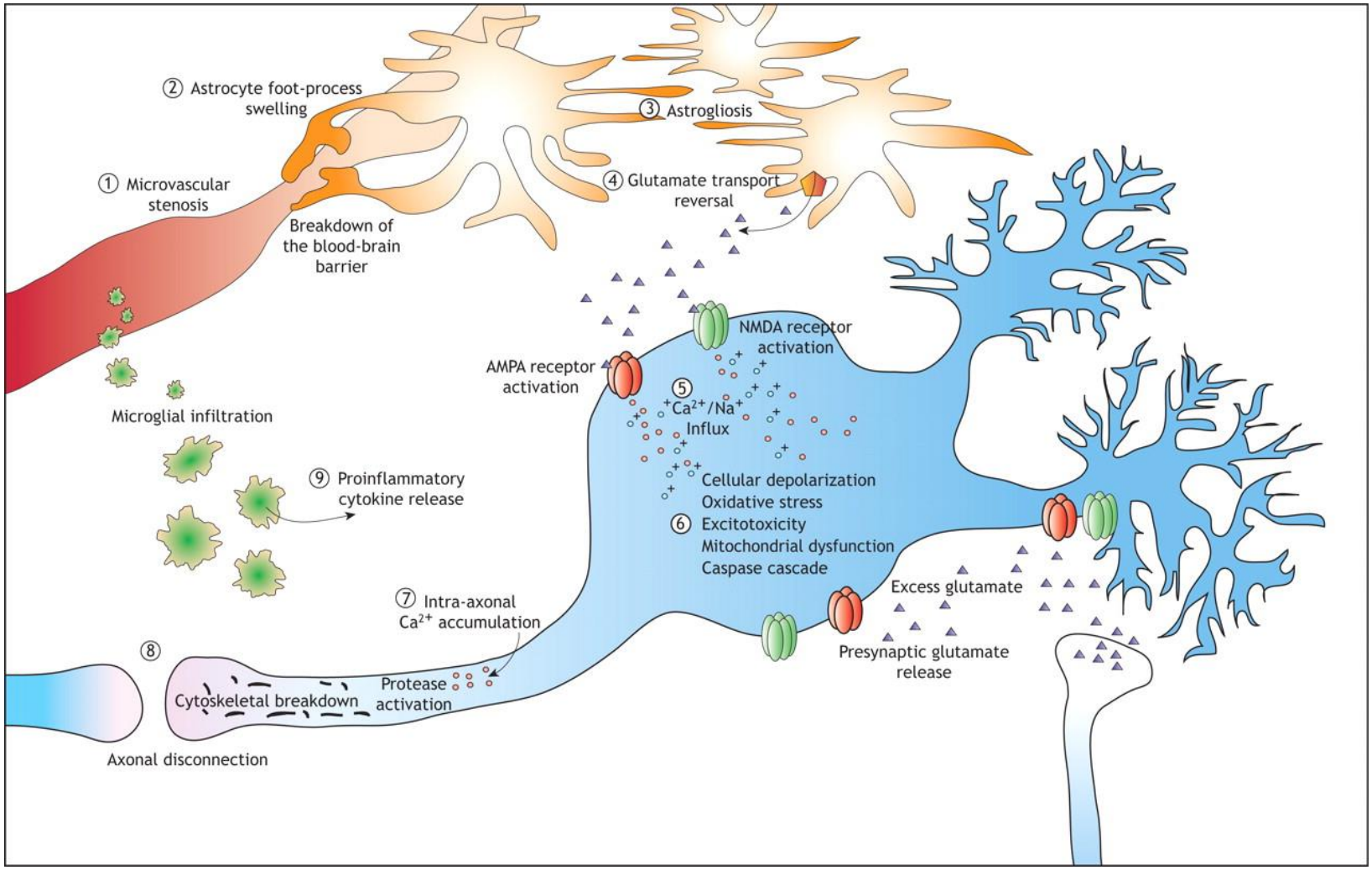
ASPET PHARMACOLOGICAL REVIEWS

Flow chart summarizing various pathophysiological events involved in cerebral ischemic and traumatic insults.



Helen M. Bramlett, and W. Dalton Dietrich J Cereb Blood Flow Metab 2004;24:133-150

Figure 1: The major pathways associated with the progression of secondary injury after a traumatic brain injury.



Park E et al. CMAJ 2008;178:1163-1170

CMAJ·JAMC

MTBI structural pathology

MTBI pathophysiology correlates with imaging

- **MTBI can characterized by the damage to the structure of the brain.**
- **DOI brain CT are abnormal in 7-20% of the mTBI cases.**
- **MTBI with abnormal CT is Complex mTBI**
- **Some of the patients with normal CT have abnormal MRI, with increased RV spaces and DAI.**
- **Contrary to popular belief MTBI does not result in shearing injury. Axons are stretched and twist without being sheared.**
- **What was originally conceptualizes as “shearing is actually a gradual process where stretched and badly damaged axons swell and eventually separate.**
- **This process in MTBI occurs in small number of the axons with vast majority, which are affected do recover over the time.**

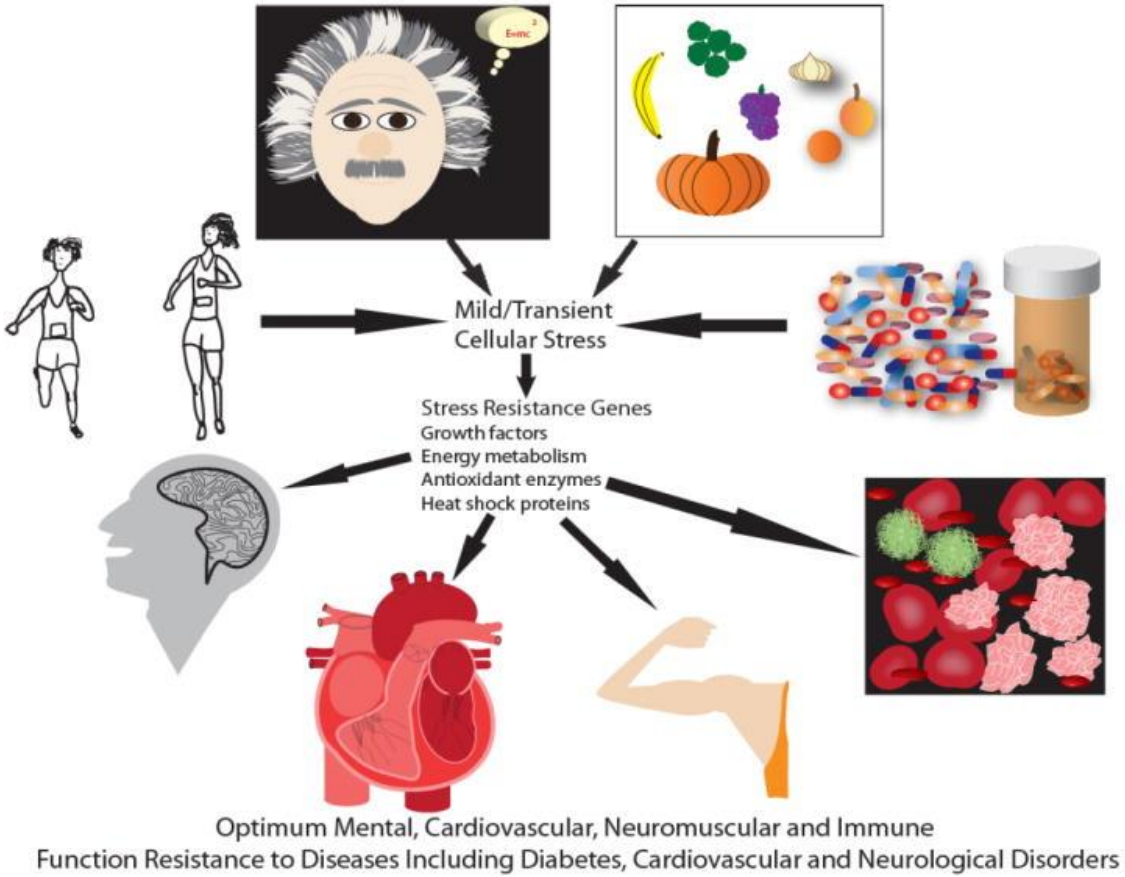
Recent Neuroimaging Techniques in Mild Traumatic Brain Injury

- Mild traumatic brain injury (TBI) is characterized by acute physiological changes that result in at least some acute cognitive difficulties and typically resolve by 3 months post injury.
- Because the majority of mild TBI patients have normal structural magnetic resonance imaging (MRI)/computed tomography (CT) scans, there is increasing attention directed at finding objective physiological correlates of persistent cognitive and neuropsychiatric symptoms through more sensitive neuroimaging techniques.
- Indeed, 43% to 68% of mild TBI patients have normal structural scans on MRI.1
- This may be either because there is no structural brain damage in those symptomatic patients with normal scans or because current technology is unable to detect it.
- Certainly, microscopic diffuse axonal injury, reported as present in autopsy studies of mild TBI, is largely undetectable using traditional neuroimaging techniques.
- When clinical neuroimaging findings are present following a mild TBI, the classification changes to "complicated mild TBI," which has a 6-month outcome more similar to moderate TBI.
- Therefore, it is in the symptomatic mild TBI patients with negative clinical neuroimaging that a search for more sensitive imaging techniques or biological markers continues.
- These include structural or chemical techniques, such as diffusion tensor imaging (DTI), FA, susceptibility weighted imaging SWI, and magnetic resonance spectroscopy, and functional techniques such as functional MRI (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT).

Heather G. Belanger; Rodney D. Vanderploeg; Glenn Curtiss; Deborah L. Warden
The Journal of Neuropsychiatry and Clinical Neurosciences 2007;19:5-20.

Hormesis Defined

- A crucial principle involved with hormesis is that the re-establishment of disrupted homeostasis can result in an adaptive condition that is more beneficial than the prior stage.



