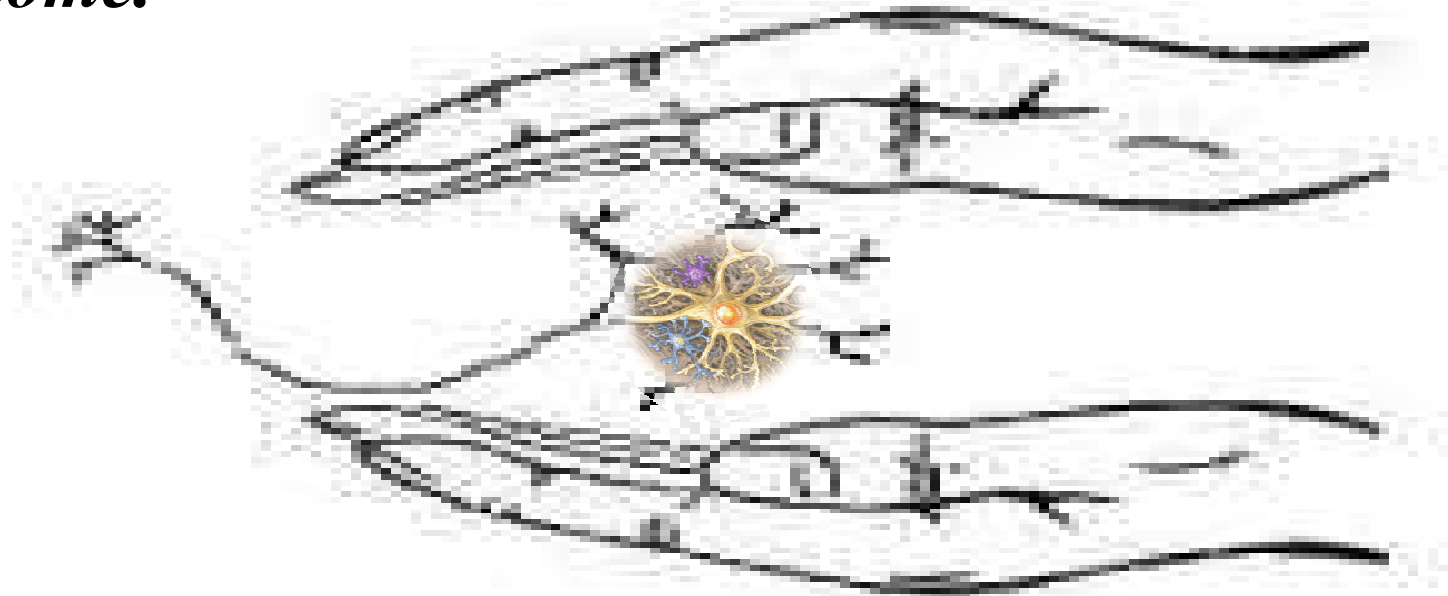


# CEREBRAL PROTECTION IN NEUROSURGERY

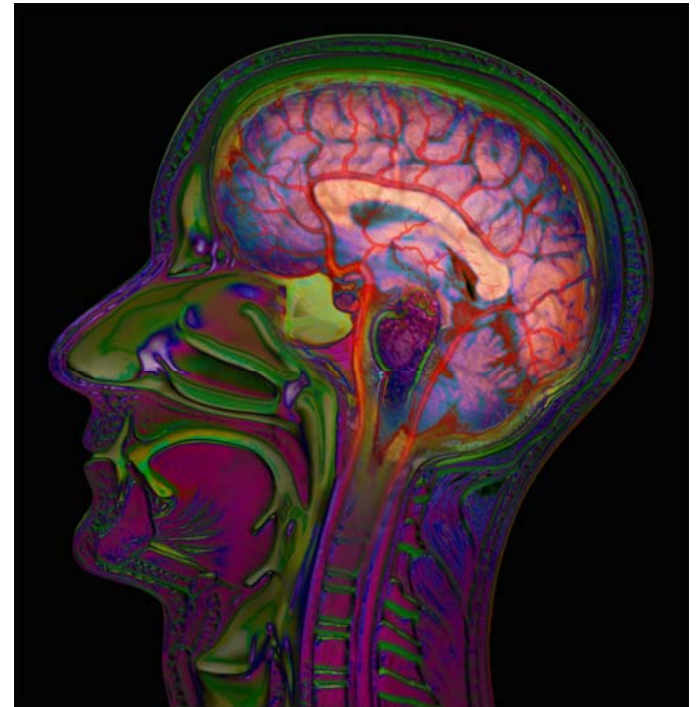


PRESENTER:  
DR SAURABH SHARMA

- *The term ‘Neuroprotection’ signifies treatments used to protect neural tissue from cellular events induced by deprivation of oxygen or glucose or both to the brain.*
- *Treatment initiated before onset of ischemia, intended to modify intra-ischemic cellular and vascular biological responses to deprivation of energy supply so as to increase tolerance of tissue to ischemia resulting in improved outcome.*



- **Cerebral protection**-physiological and pharmacological interventions that precede cerebral insult.
- **Cerebral resuscitation**-similar interventions after the insult has occurred and is a process of damage limitation.

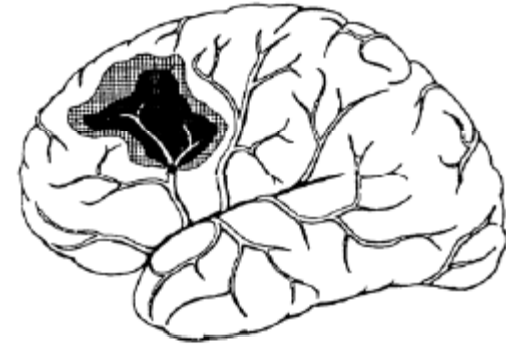


- **Aim** of brain protection is to prevent or minimise the pathological sequelae of inadequate cerebral perfusion, regardless of its cause.

- **Type**

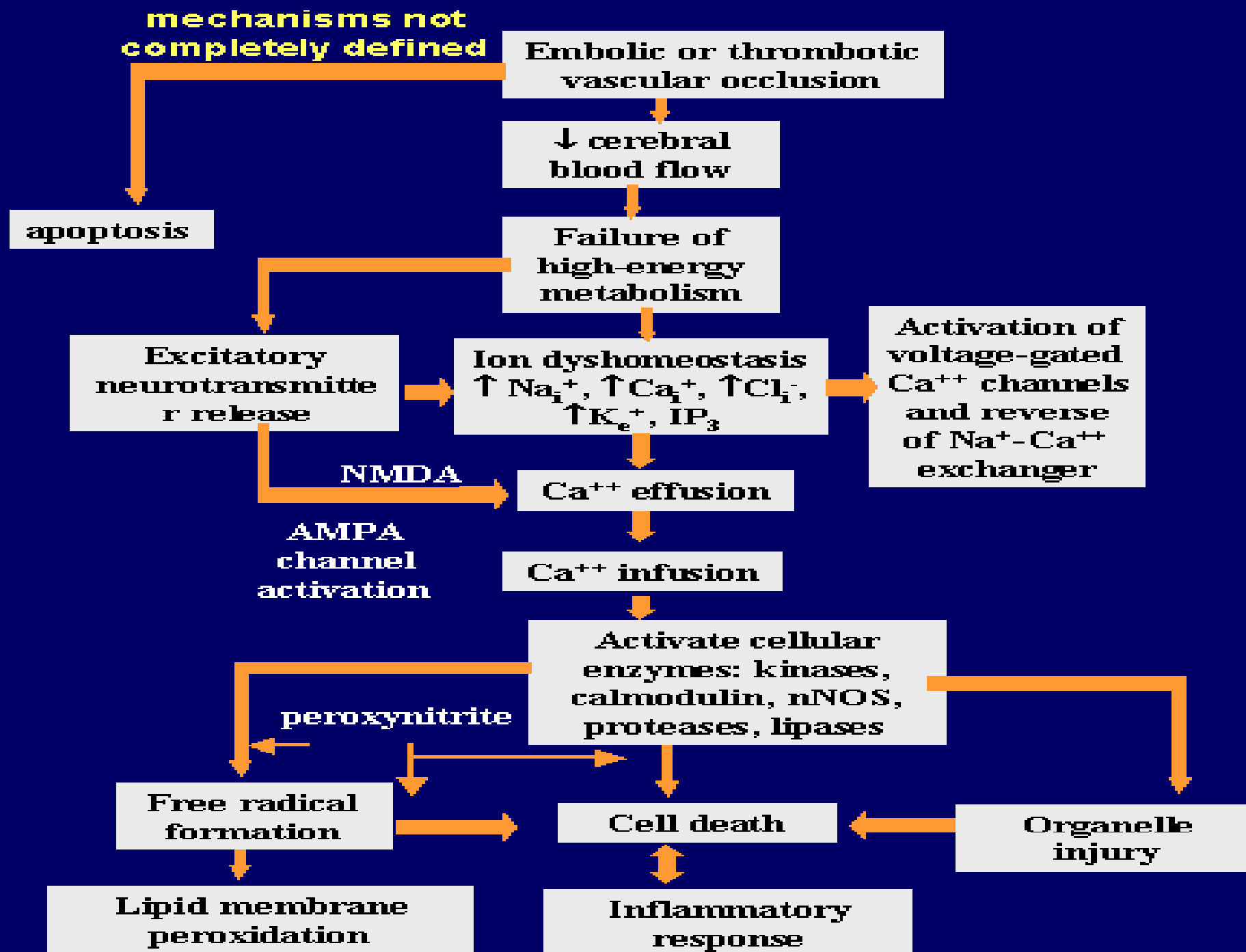
**Complete global ischemia**

**Focal (incomplete) ischemia**



- **Global ischemia is characterized by a complete cessation of CBF (e.g., cardiac arrest). Time window for the restoration of flow is very small because death of neurons is rapid.**
- **Focal ischemia is characterized by a region of dense ischemia (the so called “core”) that is surrounded by a larger variable zone that is less ischemic (the penumbra).**
- **OTHER MECHANISM OF INJURY: OPERATIVE (retraction/compression/infarction/hemorrhage/tissue handling ) OR TRAUMA**