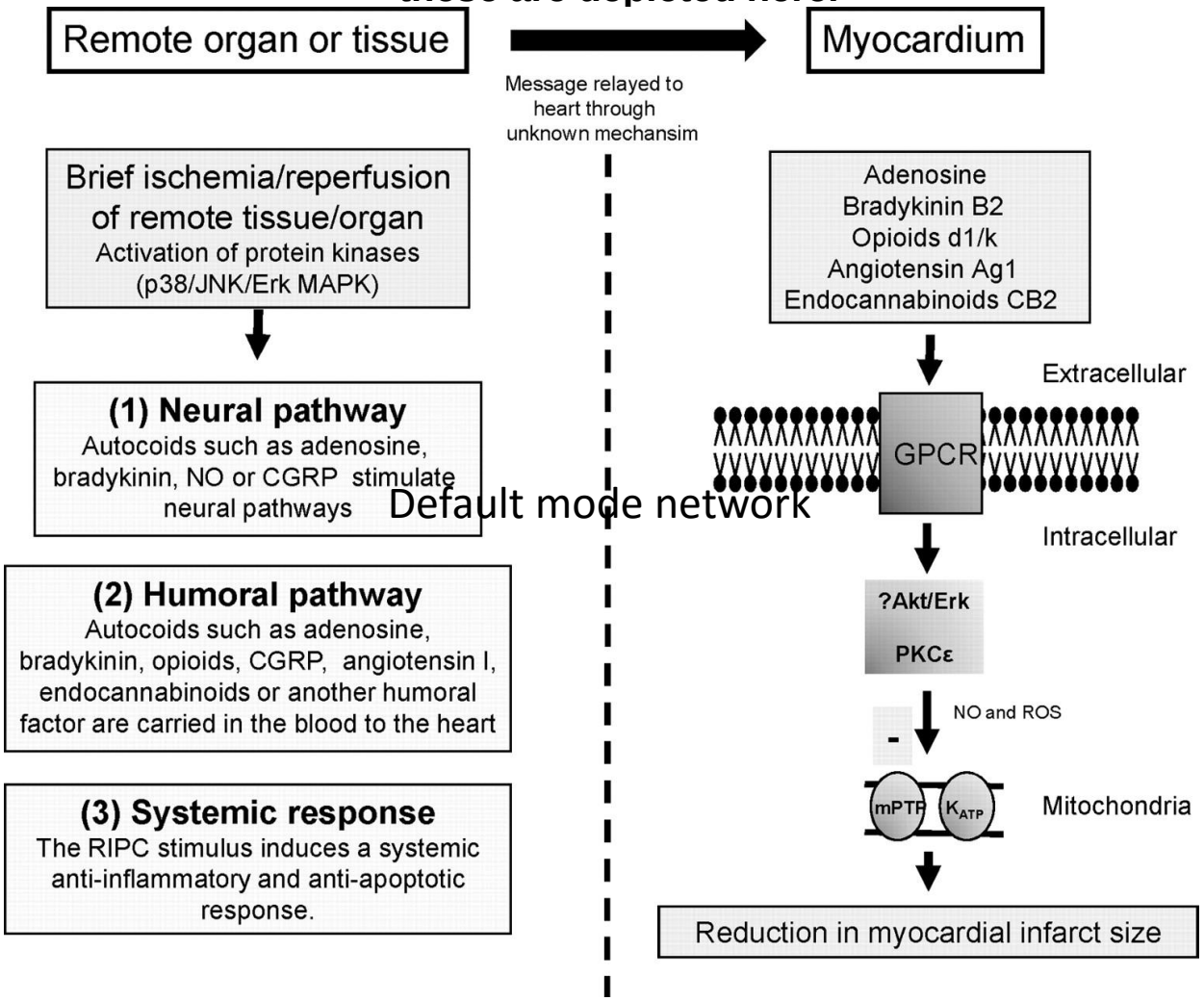
Ageing Res Rev. 2008 Jan; 7(1): 1–7.

Immune mechanisms in cerebral ischemic tolerance Evolutional explanation for the preconditioning?

- Stressor-induced tolerance is a central mechanism in the response of bacteria, plants, and animals to potentially harmful environmental challenges.
- This response is characterized by immediate changes in cellular metabolism and by the delayed transcriptional activation or inhibition of genetic programs that are not generally stressor specific (cross-tolerance).
- These programs are aimed at countering the deleterious effects of the stressor.
- While induction of this response (preconditioning) can be established at the cellular level, activation of systemic networks is essential for the protection to occur throughout the organs of the body.
- This is best signified by the phenomenon of remote ischemic preconditioning, whereby application of ischemic stress to one tissue or organ induces ischemic tolerance (IT) in remote organs through humoral, cellular and neural signaling.
- The immune system is an essential component in cerebral IT acting simultaneously both as mediator and target.
- There are multiple components of the immune system required for induction of IT and review the mechanisms by which a reprogrammed immune response contributes to the neuroprotection observed after preconditioning.
- Learning how local and systemic immune factors participate in endogenous neuroprotection could lead to the development of new stroke therapies.

Garcia-Bonilla L, Benakis C, Moore J, Iadecola C, Anrather J. Immune mechanisms in cerebral ischemic tolerance. *Frontiers in Neuroscience*. 2014;8:44. doi:10.3389/fnins.2014.00044.

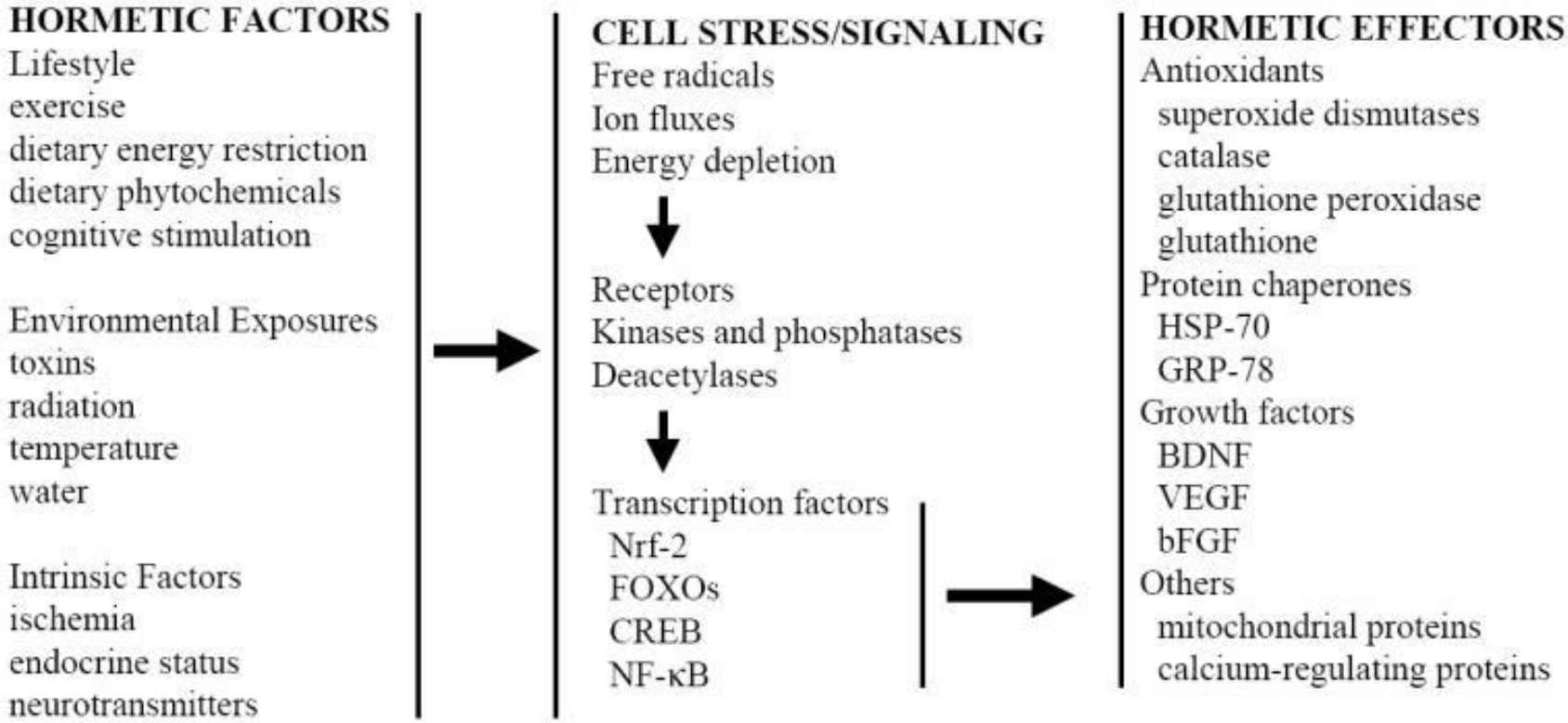
Potential mechanistic pathways underlying remote ischaemic preconditioning: the actual mechanism through which transient ischaemia and reperfusion of an organ or tissue confers cardioprotection is currently unknown although several hypotheses have been proposed and these are depicted here.



Derek J. Hausenloy, and Derek M. Yellon Cardiovasc Res 2008;79:377-386

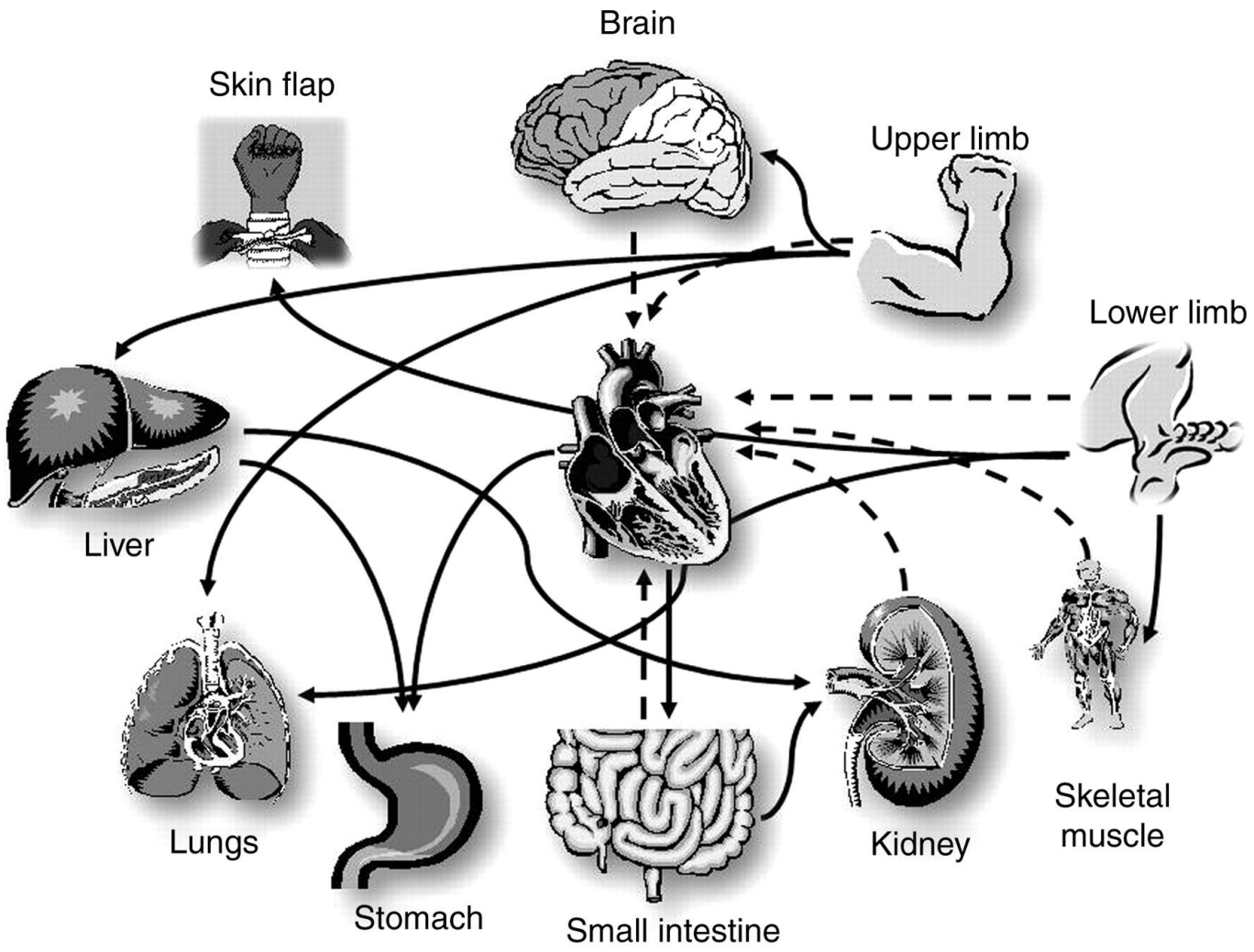
Cardiovascular Research

Hormesis Defined



Ageing Res Rev. 2008 Jan; 7(1): 1–7.