-



# Complete Global ischemia

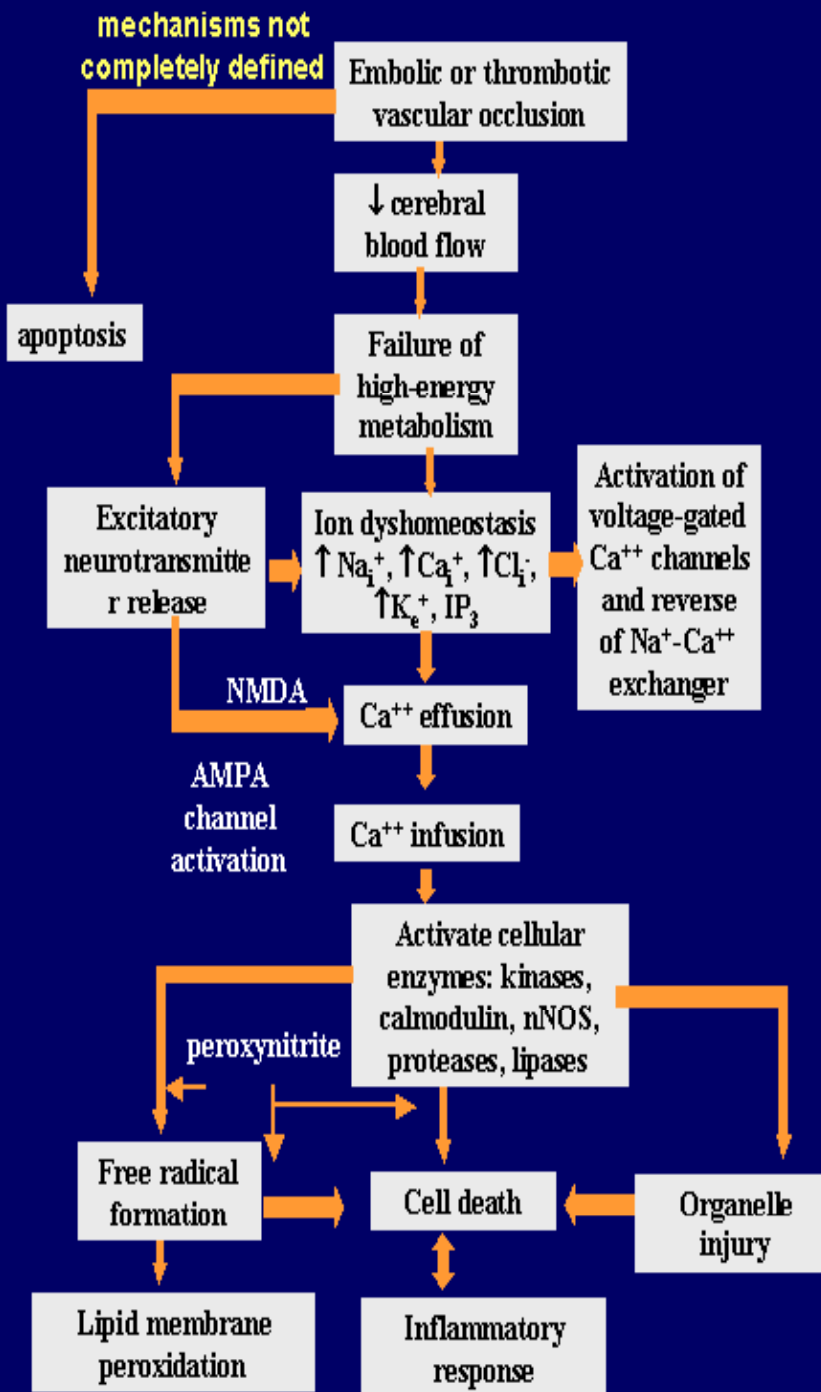
## Cascades of Death

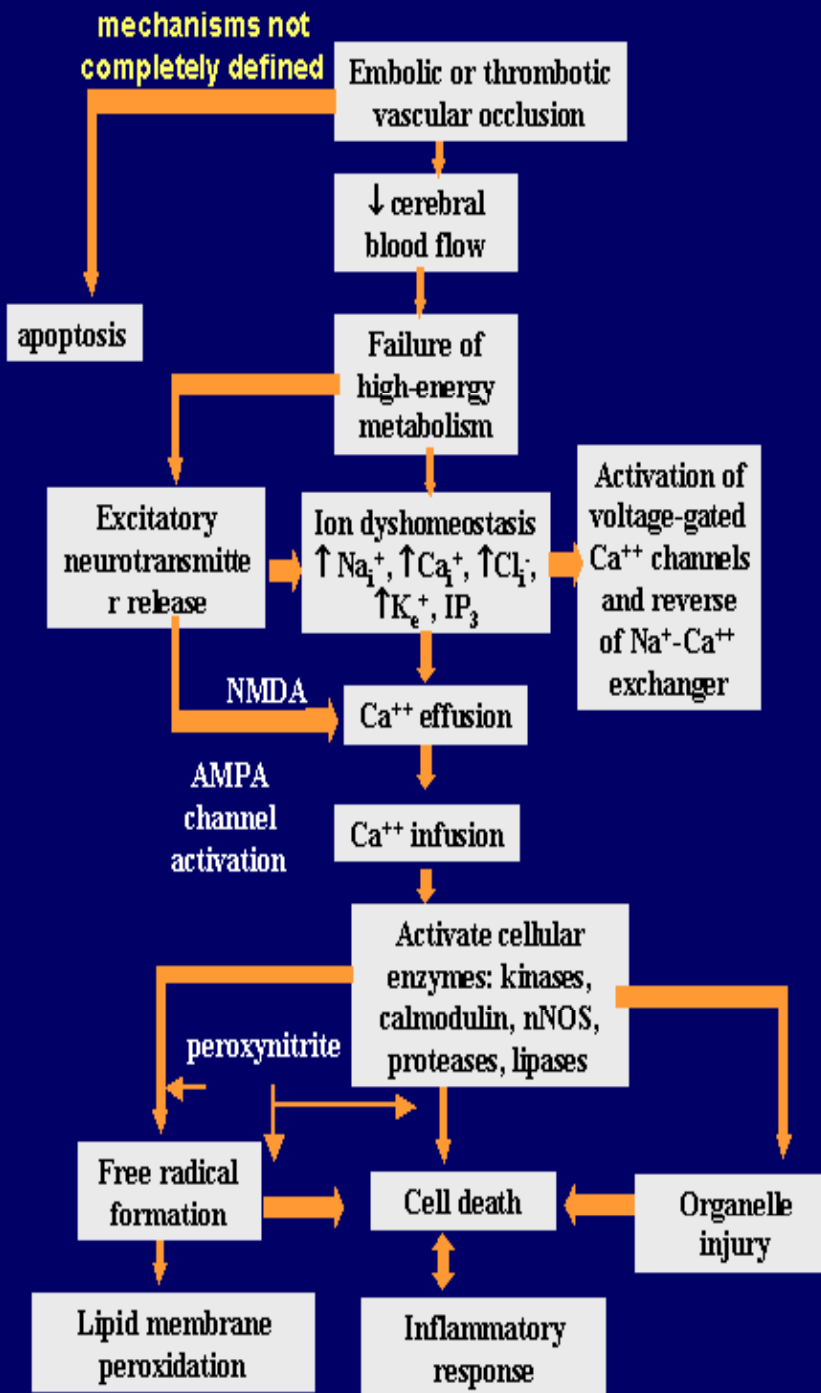
- 5–6 s after the onset of circulatory arrest, the patient loses consciousness.
- Cerebral tissue oxygen tension declines continuously reaching 0 after about 2 min.
- Simultaneously, neuronal energy in terms of adenosine triphosphate is depleted and metabolites, such as adenosine, lactate, and hydrogen ions, accumulate in the cells.

Rossen R, et al. *Arch Neurol Psychiatry* 1943;50:510–2

Cavus E, et al. *Resuscitation* 2006;71:97–106

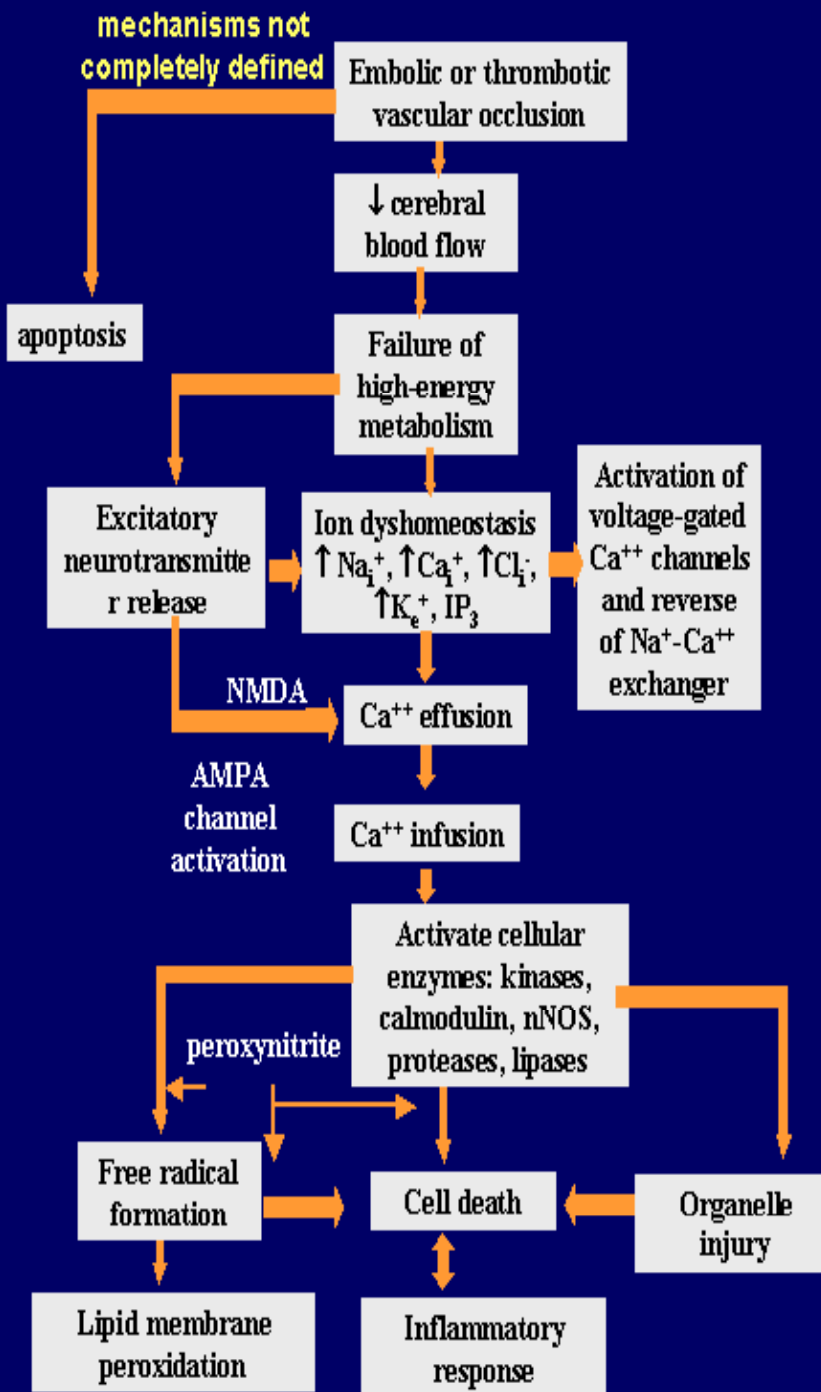
- Dysfunction of the cell membrane ion pumps leads to a severe breakdown in cellular homeostasis.





- Calcium overload is considered a key factor in cellular toxicity.
- Massive accumulation of calcium in the cell cytosol when calcium efflux pumps fail, voltage-gated calcium channels open, and ligand gated channels are activated by released excitatory amino acids, such as glutamate and aspartate.

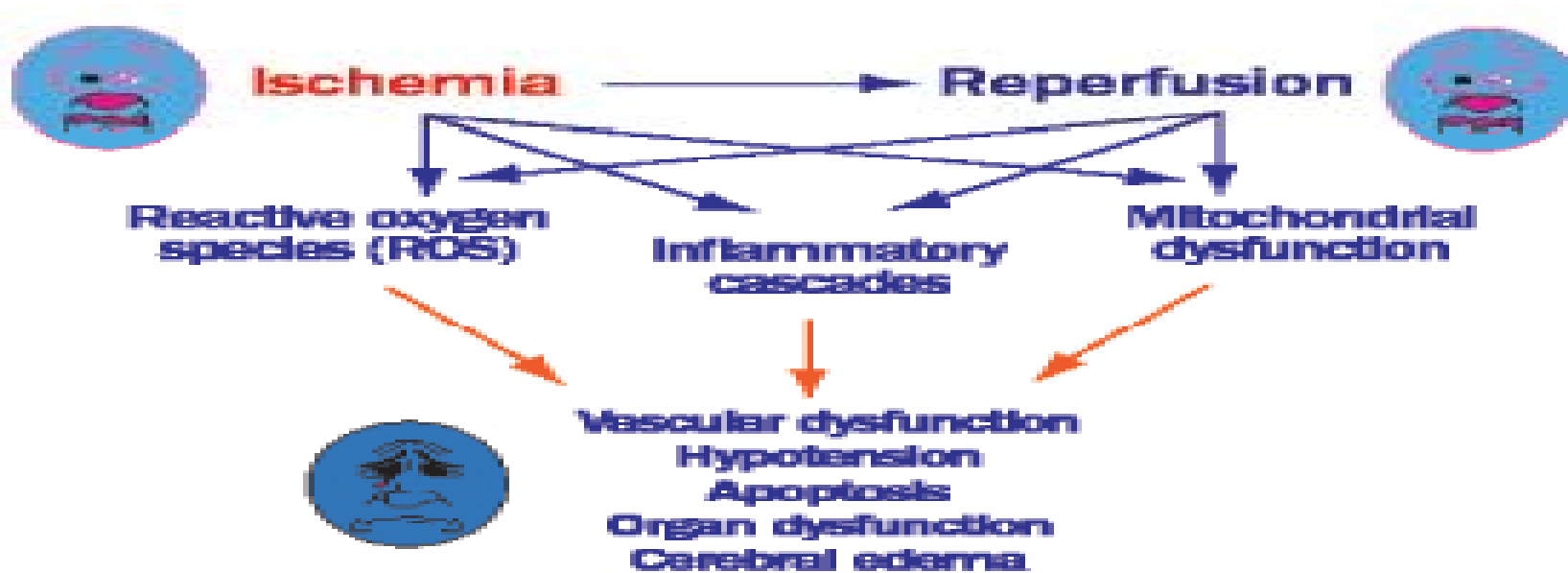
**Kristiain T, et al.**  
**Stroke**1998;29:705–18



- If neuronal energy is recovered rapidly upon return of spontaneous circulation-reperfusion does stop neuronal degeneration to a certain degree.
- During reperfusion, free radicals aggravate cellular damage.

**Sakamoto  
A, et al. Brain Res 1991;554:186-92**





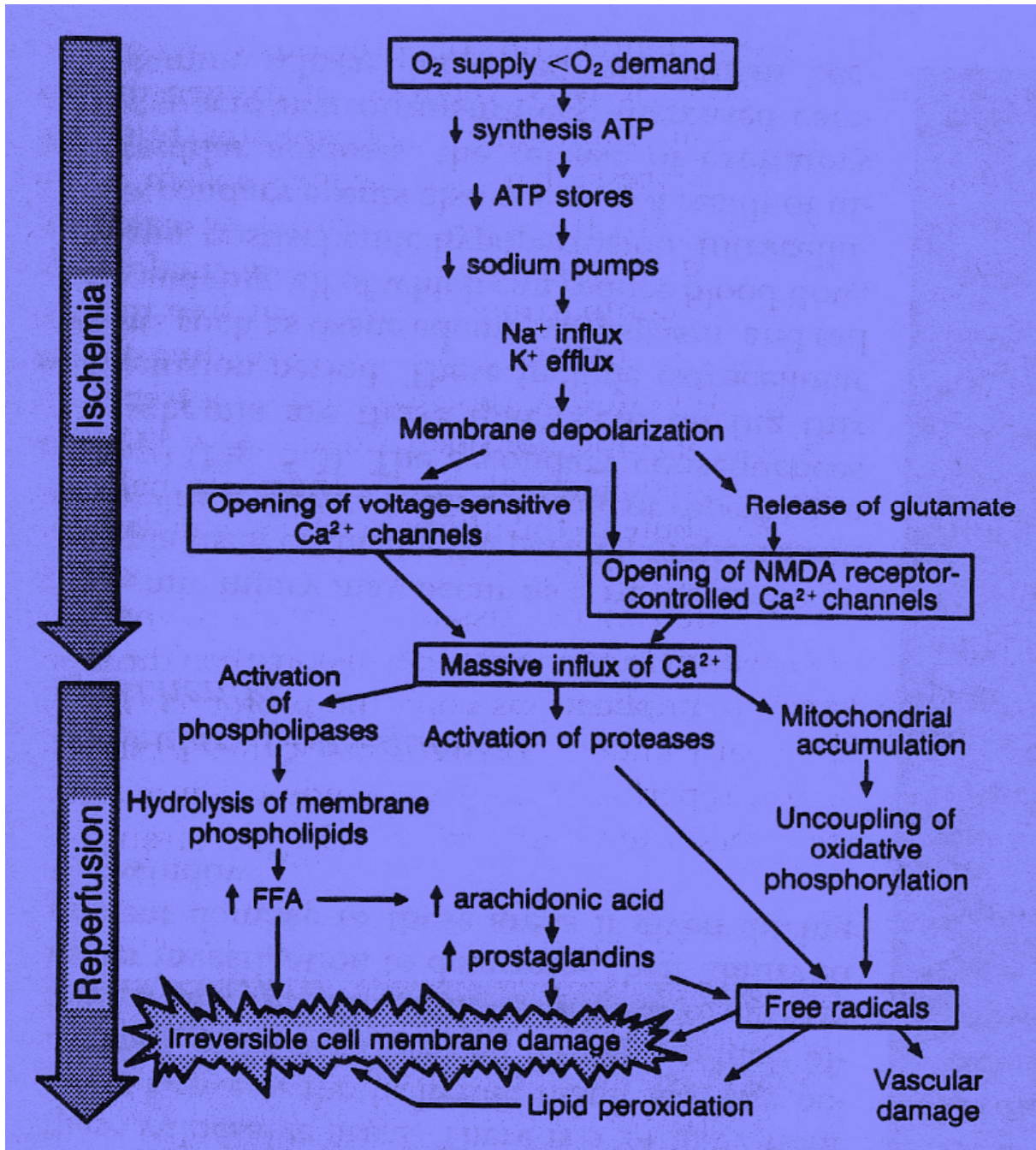
- During reperfusion, ATP gives the cell the opportunity to actively react to the damage.
- This is associated with the expression of immediate early genes, a complex machinery involving both cell survival and cell death cascades.
- The morphological correlate of “subnecrotic” cellular damage is delayed neuronal death, which shows typical signs of apoptosis and occurs mainly in the vulnerable brain areas such as the hippocampus, the nucleus reticularis thalami or distinct layers of the cortex.