Inter-organ protection against ischaemia-reperfusion injury: this figure depicts the evolution of remote ischaemic preconditioning from a concept that was initially used to denote an intramyocardial reduction in infarct size.



Derek J. Hausenloy, and Derek M. Yellon Cardiovasc Res 2008;79:377-386

Cardiovascular Research

Patterns of neuronal vulnerability in both cerebral ischemic and traumatic insults

- The neuron has classically been shown to be very sensitive to periods of cerebral ischemia. Flow reductions reaching 25ml/100g/minute in rodents are considered severe enough to lead to eventual cell death.
- In models of cardiac arrest and transient forebrain ischemia, specific populations of neurons have been shown to be vulnerable .
- After transient global ischemia such as cardiac arrest, the CA1 sector and dentate hilus of the hippocampus, dorsolateral striatum, and Purkinje neurons in the cerebellum are most vulnerable.
- In contrast, focal ischemia produces a core of severe hypoperfusion where flow is reduced to 15–18ml/100g/minute.
- This core is surrounded by a rim of viable tissue where blood flow may be only mildly depressed.
- The ischemic core, if not reperfused, generally evolves into an ischemic infarct where all cellular elements are necrotic.
- With severe focal ischemia, neuronal cell death can be demonstrated within a few hours after the insult (Plum, 1983).
- However, following periods of transient global or focal ischemia, neuronal death can take as long as 2–3 days to mature (Du et al., 1996; Kirino et al., 1984; Pulsinelli et al, 1982).
- This maturation phenomenon implies a secondary injury process and may suggest a more prolonged therapeutic window for treatment strategies.
- The penumbra region surrounding the ischemic core characteristically contains a preserved ionic state and may display scattered ischemic neurons within an intact neuropil (Back, 1998).
- Following focal ischemia, multiple episodes of cortical spreading depression have been demonstrated in the penumbra as well as more remote regions of the brain (Back, 1998; Dietrich et al., 2000; Hossman, 1996).
- These propagating waves are caused by intracellular calcium that depolarizes cells and cause metabolic stress and the induction of a variety of genes and proteins in areas away from the infarct (Kariko et al., 1998).

Clinical Application of Preconditioning and Postconditioning to Achieve Neuroprotection

- Timing Preconditioning and Postconditioning
- The molecular mechanisms whereby IPC and PostC operate against cerebral ischemia are discussed elsewhere within this issue and have been reviewed extensively in other publications [3, 10].
- There appears to be significant overlap between the protective mechanisms of these two therapies involving activation of reperfusion injury salvage kinases (RISK) pathways [25, 26] such as Akt, ERK 1/2 and MAPK or through modification of key mitochondrial targets [27].
- Acute protection from IPC likely results from post-translational protein modifications (eg phosphorylation) within cell energetic or survival systems which are immediate.
- Delayed IPC likely results from protein synthesis of previously dormant genes involved in angiogenesis, energy metabolism, vasomotor control, inflammation and cell survival (eg growth factors).
- This mechanistic hypothesis explains the delayed nature of this protective window as well as its more long lasting effects, in some cases up to a week.
- The early and late windows of IPC have been extensively studied and validated in animal models but it's less clear whether these findings are mirrored in humans.
- The TIA-stroke data cited in the preceding section supports the hypothesis that IPC is more effective within a week of the anticipated insult.

HBOT as a preconditioning in the cerebral insults

Hyperbaric oxygen preconditioning: a reliable option for neuroprotection.

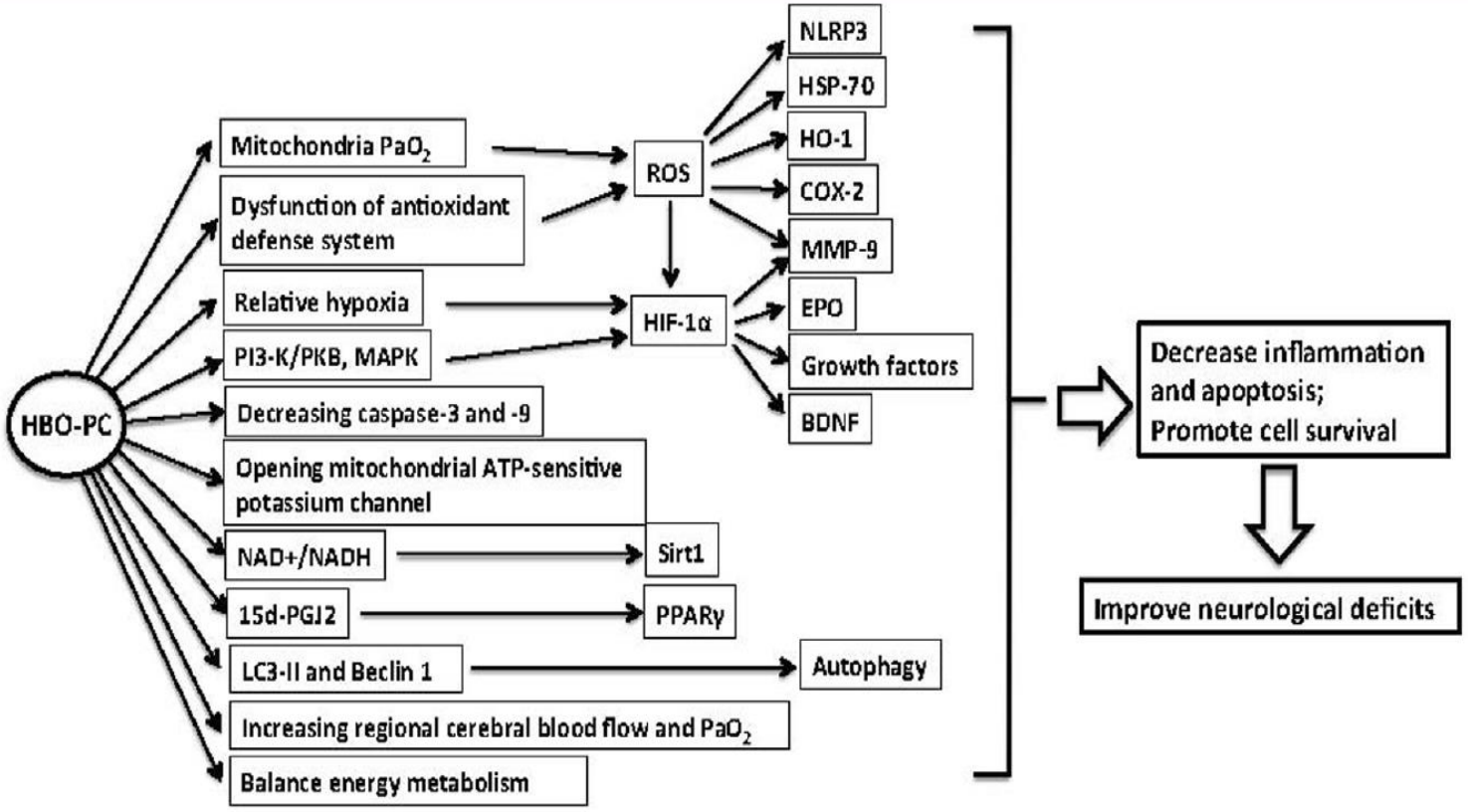


Figure 1: Potential mechanisms involved in neruoprotection of HBO-PC.

H*Hu Q, Manaenko A, Matei N, Guo Z, Xu T, Tang J, Zhang JH (2016 . Med Gas Res 6(1):20-32.)*

Hyperbaric oxygen preconditioning: a reliable option for neuroprotection.

Animal Models	Potential Mechanisms	References
Neonatal hypoxic–ischemia	1. Suppressing the activities of caspase-3 and -9. 2. Activating of different defenses against oxidative stress.	28 34
Focal cerebral ischemia	1. Upregulation of HIF-1α and its target gene EPO. 2. Increasing the activity of catalase and superoxide dismutase. 3. Suppressed mitochondrial apoptotic pathways. 4. Stabilized the glucose level and decreased both the lactate/pyruvate ratio and glycerol. 5. Increasing the expression of proteins of LC3-II and Beclin 1 and increasing the formation of autophagosomes. 6. Increasing protein level of Sirt1.	45 46 47 48 49 35
Forebrain ischemia	1. Relevant to neurotrophin and inflammatory-immune system. 2. Suppression of p38 phosphorylation.	50 51
Global cerebral ischemia	1. Increasing the level of brain BDNF and by suppression of p38 activation. 2. Induction of MMP-9. 3. Reducing cyclooxygenase-2.	52 53 37
Hemorrhagic transformation	1. Decreasing of the level of HIF-1α and suppressing the activity of MMP-2 and MMP-9. 2. Increasing 15d-PGJ2 and activate PPARγ. 3. activating reactive oxygen species/thioredoxin-interacting protein/NLRP3 pathway.	57 58 59
Intracerebral hemorrhage	1. Activation of p44/42 MAPK pathway. 2. Downregulating AQP-4 expression	61, 62 63
Surgical brain injury	Increasing COX-2.	30
Traumatic brain injury	1. Increasing regional cerebral blood flow and brain tissue oxygen pressure in rats at high altitude. 2. Suppression of the expression of MMP-9.	31 75

Hu Q, Manaenko A, Matei N, Guo Z, Xu T, Tang J, Zhang JH (2016) Hyperbaric oxygen preconditioning: a reliable option for neuroprotection. Med Gas Res 6(1):20-32.

Hormesis and HBOT in the critical stages of the stroke and severe TBI

- Hormesis is a fundamental concept in evolutionary theory.
- From the beginning through the present time, life on earth has existed in harsh environments in which cells are often exposed to free radicals and toxic substances.
- To avoid extinction organisms have developed complex mechanisms to cope with the environmental hazards.
- Typically, such hormetic response pathways involve proteins such as ion channels, kinases and deacetylases, and transcription factors which regulate the expression of genes that encode cytoprotective proteins.
- Several major categories of hormetic stress resistance proteins have been identified including protein chaperones such as the heat-shock proteins, antioxidant enzymes such as superoxide dismutases and glutathione peroxidase, and growth factors such as insulin-like growth factors and brain-derived neurotrophic facto

Hormesis Defined Ageing Res Rev. 2008 Jan; 7(1): 1–7.

To die or not to die for neurons in ischemia, traumatic brain injury and stroke: a review on the stress-activated signaling pathways and apoptotic pathways

- After a severe episode of ischemia, traumatic brain injury (TBI) or epilepsy, it is typical to find necrotic cell death within the injury core.
- In addition, a substantial number of neurons in regions surrounding the injury core have been observed to die via the programmed cell death (PCD) pathways due to secondary effects derived from the various types of insults.
- Apart from the cell loss in the injury core, cell death in regions surrounding the injury core may also contribute to significant losses in neurological functions. In fact, it is the injured neurons in these regions around the injury core that treatments are targeting to preserve.
- In this review, we present our cumulated understanding of stress-activated signaling pathways and apoptotic pathways in the research areas of ischemic injury, TBI and epilepsy and that gathered from concerted research efforts in oncology and other diseases.
- However, it is obvious that our understanding of these pathways in the context of acute brain injury is at its infancy stage and merits further investigation.
- Hopefully, this added research effort will provide a more detailed knowledge from which better therapeutic strategies can be developed to treat these acute brain injuries.