*Schmitz B, et al. J Cereb Blood Flow Metab 1998;18:1077–87*

*Chen J, et al. J Neurosci 1998;18:4914–28*

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<b>FEATURE</b>	<b>NECROSIS</b>	<b>APOPTOSIS</b>
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis- karyorrhexis- karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	disrupted	Intact, altered structure
Cellular contents	Enzymatic digestion, may leak out of cell	Intact, may be released as apoptotic bodies
Adjacent inflammation	frequent	no
Physiologic or pathologic role	invariably pathologic	Often physiologic, may be pathologic after some forms of cell injury esp DNA damage

# Cerebral metabolic rate

- 40%-integrity (i)
- 60%-electrophysiological function(e)
- Drugs-only e
- Hypothermia both I +e

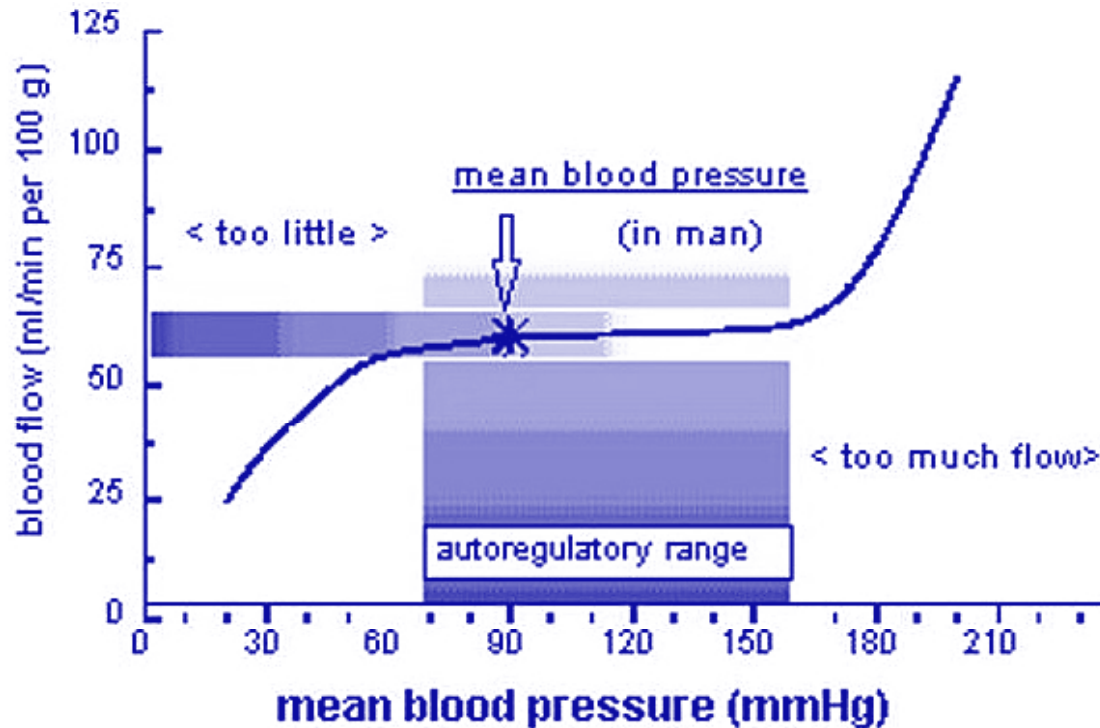
## *Decreases during*

- Sleep/coma
- Anesthesia
- Hypothermia

## *Increases during*

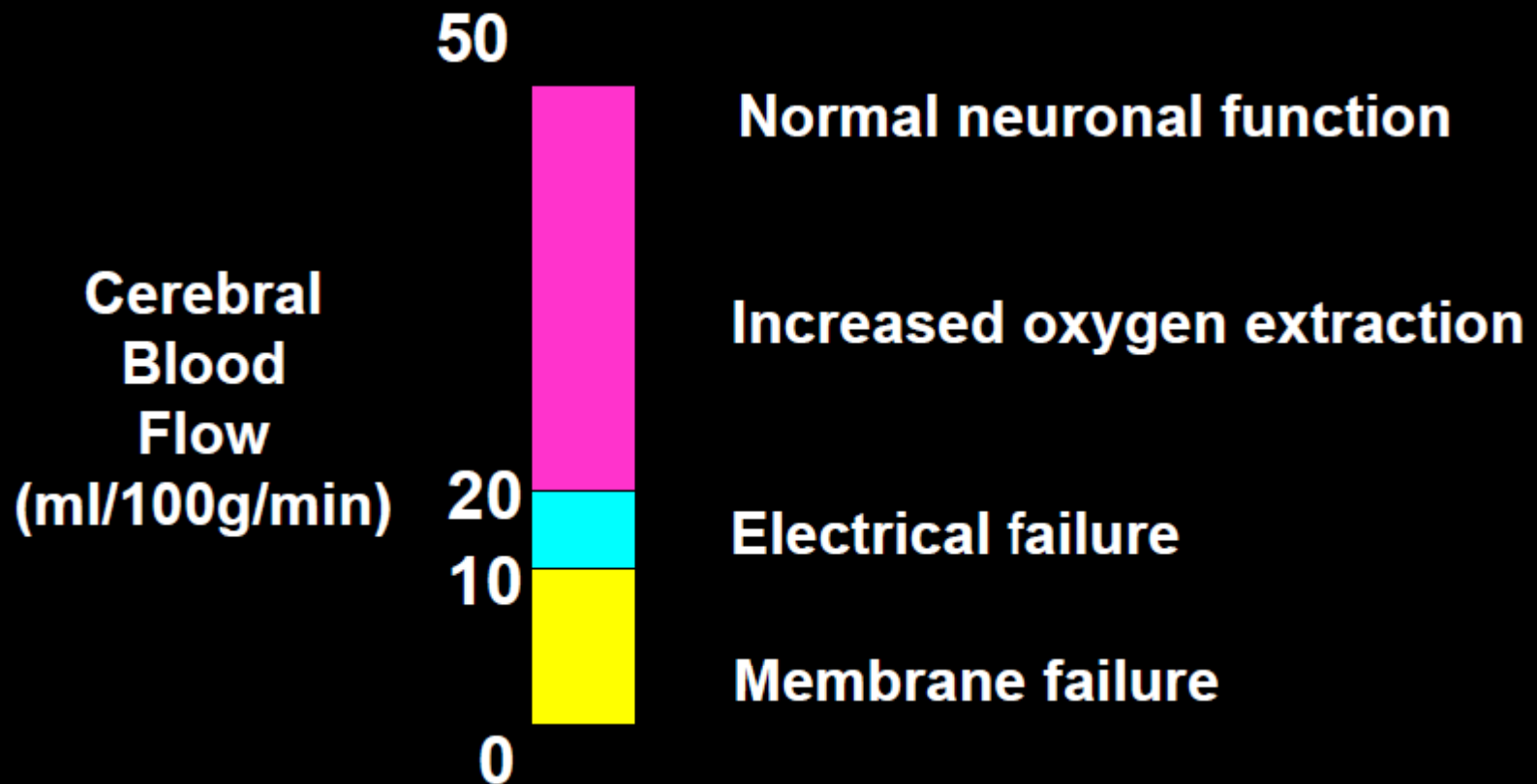
sensory stimulation  
mental tasks  
epileptiform activity  
ketamine anesthesia  
hyperthermia

# Cerebral blood flow threshold



- normal CBF = 54 ml/100g/min. (Kety and Schmidt, 1948)
- CBF > 18 ml/100g/min is necessary to maintain a normal EEG (Sundt et al)
- CBF < 6 to 12 ml/100g/min - integrity of the cell membrane is inevitably lost

# The effect of reduced CBF

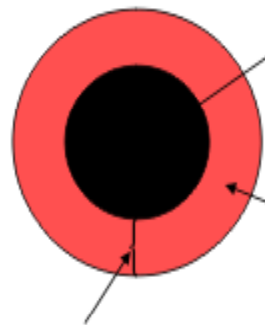


# ISCHEMIC PENUMBRA

- Potentially salvageable.
- Electrically silent but physiologically viable.
- Cells in the penumbra receive sufficient blood flow to maintain the integrity of their membranes but cannot generate synaptic activity, as manifested by a loss of electroencephalographic or evoked potential activity.
- If blood flow is reestablished within a brief time, these cells can recover their normal functions.

## Ischemic Penumbra

DWI / PWI Mismatch

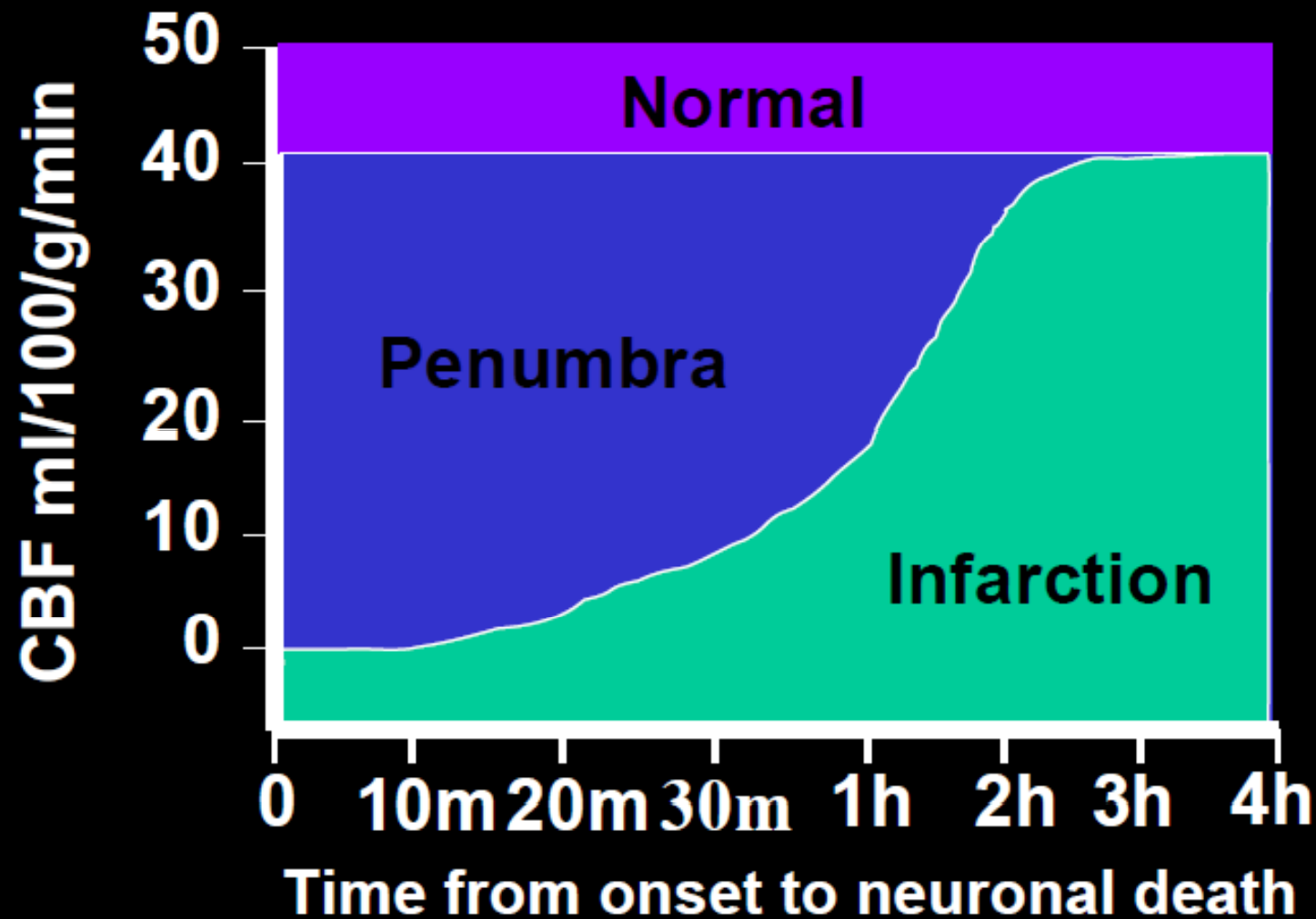


Penumbra

- Diffusion Abnormality
- CBF < 10 ml/100g/min
- Cytotoxic edema
- Irreversible ischemia

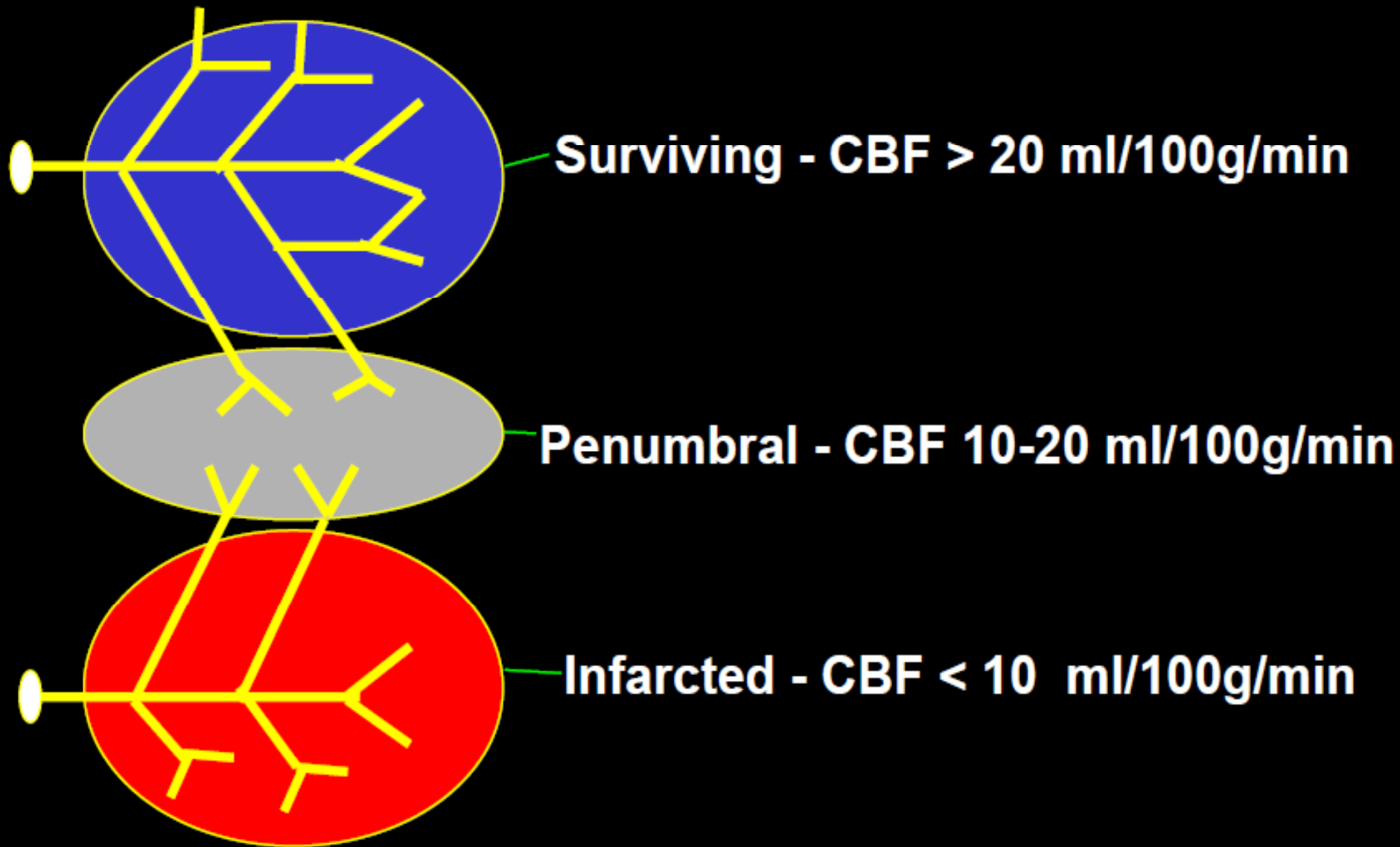
- Perfusion Abnormality
- CBF = 10-18 ml/100g/min
- Neuronal paralysis
- Reversible ischemia

# Relationship between duration and degree of cerebral blood flow (CBF) reduction





# The ischaemic penumbra



# Cerebral protection

- 1) Avoiding mechanical trauma by using refined surgical techniques
- 2) Use of various anaesthetic/pharmacological agents

LIMITING DURATION OF ISCHEMIA

AUGMENTATION OF RESIDUAL BLOOD FLOW

REDUCTION OF METABOLIC ACTIVITY-

hypothermia/barb/etomidate/propofol/glucose modulation

CYTOPROTECTIVE AGENTS-

ccb/glutamate antagonist/nos inhibitors/lubeluzole/citicoline

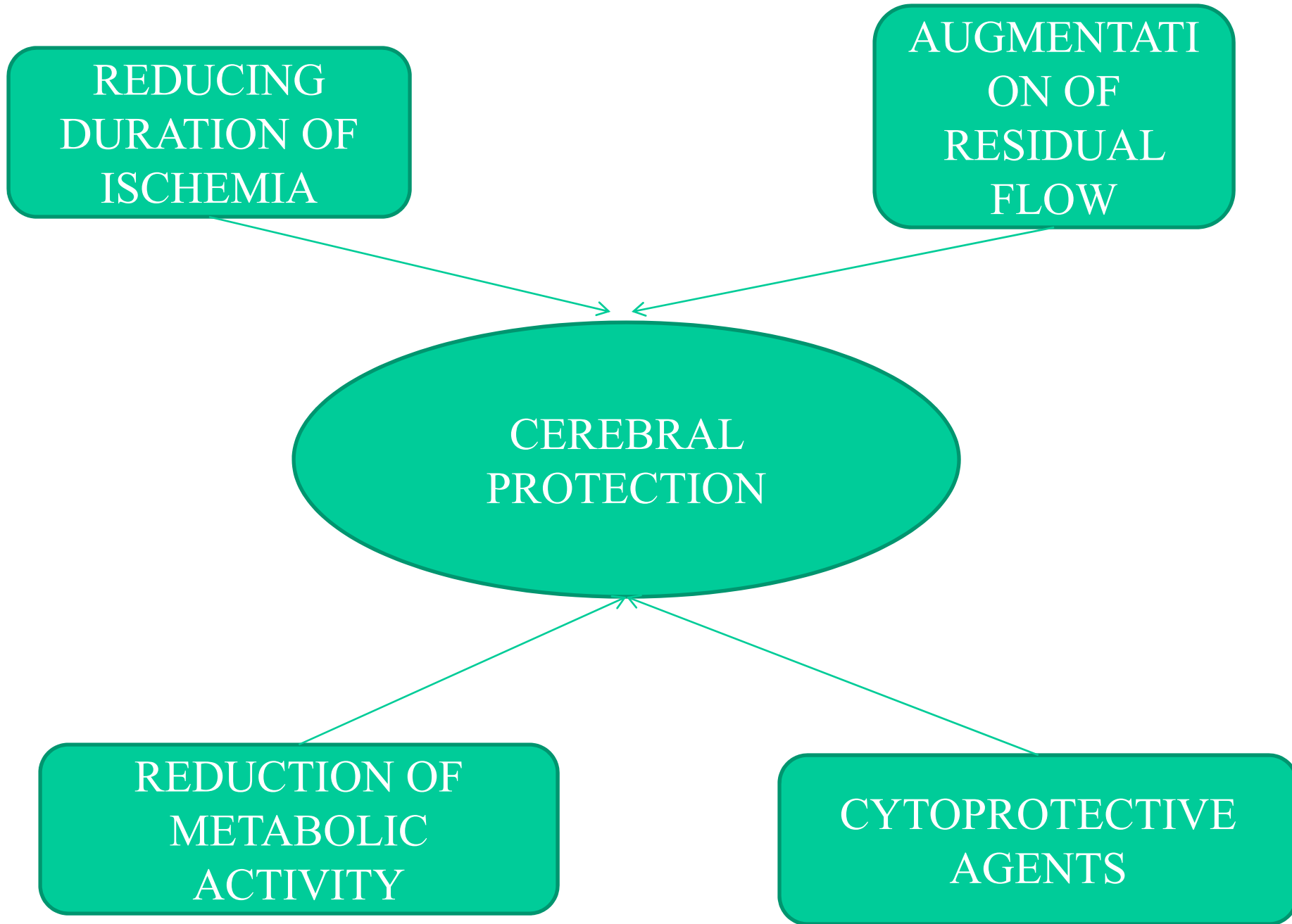
REDUCING  
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ISCHEMIA