Progress in Neurobiology
Volume 69, Issue 2, February 2003, Pages 103–142

Endogenous neuroprotection: mitochondria as gateways to cerebral preconditioning

- From single to multicellular organisms, protective mechanisms have evolved against endogenous and exogenous noxious stimuli. Preconditioning paradigms, in which stimulation below the threshold of injury results in subsequent protection of the brain, have played an important role in elucidating such endogenous protective mechanisms.
- Research on preconditioning is aimed at understanding endogenous neuroprotection to boost it, or to supplement its effectors therapeutically once damage to the brain has occurred, such as after stroke or brain trauma.
- Interest is in the common mechanisms, on which pathways of endogenous neuroprotection converge, and in particular on mitochondria, which may be considered master integrators of endogenous neuroprotection.

Neuropharmacology. 2008 Sep;55(3):334-44. doi: 10.1016/j.neuropharm.2008.02.017. Epub 2008 Mar 8.

Endogenous neuroprotection: mitochondria as gateways to cerebral preconditioning?

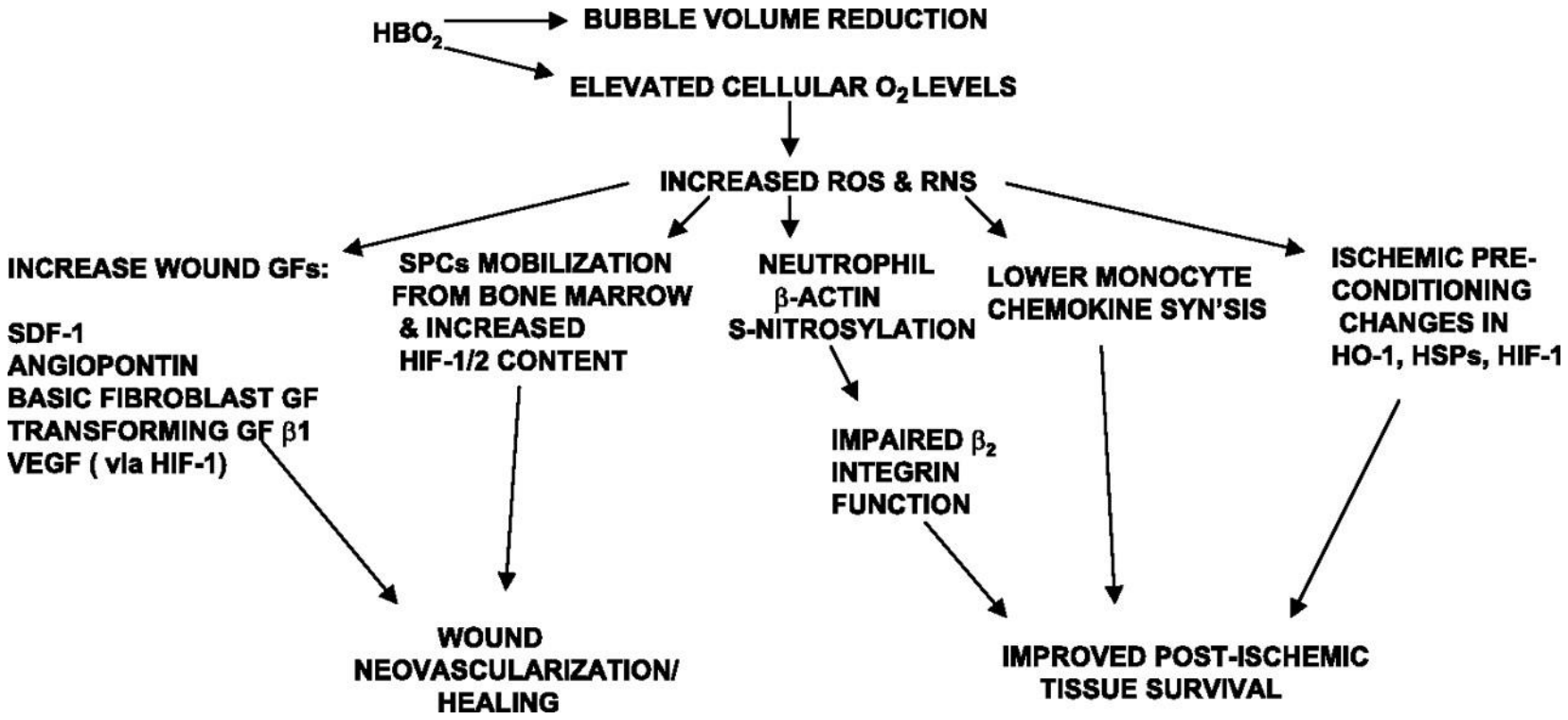
Dirnagl U[1], Meisel A.

Potential HBOT target in the ischemic and traumatic CNS insults

- Recent studies indicate that the mature mammalian central nervous system (CNS) has the potential to replenish damaged neurons by proliferation and neuronal differentiation of adult neural stem/progenitor cells residing in the neurogenic
- Furthermore, increasing evidence indicates that these endogenous stem/progenitor cells may play regenerative and reparative roles in response to CNS injuries or diseases. regions in the brain.
- Heightened levels of cell proliferation and neurogenesis have been observed in response to brain trauma or insults suggesting that the brain has the inherent potential to restore populations of damaged or destroyed neurons.

Neural Regen Res. 2014 Apr 1; 9(7): 688–692.
doi: 10.4103/1673-5374.131567
The potential of endogenous neurogenesis for brain repair and regeneration following traumatic brain injury
Dong Sun, M.D., Ph.D.

Overview on therapeutic mechanisms of hyperbaric oxygen (HBO2).



Stephen R. Thom J Appl Physiol 2009;106:988-995

Journal of Applied Physiology

Role of RIPostC in humans

- The narrow window of opportunity to provide therapy in regards to reperfusion observed by Loukogeorgakis makes it challenging to apply in clinical practice.
- In the cases of stroke before the thrombolysis or endovascular intervention window, a rapid application of RIPostC could theoretically reduce the injury induced by reperfusion.
- In the case of strokes past the thrombolysis window, reperfusion, if it occurs at all, is variable and the timing of this is not apparent.
- In the case of cardiac arrest, the timing of return of spontaneous circulation (ie reperfusion) is better documented but the surrounding chaos makes immediate application of RIPostC practically challenging though clearly possible.
- These two disease entities, non-reperfused ischemic stroke and cardiac arrest, represent well over a million cases annually in the US with considerable morbidity and mortality.
- Thus the promise of RIPostC certainly warrants consideration within these patients.

Dezfulian C, Garrett M, Gonzalez NR. Clinical Application of Preconditioning and Postconditioning to Achieve Neuroprotection. *Translational stroke research*. 2013;4(1):19-24. doi:10.1007/s12975-012-0224-3.

Clinical Application of Preconditioning and Postconditioning to Achieve Neuroprotection

- Preconditioning (PC) has classically been described as exposure of an organ to a sub-lethal physiologic stress which confers subsequent protection from lethal injury, generally by a more prolonged exposure to the same stressor.
- Ischemic preconditioning (IPC) was first described in 1986 as the use of four 5 min cycles of coronary occlusion, each individually insufficient to cause myocardial necrosis, resulting in a substantial reduction (75%) in the area of infarction after a subsequent, prolonged (40 min) coronary occlusion and reperfusion which caused infarction [1].
- Cerebral IPC was described 4 years later [2] and achieved using brief (2 min) bilateral carotid occlusions to protect against subsequent neuronal death resulting from 5 min bilateral carotid occlusion in gerbils.
- Additionally, it has been demonstrated that short bursts of ischemia *after* reperfusion is also protective in brain, a phenomenon referred to as postconditioning (PostC) [4].
- Similar to IPC, ischemic postconditioning (IPostC) was initially shown to be protective in heart [5] and subsequently brain [6]. Numerous animal and clinical trials of IPost have been conducted primarily in the last decade and have been the subject of recent reviews [7–9]. Overall IPostC appears to provide the same degree of cardioprotection and neuroprotection as IPC though the requirements for execution immediately at reperfusion are stricter.

Dezfulian, Cameron, Matthew Garrett, and Nestor R. Gonzalez. “Clinical Application of Preconditioning and Postconditioning to Achieve Neuroprotection.” *Translational stroke research* 4.1 (2013): 19–24. *PMC*. Web. 17 Aug. 2016.

IPC and RIPostC two windows

- The clinical implication of these studies is that IPC, or at least RIPC, permits for two windows where protection can be delivered assuming foreknowledge of the ischemic or traumatic event.
- This may be relevant in preventing possible brain IR injury that can be anticipated such as in surgery requiring cardiopulmonary bypass or carotid endarterectomies or traumatic sports.
- Successful RIPostC may require application immediately at the time of reperfusion and without delay immediately after the sports trauma. This still could be of clinical relevance as RIPostC could be given at the time of thrombolysis in the case of stroke or during cardiopulmonary resuscitation in the case of cardiac arrest.

Clinical Application of Preconditioning and Postconditioning to Achieve Neuroprotection in TIA

- TIA appear to be neuroprotective when they are recent (within a week), multiple (2–3 but not more) and of brief duration (<20 min).
- This replicates experimental IPC findings.
- TIA is not effective in protecting against lacunar strokes which are smaller and tend to differ in etiology.
- TIA also do not appear to protect in the elderly brain consistent with human results in angina-MI and animal IPC data in brain.
- The nature of this protection is both direct (smaller infarct with similar perfusion defect) and a indirect by facilitating faster thrombolysis

HBOT and neuroplasticity in the acute and subacute stroke

Adult neurogenesis in the mammalian brain and its function

- The region of neurogenesis in the mature mammalian brain is primarily confined to the subventricular zone (SVZ) surrounding the lateral ventricle and the dentate gyrus (DG) of the hippocampus (Altman and Das, 1965; Lois and Alvarez-Buylla, 1993).

Hyperbaric Oxygen Therapy in Acute Ischemic Stroke

- Hyperbaric medicine, as an emerging interdisciplinary subject, has been applied in the treatment of cerebral vascular diseases since the 1960s.
- Now it is widely used to treat a variety of clinical disorders, especially hypoxia-induced disorders.
- However, owing to the complex mechanisms of hyperbaric oxygen (HBO) treatment, the
- therapeutic time window and the undefined dose as well as some common clinical side effects (such as middle ear barotrauma), the widespread promotion and application of HBO was hindered, slowing down the hyperbaric medicine development.
- In August 2013, the US Food and Drug Administration declared artery occlusion as one of the 13 specific indications for HBO therapy.
- This provides opportunities, to some extent, for the further development of hyperbaric medicine. Currently, the mechanisms of HBO therapy in the limited in acute time window and are still not very clear in the subacute or chronic ischemic stroke.
- Numerous studies have demonstrated that HBO treatment is capable of increasing oxygen supply, ameliorating cerebral circulation insufficiency, reducing ischemia-reperfusion injury and alleviating the extent of irreversible neurological impairment.
- Recently randomized, prospective trial [20] has shown that HBO therapy can activate the neuroplasticity of brain tissues in post-stroke patients, even in the chronic phase.