AUGMENTATI  
ON OF  
RESIDUAL  
FLOW

CEREBRAL  
PROTECTION

REDUCTION OF  
METABOLIC  
ACTIVITY

CYTOPROTECTIVE  
AGENTS



# Nonpharmacological treatment

- **Hypothermia**
- **Avoidance of hyperglycemia**
- **Prevention and treatment of**
  - Hypotension**
  - Hypoxia**
  - Hypercapnia**
- **Hemodilution**
- **Normalisation of increased ICP**
- **Correction of acidosis and electrolyte imbalance**

# Pharmacological treatment

- **Barbiturate**
- **Inhaled anaesthetic agent**
- **Other intravenous anaesthetic agent**  
(propofol, etomidate, benzodiazepine, lignocaine)
- **Calcium channel blocking drug**
- **Anticonvulsant**
- **Steroids**
- **Experimental modalities under investigation**  
(Prostanoids, Free radical scavengers, lipid membrane peroxidation inhibitors, NMDA receptor antagonists, 21-aminosteroids, Erythropoietin (EPO), Sodium channel blocking drug, Potassium channel-opening drug, NO)

# During surgery

- Patient positioning
- Avoid undue exposure
- Continuous exposure
- Decreased retraction and brain handling
- Decreasing volume of csf-cistern/drain
- Use of stereotaxis
- Intraoperative monitoring

# MILD THERAPEUTIC HYPOTHERMIA

- The first reports of postischemic therapeutic hypothermia were published in the late 1950s.

**Benson DW, et al. Anesth Analg 1959;38:423–8**

- Beneficial effects of mild therapeutic hypothermia after cardiac arrest is provided by two major randomized clinical trials that were published in 2002.

- Both studies investigated mild therapeutic hypothermia in comatose adult patients after out-of-hospital cardiac arrest because of ventricular fibrillation.

- *The European multicenter trial - Hypothermia After Cardiac Arrest study group included 275 patients, of whom 137 were cooled to 32°C–34°C for 24 h while body temperature in the control group was not decreased. Regarding outcome at 6 month, MORTALITY WAS REDUCED BY 26% (41% VS 55%, P 0.02) AND THE FAVORABLE NEUROLOGICAL OUTCOME INCREASED BY 40% (55% VS 39%, P 0.09). Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56*

- **The Australian trial by Bernard et al., covered 77 patients; hypothermia of 33°C for 12 h was applied in 43 patients. At hospital discharge, THE LIKELIHOOD FOR GOOD NEUROLOGICAL OUTCOME WAS 85% HIGHER IN THE HYPOTHERMIC GROUP (49% VS 26%, P 0.046). Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63**

- *The International Liaison Committee on Resuscitation recommended ( 2003) that mild therapeutic hypothermia be used in comatose adult patients after out-of-hospital cardiac arrest because of ventricular fibrillation.*
- *This recommendation was implemented into the revised international guidelines on CPR in 2005.*

Table 1. Indications for Mild Therapeutic Hypothermia<sup>53</sup>

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Unconscious adult patients with spontaneous circulation after out-of-hospital ventricular fibrillation cardiac arrest should be cooled to 32°C–34°C. Cooling should be started as soon as possible and continued for at least 12–24 h.

Induced hypothermia might also benefit unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a nonshockable rhythm or cardiac arrest in hospital.

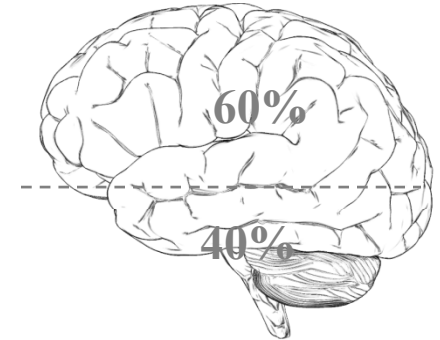
A child who regains a spontaneous circulation but remains comatose after cardiopulmonary arrest may benefit from being cooled to a core temperature of 32°C–34°C for 12–24 h.

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# Physiological effects of hypothermia

- **Decrease in cerebral metabolism**
- **Maintains integrity of membranes**
- **Preserves ion homeostasis**
- **Decreases excitatory AA release**
- **Decrease Ca influx**
- **Decrease lipid peroxidation**
- **Decrease free radical formation**
- **Decrease nitric oxide synthase activity**
- **direct inhibition of apoptosis**
- **inhibition of coagulation cascades and inflammatory reaction**
- **alters gene expression by enhancing the expression of brain-derived neurotrophic factor (BDNF), the antiapoptotic protein Bcl-2, and suppressing the proapoptotic protein Bax or matrix metalloproteinase-9.**



# *CMRO2 & Temperature*

**CMRO2<sub>37deg</sub> = 3ml/min/100gm brain**

**CMRO2<sub>27deg</sub> = 1.4ml/min/100gm brain**

- **Hypothermia can be induced by different methods, surface cooling, ice-cold infusions or endovascular cooling catheters.**

- **Recommendation is that hypothermia should be initiated with minimal delay after cardiac arrest.**

*Circulation 2005;112:IV1–IV211*

- **Surface cooling or ice-cold infusions can be used preclinically.**
- **Kim et al. conducted a randomized clinical trial in which patients were assigned to either receiving 4°C normal saline or not in the out-of-hospital setting, Survival rates was higher in patients who had received out-of-hospital cooling treatment.**

*Circulation 2007;115:3064–70*

# DETRIMENTAL EFFECTS OF HYPOTHERMIA

- **Circulatory:** ↑ afterload, 3<sup>rd</sup> spacing, viscosity, diuresis, hypovolemia, hypotension
- **cardiac:** decrease cardiac output, arrhythmias
- **Pulmonary:** pulmonary edema
- **Neurologic:** ICP w/ rewarming, affects neuromonitoring
- **Coagulation:** platelet dysfunction, fibrinolysis , bleeding
- **Metabolic:** shifts O<sub>2</sub> dissociation curve left, metabolic acidosis, respiratory alkalosis (CO<sub>2</sub> more sol), drug metabolism
- **Immunologic:** decrease leukocyte mobility & phagocytosis

# Hypothermia in neurosurgery

- **1<sup>st</sup> reported use of therapeutic hypothermia in TBI in 1943.**
- **1<sup>st</sup> reported use as a protective adjunct to neurosurgery in 1955.**
- **Abandoned from common practice in 70's-80's d/t associated complications.**
- **Revived interest in 90's after multiple animal studies showed neuroprotective benefit with even mild hypothermia.**

**Mild Intraoperative Hypothermia during Surgery for Intracranial Aneurysm (IHAST) Conclusions-** Intraoperative hypothermia did not improve the neurologic outcome after craniotomy among good-grade patients with aneurysmal subarachnoid hemORRHAGE **New England Journal of Medicine Vol: 352, No2, January, 13 2005**

*Association between Intraoperative Hypothermia or Supplemental Protective Drug and Neurologic Outcomes in Patients Undergoing Temporary Clipping during Cerebral Aneurysm Surgery*  
**Conclusion: In the Intraoperative Hypothermia for Aneurysm Surgery Trial, neither systemic hypothermia nor supplemental protective drug affected short- or long-term neurologic outcomes of patients undergoing temporary CLIPPING**  
**Anesthesiology 2010; 112:86 –101**

- *No Association between Intraoperative Hypothermia or Supplemental Protective Drug and Neurologic Outcomes in Patients Undergoing Temporary Clipping during Cerebral Aneurysm Surgery* **Anesthesiology 2010; 112:86 –101**
- **Conclusion: In the Intraoperative Hypothermia for Aneurysm Surgery Trial, neither systemic hypothermia nor supplemental protective drug affected short- or long-term neurologic outcomes of patients undergoing temporary clipping**
- **NO BENEFIT**

# Hypothermia in brain injury pt.

- Initial pilot studies showed neuroprotective effect but later studies did not.
- Bench-to-bedside review: Hypothermia in traumatic brain injury  
*Critical Care 2010, 14:204*
- The use of hypothermia in patients with traumatic brain injury may have beneficial effects in both ICP reduction and possible neuro-protection, supported by the **Eurotherm3235Trial protocol.**

# Hypothermia in stroke

- Studies demonstrated the efficacy of induced moderate hypothermia

*Moderate Hypothermia in the Treatment of Patients With Severe Middle Cerebral Artery Infarction  
S. Schwab, et al. Stroke 1998;29;2461-2466*

*Conclusions—Moderate hypothermia in the treatment of severe cerebral ischemia is not associated with severe side effects. Moderate hypothermia can help to control critically elevated ICP values in severe space-occupying edema after MCA stroke and may improve clinical outcome in these patients.*

*Cooling for Acute Ischemic Brain Damage (COOL AID): An Open Pilot Study of Induced Hypothermia in Acute Ischemic Stroke  
Derk W. Krieger et al, Stroke 2001;32;1847-1854*

*CONCLUSION: Induced hypothermia appears feasible and safe in patients with acute ischemic stroke even after thrombolysis. Refinements of the cooling process, optimal target temperature, duration of therapy, and, most important, clinical efficacy, require further study.*



# Avoid Hyperthermia

- **Brain metabolic rate alters in direct proportion to core temp.**
- **Above normal temp. markedly increase CMRO<sub>2</sub> and exacerbate ischemic injury**
- **Ischemia that normally results in scattered neuronal necrosis produces cerebral infarction when body temperature is elevated.**

# Hyperventilation or Normocapnia

- Available data do not support reduction of PaCO<sub>2</sub> as a routine intervention to reduce cerebral injury, but its important for reduction in ICP

*ASA Refresher Courses (29) 2001*

*ASA Annu Rev (54)*

- In head injury pt, application of prophylactic hyperventilation is associated with a worse outcome as the ischemic regions increase dramatically with hypocapnia.
- The Brain Trauma Foundation has recommended that prophylactic hyperventilation be avoided during the early stages after head injury.

**J Neurotrauma 2000;17:513-20.**

- Prophylactic hyperventilation has not been shown to be of any benefit in patients with stroke.

**Ruta TS, et al. Anesthesiology 1992;78:134-40.**

- *“Therapeutic Hypercapnia” after Ischemic Brain Injury  
Is There a Potential for Neuroprotection?(Zhou et al. Anesthesiology 2010; 112:274 – 6)*
- *conclusion : mild and moderate hypercapnia were associated with better neurologic deficit scores, fewer ultrastructural histopathologic changes, and reduced neuronal apoptosis compared with normocapnia*

# GLYCEMIC CONTROL FOR NEUROPROTECTION

- **Why to maintain normoglycemia-EXPANSION OF ISCHEMIC LESION + DELAYED RECOVERY AFTER ISCHEMIC INSULT**
- **Target:Non diabetic- 80 to 155 mg/dL**  
**:Poorly-controlled diabetes 100 to 200 mg/dL.**

**Wass CT,et al . Mayo Clin Proc. 1996;71:801–812.**

- *Insulin therapy protects the central and peripheral nervous system of intensive care patients( Van den Berghe G, et al. Neurology 2005; 64: 1348–1353. )surgical patients admitted with isolated brain injury showed reduced mean and maximum intracranial pressure with IIT, while cerebral perfusion pressures were maintained identical with eightfold less vasopressors. Seizures occurred less frequently and there was a trend towards a reduction in diabetes insipidus.*
- **Differential temporal profile of lowered blood glucose levels (3.5 to 6.5 mmol/l versus 5 to 8 mmol/l) in patients with severe traumatic brain injury(Regula Meier, Critical Care 2008, 12:R98)**  
**Conclusion :Maintaining blood glucose within 5 to 8 mmol/l appears to yield greater benefit during the first week. During the second week, 3.5 to 6.5 mmol/l is associated with beneficial effects in terms of reduced intracranial hypertension and decreased rate of pneumonia, bacteraemia and urinary tract infections.**
- *The Effect of Intensive Insulin Therapy on Infection Rate, Vasospasm, Neurologic Outcome, and Mortality in Neurointensive Care Unit After Intracranial Aneurysm Clipping in Patients With Acute Subarachnoid Hemorrhage: A Randomized Prospective Pilot Trial,-CONCLUSION-The benefit of strict glycemic control on postoperative vasospasm, neurologic outcome, and mortality rates does not seem to be affected by intensive insulin therapy.*  
*Journal of Neurosurgical Anesthesiology: July 2007 - Volume 19 - Issue 3 - pp 156-1*

# **Insulin-related decrease in cerebral glucose despite normoglycemia in aneurysmal subarachnoid hemorrhage**

**Florian S, et al. *Critical Care* 2008, 12:R9**

- **In prospective, nonrandomized study, 31 SAH patients in an intensive care unit (age  $52 \pm 10$  years, World Federation of Neurological Surgeons grade  $2.9 \pm 1.6$ ). A microdialysis catheter was inserted into the vascular territory of the aneurysm after clipping.**
- **Blood glucose levels above 140 mg/dl were treated with intravenous insulin and the microdialysates were analyzed hourly for the first 12 hours of infusion.**

## **Results**

- **Twenty-four patients were treated with insulin for glucose control. Higher age and World Federation of Neurological Surgeons score were risk factors for need for insulin treatment ( $P < 0.05$ ).**
- **blood glucose remained stable after initiation of insulin infusion, insulin induced a significant decrease in cerebral glucose at 3 hours after onset of the infusion until the end of the observation period ( $P < 0.05$ ), reflecting high glucose utilization.**
- **The lactate/pyruvate ratio and glutamate did not increase, excluding ischaemia as possible cause of the decrease in glucose.**
- **Glycerol tended toward higher values at the end of the observation period (9 to 12 hours), reflecting either tissue damage after SAH or the beginning of cellular distress after insulin infusion.**

## **Conclusion**

- **Higher SAH grade was among the risk factors for need for insulin.**
- **Intensive glycaemic control using insulin induced a decrease of cerebral glucose and a slight increase in glycerol.**

# HEMODILUTION

- **Target hematocrit 30%- 35%**
- **Beneficial effect by**
  - 1. decreases viscosity**
  - 2. increases CBF**
  - 3. Increases oxygen delivery**

**-No role in stroke,**

**-Definitive role in vasospasm**

**The Lancet Neurology, Volume 2, Issue 10, 2003**

# AVOID HYPOTENSION

- Hypotension has been shown to be deleterious to the injured brain
- Hypotension can increase cerebral infarct volumes significantly and should be avoided
- In head injured patients ,a higher than normal CPP is required to maintain normal CBF.
  
- Chan and colleagues have shown that CPP of about 70 mmHg is adequate in head injured patients(**Chan KH, et al. Neurosurgery 1993;32:547-52.**)
- Patients who have sustained an ischemic cerebral injury may benefit from an augmentation of cerebral blood flow by induced hypertension(**Schwarz S, et al. Stroke 2002;33:998-1004**)
  
- Induced hypertension, with an increase in mean arterial pressure 20% above baseline pressure, can lead to a clinical improvement in a patients with acute stroke in whom thrombolysis is not feasible. The potential risk for hemorrhagic conversion of the stroke exists. **Rordorf G, et al. Neurology 2001;56:1210-3.**
- Maintenance of an adequate MAP and CPP
  - MAP 70-80 mmHg
  - CPP >60 mm Hg
  - SAH induced vasospasm- SBP 180-220 mm Hg
  
- Elevation of MAP by alpha agonists

# Thrombolysis

## **Rationales for using thrombolytics during CPR.**

- **Cardiac arrest is caused by acute myocardial infarction or pulmonary embolism in 50%–70% of patients.**
- **Coagulation disorders are involved in the no-reflow phenomenon.**
- **Microscopic examination of cerebral vessels shows that multiple microemboli develop during cardiac arrest and resuscitation.**
- **The European multicenter Thrombolysis in Cardiac Arrest trial.**

**After inclusion of 1050 patients, the study was prematurely stopped, because preliminary findings indicated that there was no likely benefit of thrombolytic therapy over placebo.**

***Thrombolysis in Cardiac Arrest (TROICA) Study. Eur J Clin Invest  
2005;35:315–23***

# **HYPERTONIC, HYPERONCOTIC INFUSIONS TO PROMOTE MICROCIRCULATION**

- **Several animal studies have shown that hypertonic-hyperoncotic solutions given during CPR, or immediately after restoration of spontaneous circulation, decrease cerebral no-reflow.**

*Krep H, et al. Resuscitation 2004; 63:73–83*

*Noppens RR, et al. Crit Care Med 2006;34:2194–200*

- **Besides having positive effects on cerebral microcirculation, hypertonic saline also seems to ameliorate cardiac function during and after CPR.**
- **Benderet al. randomized 66 patients who suffered out-of-hospital cardiac arrest into two groups. The patients received 2 mL / kg/ 10 min of either hypertonic saline with HES (7.2% NaCl with 6% HES 200,000/0.5) or HES alone during continuous CPR.**
- **Resuscitation success tended to be higher in patients receiving hypertonic saline with HES (66.7% vs 51.5%,  $P$  0.21) and hospital admission rates were also increased (57.6% vs 39.4%,  $P$  0.14)**

*Resuscitation 2007;72:74–81*



# SENDAI COCKTAIL

- 20% MANNITOL+VITAMIN E+ DEXAMETHASONE
- *Surgical treatment of AVMs occluding these feeders during removal--utilizing the intraoperative balloon catheter and brain protective substances ("Sendai cocktail")* [Takahashi A, Suzuki J, Sugawara T, Yoshimoto T](#)

# BARBITURATES

- **The Brain Resuscitation Clinical Trial failed to demonstrate any improved outcome due to thiopental therapy following cardiac arrest.**
- ***Thiopentone, methohexital- Do not improve outcome in global or complete ischemia after cardiac arrest***
- **Pentobarbital(mechanism similar to thiopental(long acting ):Current clinical indication- BARBITURATE COMA**
- **Barbiturates have been found to be efficacious in the treatment of focal ischemia and can reduce the extent of cerebral injury.**

**Warner DS, et L. J Cereb Blood Flow Metab 1991;11:794-802.**

**Drummond JC. Anesthesiology 1993;78:611-3.**

**BARBITURATES IN HEAD TRAUMA: Barbiturates provide a means of reducing and maintaining ICP but not necessarily corresponds to improved outcome. (*Ward JD, et al. J Neurosurg 1985; 62: 383-8*)**



# INHALATIONAL AGENTS

**Protects both against focal and global ischemia**

## **Mechanism**

- 1. Metabolic electrical suppression**
- 2. Inhibition of excitatory neurotransmitter**
- 3. Potentiation of inhibitory receptor**
- 4. Decrease Ca<sup>+</sup> influx**
- 5. Activation of mitochondrial K<sup>+</sup> channels**

E.g. isoflurane /desflurane/sevoflurane/halothane

**When compared with other volatile anaesthetics,**

**isoflurane has demonstrated superior protection during focal ischaemia**

***Michenfelder JD, et al. Anesthesiology 1987; 67: 336-40.***

# NITRIC OXIDE SYNTHATASE INHIBITORS

1. Increase blood flow in ischemic tissue by action on platelet aggregation and leukocyte adhesion
2. Limits NMDA-linked calcium influx, scavanges free radicals, inhibits acidosis

Tirilazad mesylate is a potent inhibitor of lipid peroxidation caused by suppression of inducible NOS.