Zheng Ding,[a] Wesley C. Tong,[b] Xiao-Xin Lu,[a] and Hui-Ping Peng[a] Interv Neurol. 2014 Aug; 2(4): 201–211

Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospective trial.

- Recovery after stroke correlates with non-active (stunned) brain regions, which may persist for years.
  A prospective, randomized, controlled trial including 74 participants who suffered a stroke 6-36 months prior to inclusion and had at least one motor dysfunction.
- After inclusion, patients were randomly assigned to "treated" or "cross" groups.
- Patients in the treated group were evaluated twice: at baseline and after 40 HBOT sessions. Patients in the cross group were evaluated three times: at baseline, after a 2-month control period of no treatment, and after subsequent 2-months of 40 HBOT sessions.
- HBOT protocol: Two months of 40 sessions (5 days/week), 90 minutes each, 100% oxygen at 2 ATA.
- **Results** neurological functions and life quality of all patients in both groups were significantly improved following the HBOT sessions while no improvement was found during the control period of the patients in the cross group.

- **CONCLUSIONS:**
- The results indicate that HBOT can lead to significant neurological improvements in post stroke patients even at chronic late stages.

PLoS One. 2013;8(1):e53716. doi: 10.1371/journal.pone.0053716. Epub 2013 Jan 15.
Efrati S[1], Fishlev G, Bechor Y, Volkov O, Bergan J, Kliakhandler K, Kamiager I, Gal N, Friedman M, Ben-Jacob E,Golan H.

Hyperbaric oxygen preconditioning attenuates hyperglycemia-enhanced hemorrhagic transformation by inhibiting matrix metalloproteinases in focal cerebral ischemia in rats

- HBO-PC (2.5 ATA, 100% O_2, 1 h/day for 5 days) decreased the expression of HIF-1α and down-regulated the activity of MMP-2 and MMP-9 in ischemic brain tissue thereby protected BBB against ischemia/reperfusion damage.
- The results suggest that a sub-injury level of ROS generation by HBO-PC triggers the cascade in cellular events leading to increased HIF-1α before MCAO, which facilitate adaptation to the subsequent oxidative stress and decrease the activity of MMP-2 and MMP-9, attenuating hyperglycemia enhanced HT after cerebral ischemia.
- Thus, the induction of ROS and the sub-injury increase of HIF-1α and MMPs before MCAO may possibly be one of potential mechanisms for HBO-PC-induced enhancement of tolerance to sustain the oxidative cascade in hyperglycemic rats.
- HBO-PC may hold therapeutic value for treating HT in ischemic stroke patients with hyperglycemia.

Yoshiteru Soejima, Qin Hu, Paul R. Krafft, Mutsumi Fujii, Jiping Tang, andJohn H. Zhang* Exp Neurol. 2013 Sep; 247: 737–743.

How HBO-PC up or down-regulated the expression of HIF-1α?

- There are three distinct HIF-α proteins: HIF-1α, -2α, and -3α. HIF-1 and -2 coordinate many cell responses involved with neovascularization by regulating gene transcription, and, although there is substantial overlap in their activity, there are also a number of genes preferentially regulated by either HIF-1 or -2
- HIF-1 is responsible for induction of genes that facilitate adaptation and survival from hypoxic stresses (103), and so it has been a focus of interest when examining HBO_2 therapeutic mechanisms in ischemia-reperfusion models.
- HIF-1 is involved with pro- as well an antiapoptotic pathways and in brain, promotes astrocyte mediated-chemokine synthesis (1, 88).
- In several models, exposure to HBO_2 appears to ameliorate post ischemic brain injury by decreasing HIF-1 expression (26, 73).
- When HBO_2 is used in a prophylactic manner to induce ischemic tolerance, however, its mechanism appears related to up-regulation of HIF-1 and at least one of its target genes, erythropoietin (48).
- Thus, as was the case in wound healing models, timing of HBO_2 application appears to influence cellular responses.

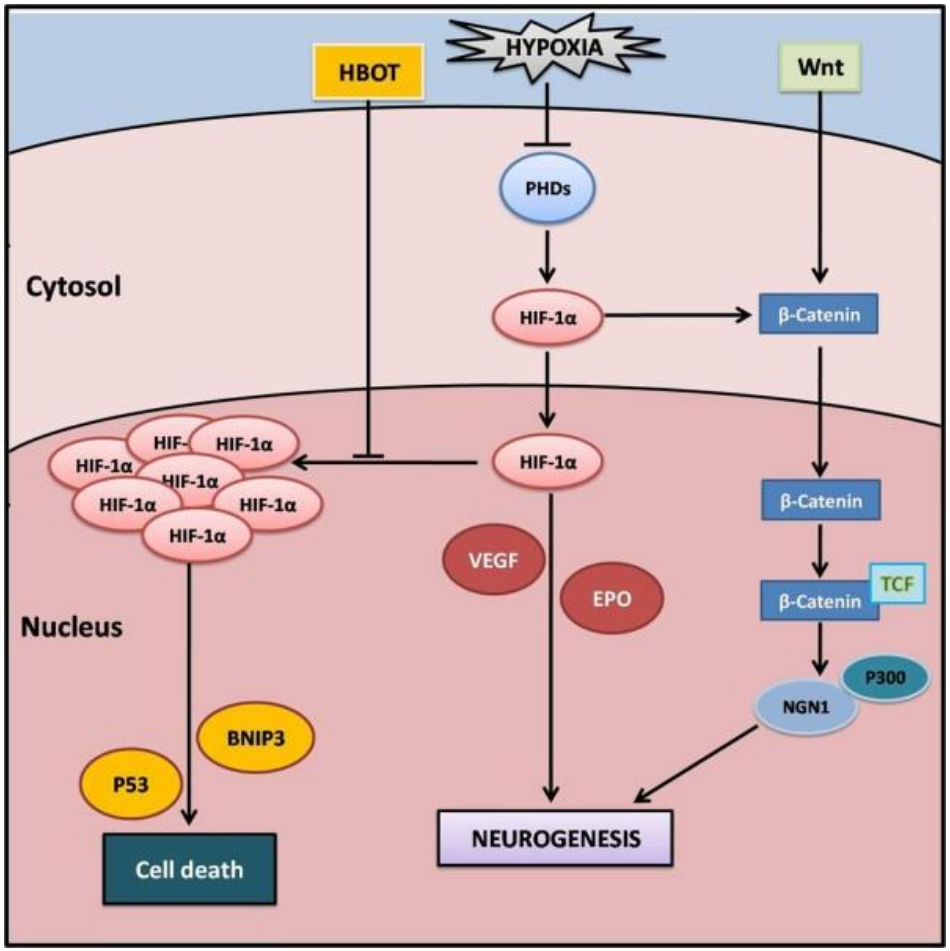
Stephen R. Thom J Appl Physiol 2009 Mar; 106(3): 988–995.

Hyperbaric oxygen therapy promotes neurogenesis: where do we stand?

- Neurogenesis is defined as generation of neurons within the brain. In adults, neurogenesis occurs primarily in two brain regions: the subventricular (SVZ) and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG).
- Injury to the central nervous system (CNS) including trauma, cerebral ischemia and epileptic seizures have been reported to induce neurogenesis, and surviving cells may be functionally integrated into existing neural circuits
- Consequently, further endogenous promotion of neurogenesis may hold promise for restoration of cerebral functions after CNS injury.

Potential mechanisms of HBOT in neurogenesis and HIF-1α.

- In hypoxia, HIF-1α activates EPO and VEGF to promote neurogenesis. The accumulation of HIF-1α further induces the expression of p53 protein and BNIP3, leading to cell death.
- HBOT stabilizes HIF-1α, preventing it from overexpression and further, activates the Wnt pathway. Abbreviation: PHDs, prolyl hydroxylase; HIF-1α, hypoxia-inducible factor 1α; EPO, e rythropoietin; VEGF, vascular endothelial growth factor; NGN1, Neurogenin1; TCF, T-cell factor.



Med Gas Res. 2011; 1: 14.

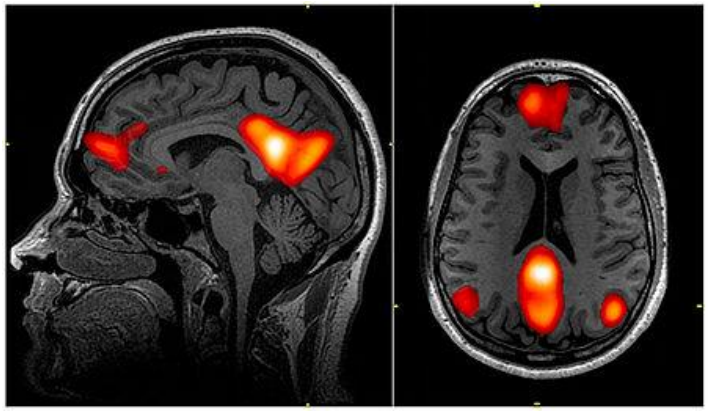
HBOT and stroke

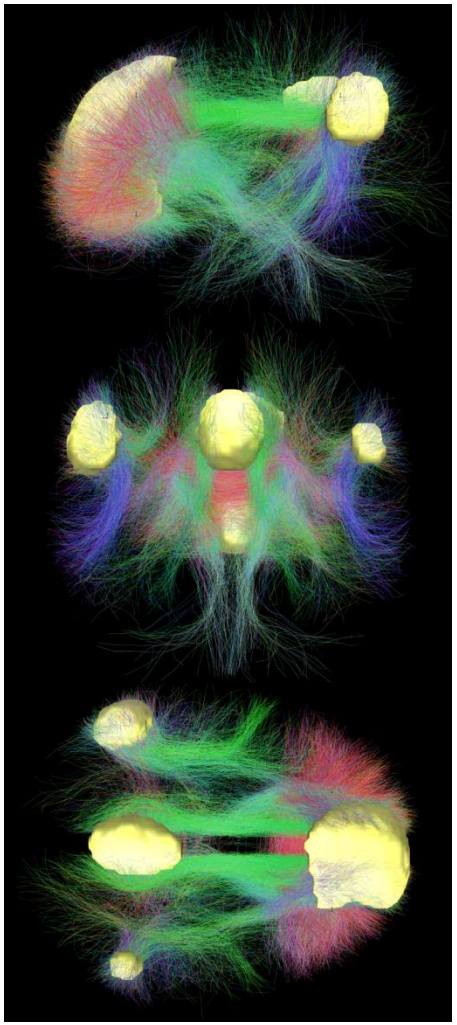
- In contrast to these preclinical results no benefit of HBOT was found in stroke patients and HBOT did not improve the clinical outcome in patients 6 months after acute stroke.
- However, Singhal concluded that HBOT might extend the time window and increase the efficiency of FDA approved r-tPA thrombolysis after acute ischemic stroke.
- Most clinical trials presented small sample sizes, undifferentiated stroke types, diverse time windows and varying application of HBOT.
- To bridge the gap between basic science and clinical studies, large scale, well designed, randomized controlled clinical trials are needed to examine the effects on HBOT in terms of acute sensorimotor and chronic cognitive function in patients.

Default mode network function

- The default mode network is known to be involved in many seemingly different functions:
- Information regarding the self:
- *Autobiographical information:* Memories of collection of events and facts about one's self
- *Self-reference:* Referring to traits and descriptions of one's self
- *Emotion of one's self:* Reflecting about one's own emotional state
- Thinking about others
- *Theory of Mind:* Thinking about the thoughts of others and what they might or might not know
- *Emotions of other:* Understanding the emotions of other people and empathizing with their feelings
- *Moral reasoning:* Determining just and unjust result of an action
- *Social evaluations:* Good-bad attitude judgments about social concepts
- *Social categories:* Reflecting on important social characteristics and status of a group
- Remembering the past and thinking about the future:
- *Remembering the past:* Recalling events that happened in the past
- *Imagining the future:* Envisioning events that might happen in the future
- *Episodic memory:* Detailed memory related to specific events in time
- *Story comprehension:* Understanding and remembering a narrative

Default mode network and HBOT





In neuroscience, the **default mode network** (DMN), (also **default network**, or **default state network**), is a network of interacting brain regions known to have activity highly correlated with each other and distinct from other networks in the brain.
rCBF distribution increase during HBO in sensory-motor and visual cortices, and it showed for the first time a higher perfusion tracer distribution in areas encompassed in dorsal attention system and in default mode network.
These findings unfold both the externally directed cognition performance improvement related to the HBO and the internally directed cognition states during resting-state conditions, suggesting possible beneficial effects in TBI and stroke patients

The Influence of Oxidative Metabolism on Synaptic Plasticity and Mental Capacity

- Reactive oxygen species (ROS) are generated during cellular respiration, and their levels are greatly increased as a result of abnormal cell metabolism.
- Cells normally have buffering mechanisms to defend against damage induced by ROS.
- However, when ROS production exceeds the buffering capacity, cell function and viability are at risk (Gilgun-Sherki et al., 2002).
- Increase in ROS production has been identified as an important mechanism by which neuronal plasticity is compromised during aging

Ageing Res Rev. 2008 Jan; 7(1): 49–62.

Axonal pathology in TBI

White matter trauma is an active progressive process

- Following trauma, white matter exhibits active lesions of inflammation, cytoskeletal breakdown and, finally, axonal disconnection. It is a phenomenon known to occur across a range of injury severities.
- Further complicating the issue is the finding that all axons are not created equal, with varying susceptibilities dependent on subcellular make-up.
- White matter lesions may be responsible for more symptoms than previously thought and that they may be the source of the ongoing neuro-cognitive issues that affect patients following mild traumatic brain injury

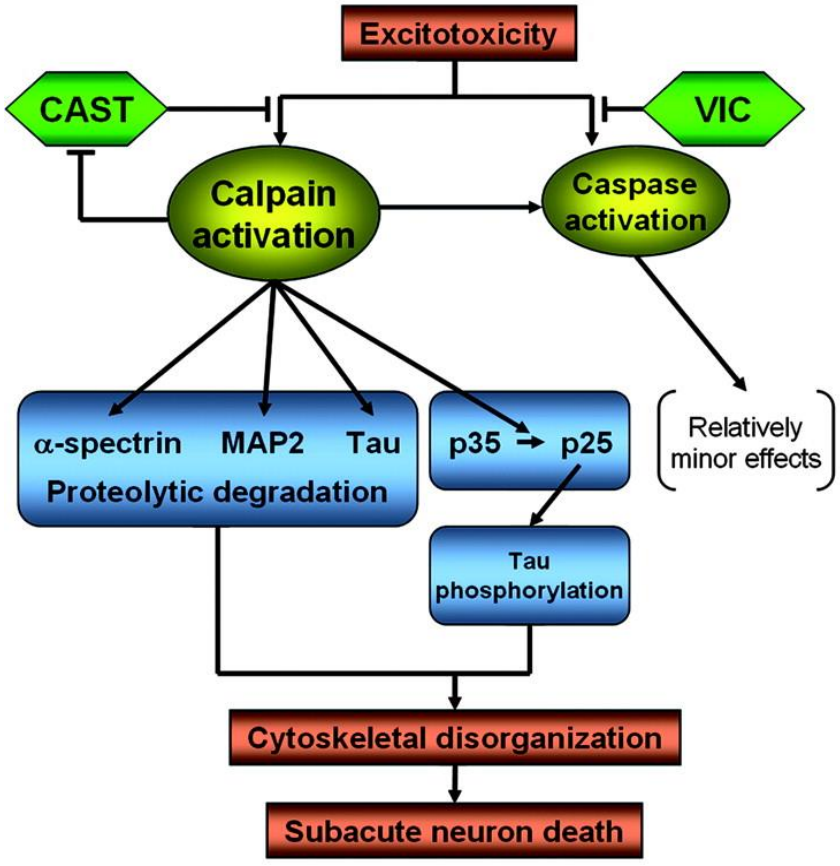
Axonal pathology in mTBI

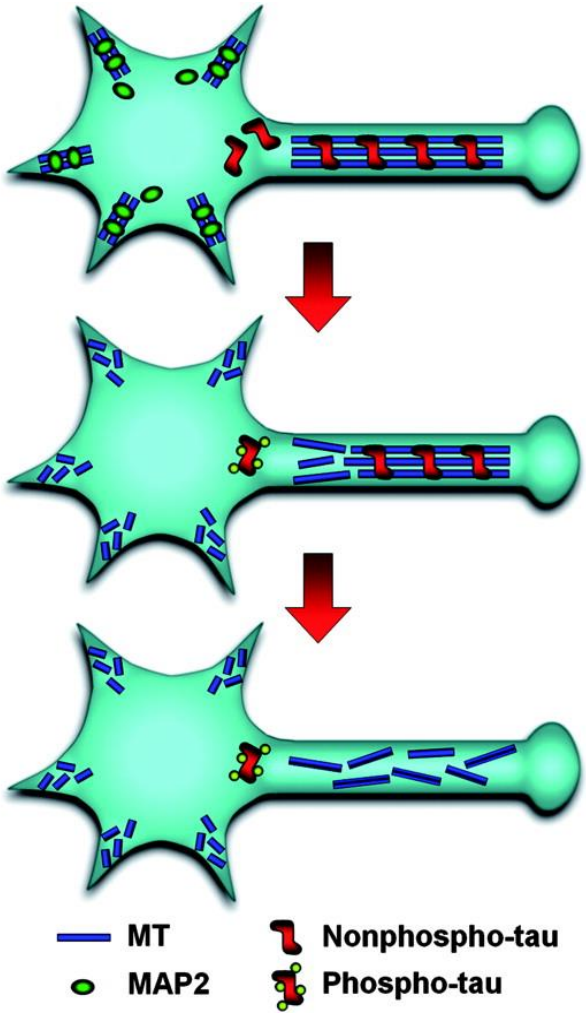
- In animal model single acceleration deceleration event stretch at different length can produce
- 4 mm no morphological or metabolic changes.
- 5 mm change in VEP
- 6 mm retraction ball and axonal swelling
- Therefore single event might result in
- No change in structure function.
- Metabolic and functional change
- Structural and functional change
- These outcomes are dependent on the force applied

White matter trauma is a process

- Studies have revealed that white matter trauma is an active progressive process.
- Following trauma, white matter exhibits active lesions of inflammation, cytoskeletal breakdown and, finally, axonal disconnection.
- It is a phenomenon known to occur across a range of injury severities.
- Further complicating the issue is the finding that all axons are not created equal, with varying susceptibilities dependent on subcellular make-up.
- We are beginning to recognize that white matter lesions may be responsible for more symptoms than previously thought and that they may be the source of the ongoing neuro-cognitive issues that affect patients following mild traumatic brain injury.

A proposed scheme for calpain-mediated neurodegenerative processes focusing on cytoskeletal disorganization.

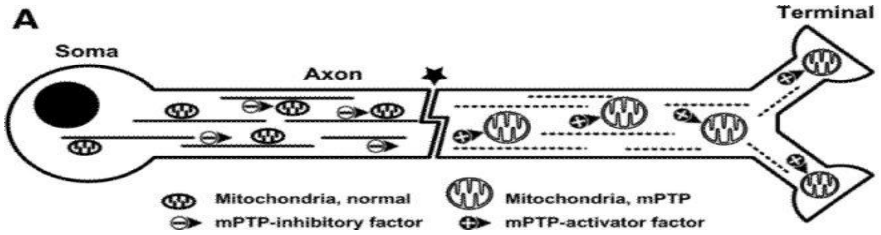




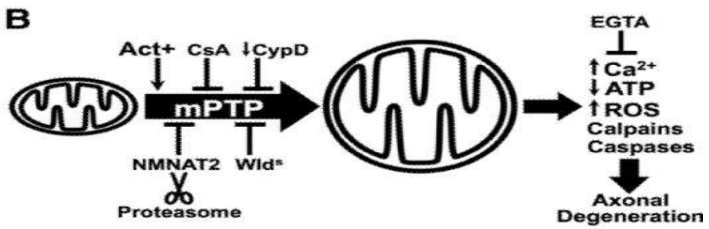
Higuchi M et al. J. Biol. Chem. 2005;280:15229-15237

jbc

Model of mPTP-dependent degeneration of the axonal compartment



Mitochondria are transported along the axon by a microtubule-dependent mechanism; function of the mitochondria largely requires transport of nuclear-encoded proteins from the cell body, including proteins that seem to inhibit mPTP activation (depicted by minus sign). Defects in axonal transport (star), which could be complete (e.g.,nerve transection) or partial (e.g.,toxic agents, protein aggregates, or genetic disorders), disturb the physiological equilibrium between the nuclear encoded mPTP inhibitors and locally produced activators of the mPTP.

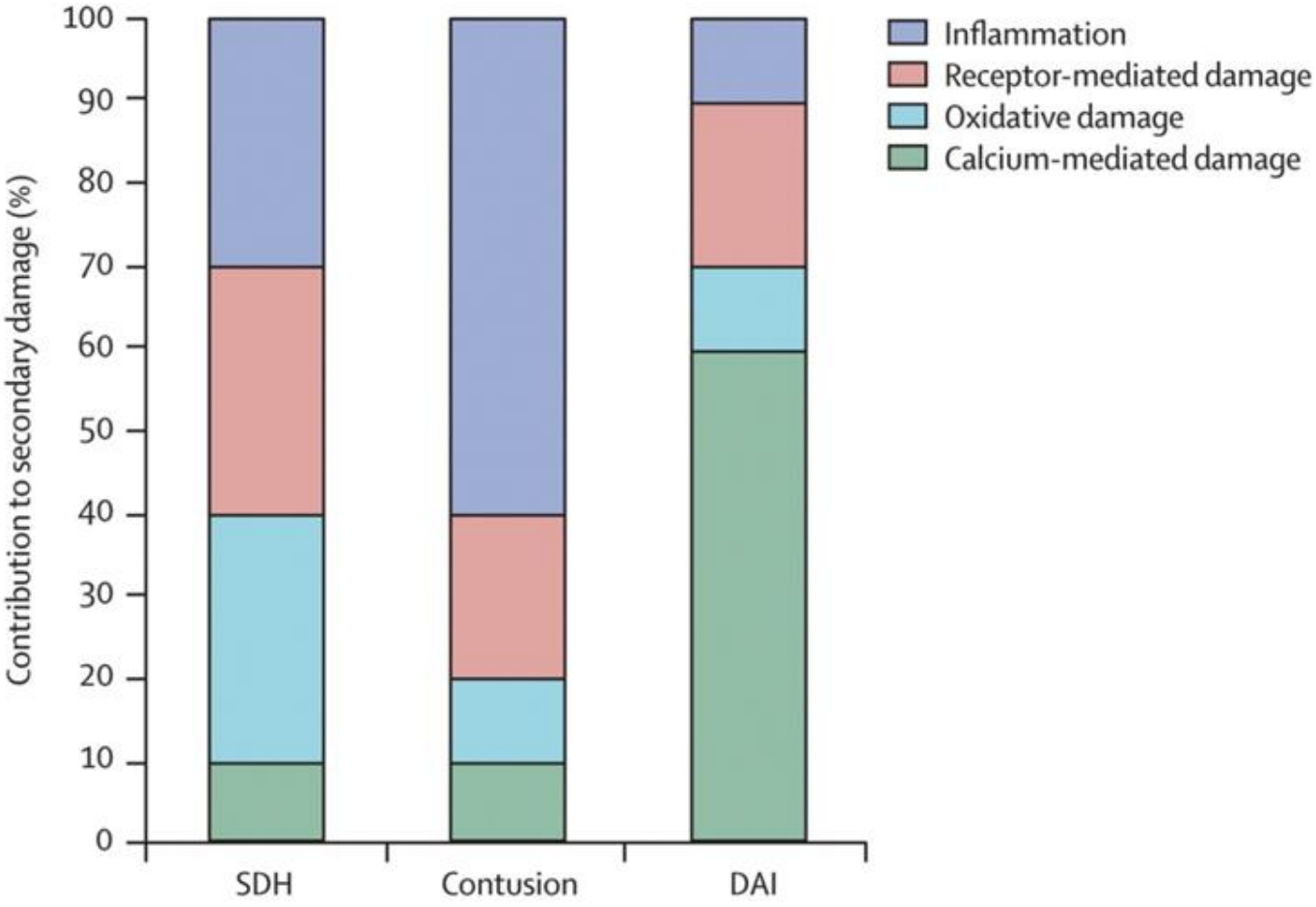


Proposed molecular species involved in mPTP activation and axonal degeneration.

In axons, mPTP formation is inhibited by NMNAT2, which is delivered from the cell body and is a target for the proteasome in injured axons.

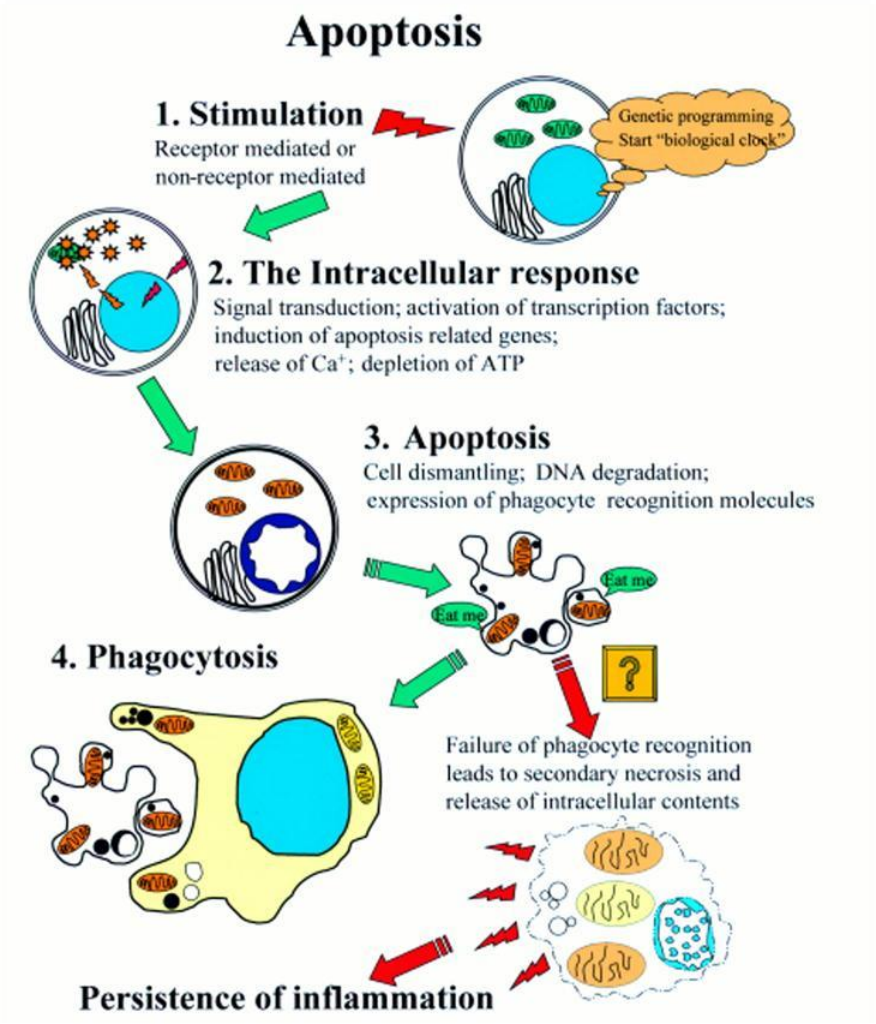
mPTP activation will lead to calcium overload in the axon, decrease in ATP production, increase in ROS generation, and liberation of prodegenarative factors, which are potentially involved in degeneration of axonal components as well as triggering further mitochondrial dysfunction.

The Mechanisms of Damage from TBI



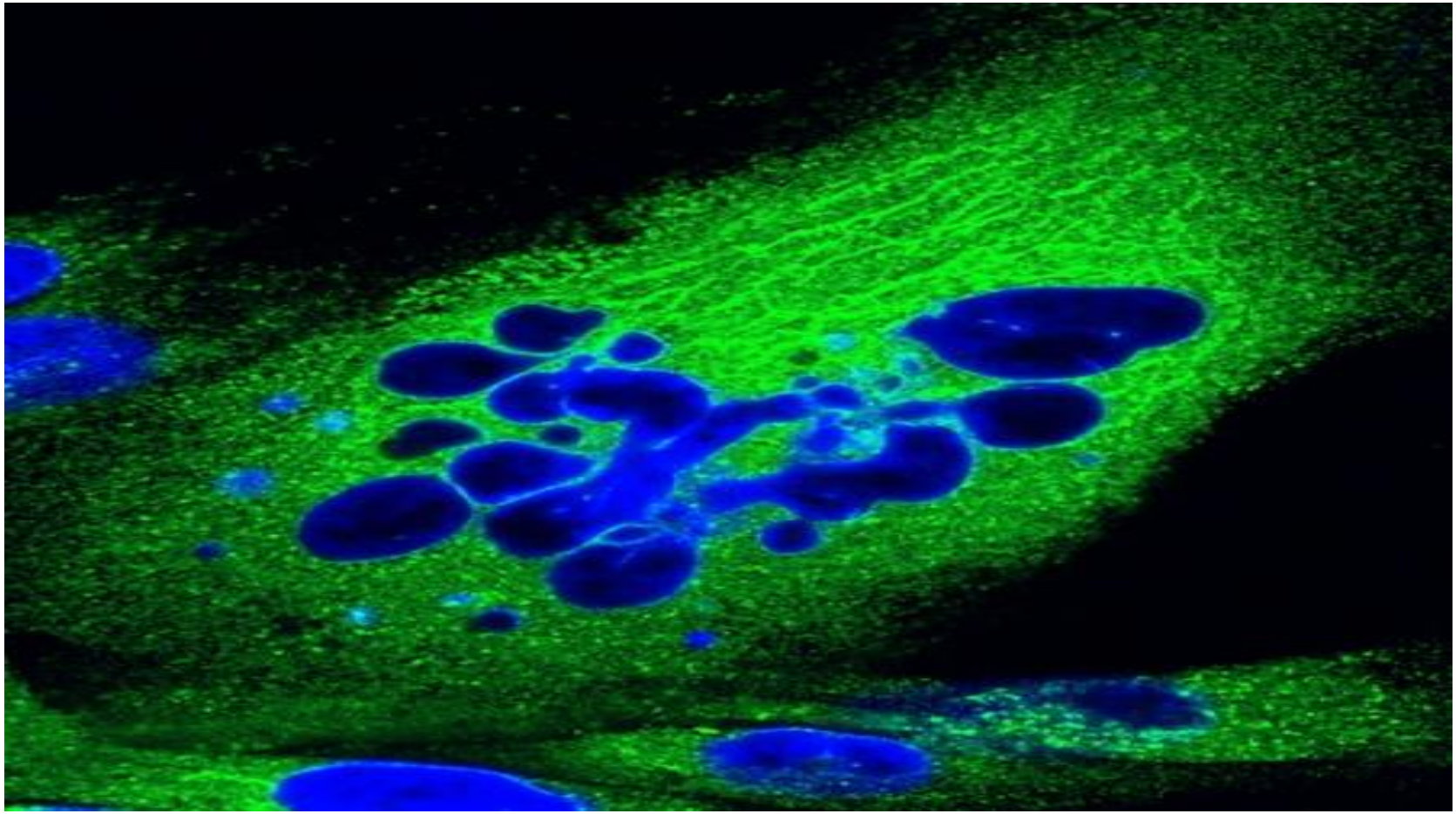
Apoptosis

The stages of apoptosis.



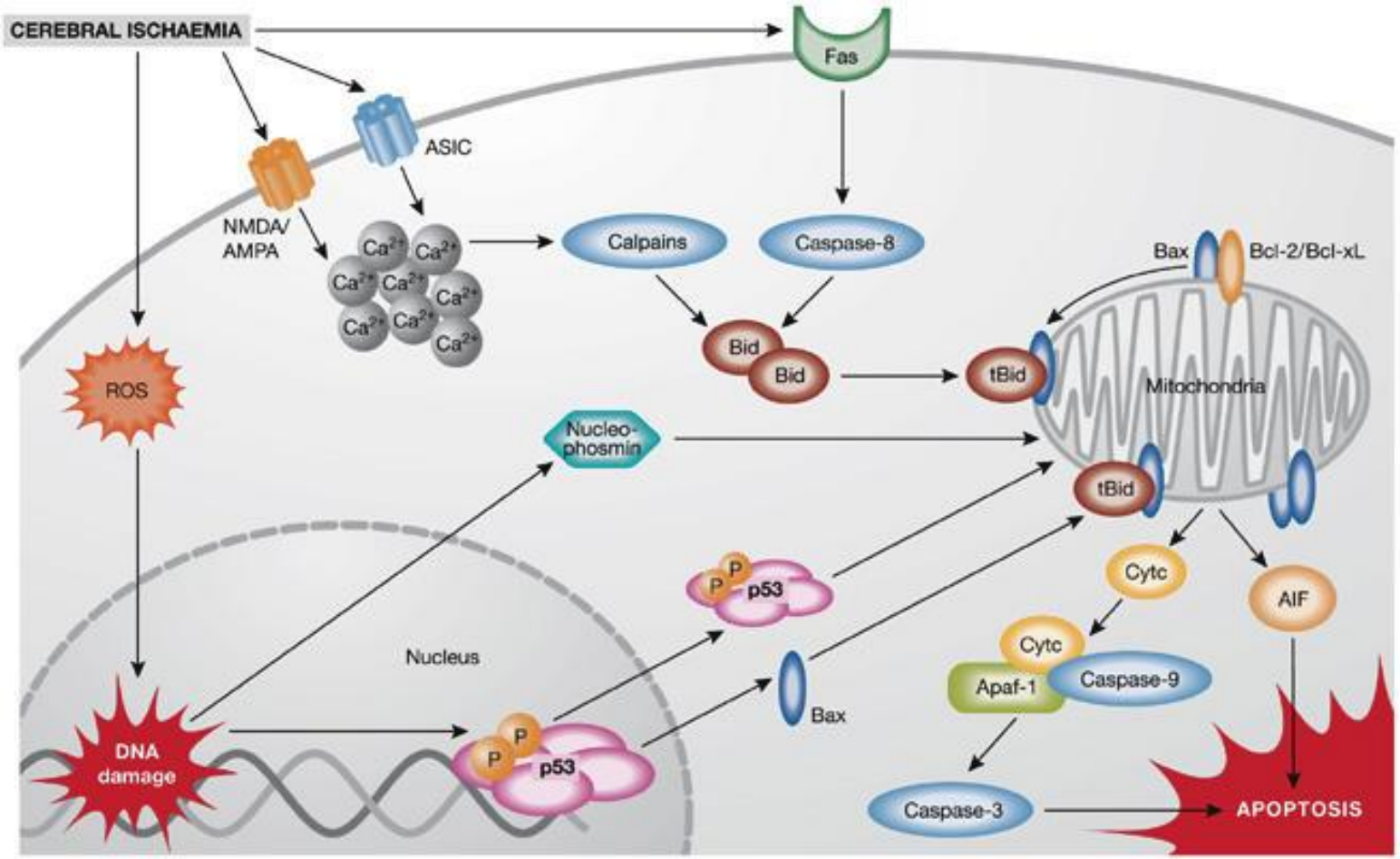
Afford S , Randhawa S Mol Path 2000;53:55-63

Apoptosis- falling apart



- Human fibroblast undergoing nuclear fragmentation in a late stage of apoptosis. The nucleus is stained in blue and the cytoplasm in green. Photomicrograph by Joerg Schroeer.

Apoptosis and accidental cell death

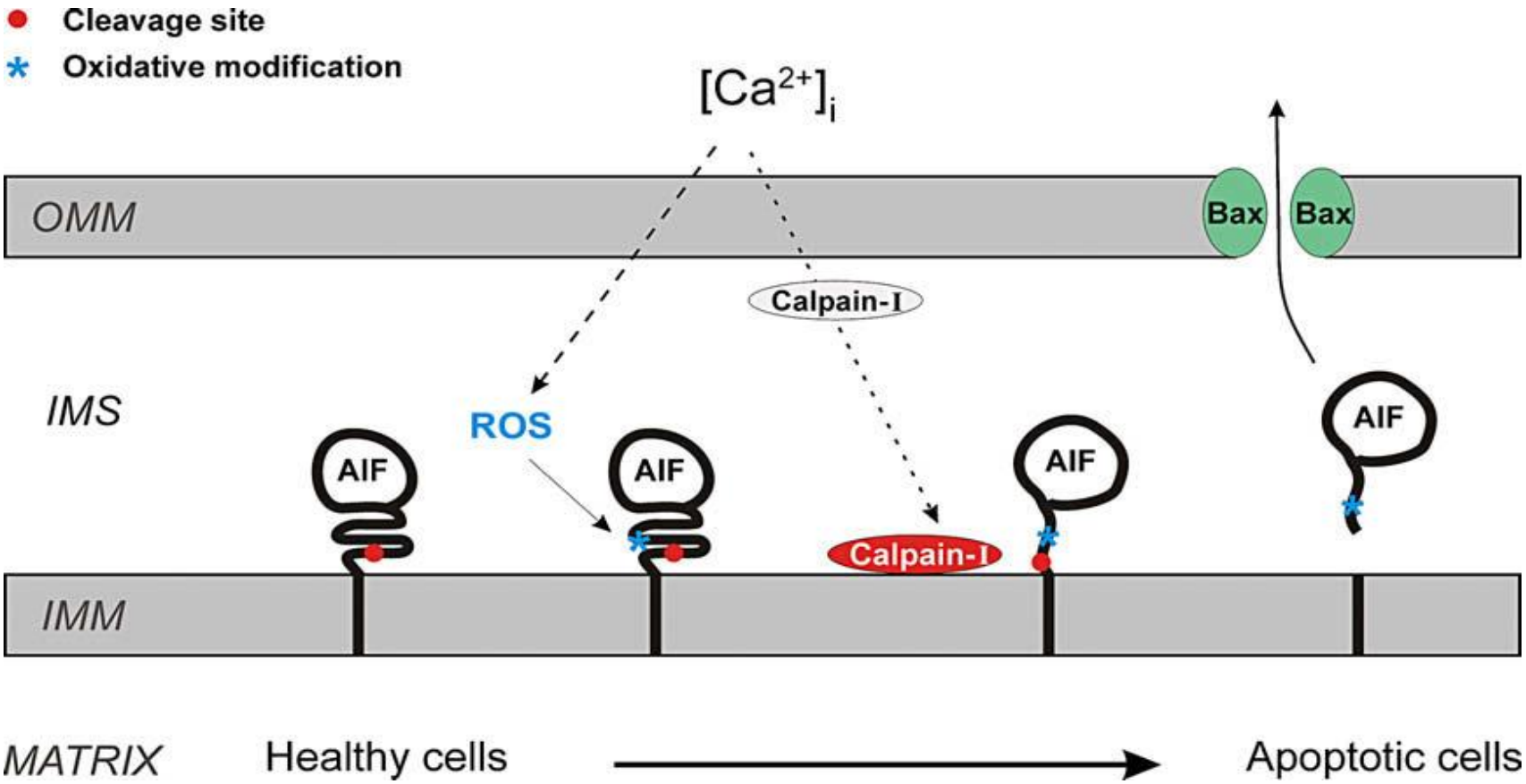


Evaluation of the Apoptosis-Related Proteins of the Bcl-2 Family in the Traumatic Penumbra Area of the Rat Model of Cerebral Contusion, Treated by Hyperbaric Oxygen Therapy

- The growth and progression of traumatic brain injury (TBI) lesions depend significantly on developments in the traumatic penumbra area, perilesional region, where delayed neuronal death occurs.
- Recent data supports the important role of apoptosis in delayed cell death in TBI.
- The expression of Bcl-2 in hypoxemic animals was lower than in non-hypoxemic animals, but a significant increase in Bcl-2 expression was seen in both groups after HBO treatment.
- Bcl-xL also demonstrated an increase after HBO treatment but less significant. Staining for Bax protein did not demonstrate significant change after treatment.
- These data correlate well with the reduction of TUNEL-positive cells in traumatic penumbra after HBO treatment.
- This proves that the apoptotic mechanisms are important in delayed cell death in TBI and that post-traumatic hypoxemia increases the intensity of apoptosis, probably through a decrease in Bcl-2 and Bcl-xL expression which normally repress apoptosis.
- The beneficial effect of HBO treatment in animal model of brain contusion correlates well with the increased expression of anti-apoptotic proteins (Bcl-2 and Bcl-xL) following treatment and the appropriate decrease in the extent of apoptosis.
- In light of these results, the usage of HBO is justified as neuroprotective treatment in TBI.

Acta Neuropathologica 110(2):120-6 · September 2005

AIF processing is sequentially regulated by Ca2+ and ROS



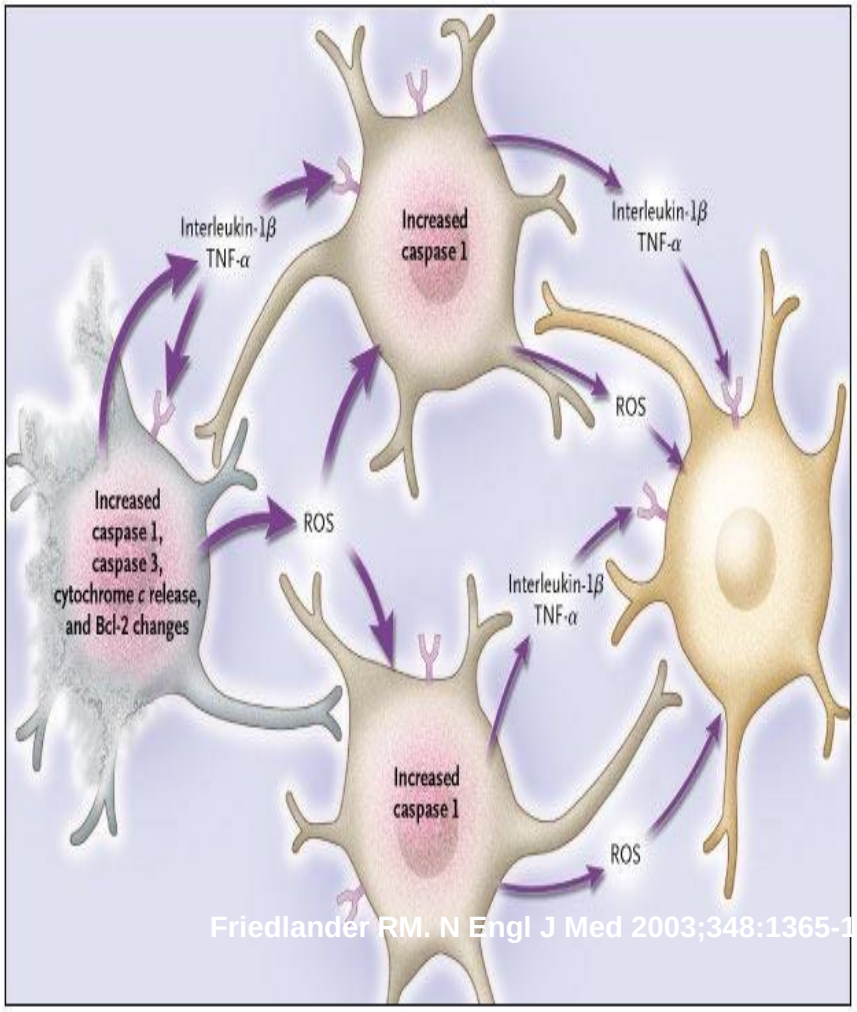
E. Norberg et al. / Biochemical and Biophysical Research Communications 396 (2010) 95–100

Contagious Apoptosis ("The Kindergarten Effect")

Apoptosis and Caspases in Neurodegenerative Diseases

Robert M. Friedlander, M.D.

N Engl J Med 2003; 348:1365-1375April 3, 2003



Contagious Apoptosis and Cell Dysfunction. As one initial neuron (gray) proceeds through the cell-death pathway, apoptotic cascades are activated and diffusible toxic factors (interleukin-β, tumor necrosis factor α [TNF-α], and reactive oxygen species [ROS]) are released. These factors induce neighboring cells (tan) to enter the cell-death cascade ("the kindergarten effect"), and the earliest detectable change is the up-regulation of caspase 1. As these neurons become dysfunctional, they begin to secrete the same toxic factors, which will, in turn, affect the surrounding healthy neurons (pink). Once a lethal threshold has been reached, the cell dies.

Conclusions

- These findings encourage further studies in hyperoxic environment as well as physician initiated clinical trials to explore future possible HBO applications in TBI and stroke patients.