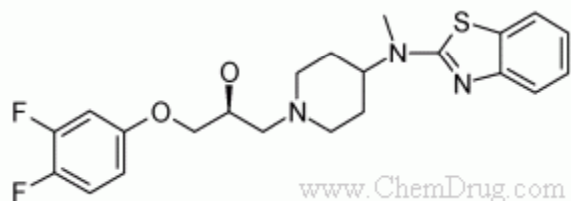
Multicentric trial was halted prematurely because of lack of benefit.

# GLUTAMATE ANTAGONIST

1. Reduce infarct volume in focal ischemia
2. Block episodic depolarization in ischemic areas

e.g. dextrorphan, dextromethorphan, licostinel and magnesium

Mg has reduced the extent of infarction in several experimental models



# LUBELUZOLE

- Effective therapy for focal ischemia.
  1. Postischemic release of glutamate and taurine.
  2. Blocks calcium and sodium channels .
  3. Inhibits the glutamate-activated NOS pathway.
- In focal ischemia models, lubeluzole reduces infarct volume by appropriately 25% and studies in humans have shown few side effects.
- Three randomized, placebo-controlled studies of patients with acute ischemic stroke have reported encouraging results. Improvement was measured by a different outcome in each study. Further clinical trials are needed to elucidate these disparate findings before routine use of this drug can be recommended.

# CITICOLINE

- Citicoline (cytidine 5- diphosphocholine) supplies choline and cytidine , both of which are necessary substrates for the synthesis of phosphatidylcholine , a key membrane component.
- In animal models of focal ischemia , citicoline administration has been associated with reduced infarct volume.
- In a single multicentric randomized , placebo controlled, and blinded study of patients treated within 24 hours of ischemic stroke , citicoline was associated with improved neurological , cognitive , and functional outcomes.



# Etomidate

- Reduces CMRO<sub>2</sub>(50%)
- Decreases CBF
- Decreases ICP
- But maintains cardiovascular stability and CPP
- CO<sub>2</sub> reactivity is preserved
- *Batjer's group report using etomidate 1 mg/kg-1 as a bolus followed by an infusion of 10 mg/kg-1min-1 to maintain burst suppression during temporary arterial occlusion for complex intracranial aneurysms. This regimen was well tolerated. Batjer HH. Cerebral protective effects of etomidate: experimental and clinical aspects. Cerebrovascular and brain metabolism reviews 1993; 5: 17-32*
- Models of focal ischemia revealed that etomidate actually increased the volume of brain infarction by reducing nitric oxide levels in ischemic brain tissue .

**Drummond JC, et al. Anesth Analg 2005;100:841-6**

AVAILABLE DATA **DO NOT SUPPORT** THE USE OF ETOMIDATE AS A NEUROPROTECTIVE AGENT.

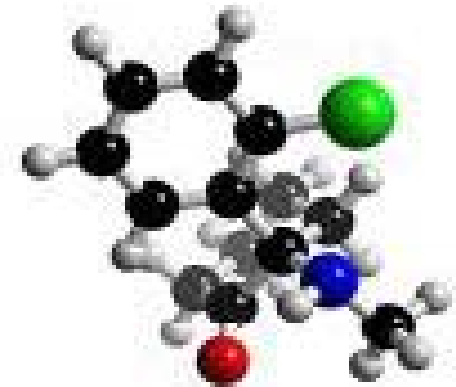
# Benzodiazepine

- **Stimulate inhibitory neurotransmitter GABA**
- **Decreases CMRO<sub>2</sub>, CBF while preserving CO<sub>2</sub> reactivity**
- **Commonly used are diazepam, midazolam, lorazepam**
- **Diazepam improved the oxygen supply: demand ratio**
- **Reduces energy required for synaptic transmission**
  - Marana E, et al. Resuscitation 1982 10: 89-100.**
  - Cotev S, et al. Anesthesiology 1975; 43:117-22**

**May be neuroprotectant in both global and focal ischaemia.**



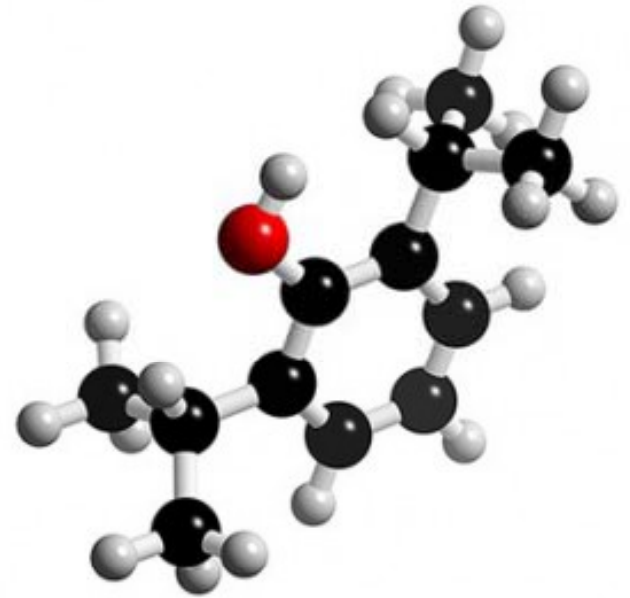
# Ketamine



- Ketamine is a noncompetitive antagonist at NMDA receptors & may therefore offer protection from the adverse effects of cerebral ischaemia



# PROPOFOL



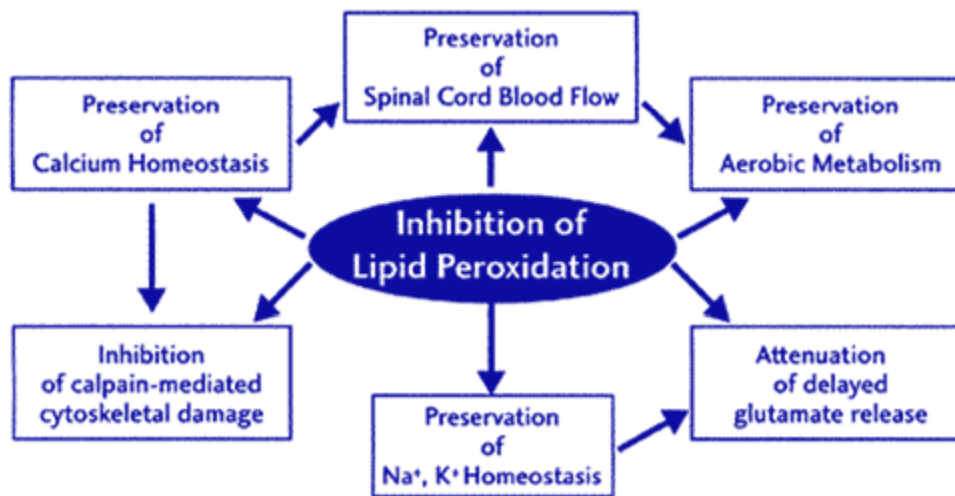
1. Decrease CMR/CBF/EEG ACTIVITY
2. FREE RADICAL SCAVENGING

- Administration of propofol to head injured patients with elevated ICP has been associated with a reduction in ICP ***Toner CC, Stamford J. General anesthetics as neuroprotective agents. In: Bailliere Tidall, editor. Bailliere's Clinical Anesthesiology. International practice and research. UK, Saunders, 1996, Vol 10/ No. 3: 515-33.***
- Propofol infusion titrated to produce unresponsiveness (8 mgkg<sup>-1</sup>hr<sup>-1</sup>) in humans, resulted in 55% depression in CMR for glucose, as measured using positron emission tomography.

# STERIODS

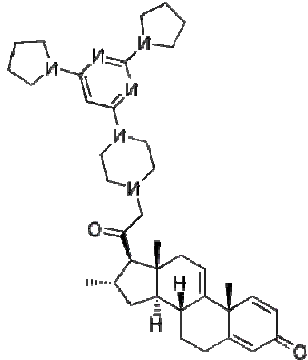
- **Antiinflammatory properties, alter the normal response to injury and may alter the neurological outcome following an ischaemic insult.**
- **Insufficient evidence to define role of glucocorticoids in focal ischemia**  
**(Cochrane Database Syst Rev 2002)**
- **In double-blind study, administration of dexamethasone to acute stroke victims concluded that dexamethasone can be a useful adjunct to the treatment of the patient with a severe stroke and the beneficial effects of steroids are in part due to their ability to decrease brain oedema secondary to massive brain infarction.**  
***Patten BM, et al. Neurology 22: 377-83.***
- **Glucocorticoids exacerbate injury from global ischemia by increasing plasma glucose**

- efficiency in reducing vasogenic peritumoral edema is well documented (*Andrews RJ, Giffard RG. Clinically useful nonanesthetic agents. In: Andrews RJ, editor. Intraoperative Neuroprotection. USA: Williams and Williams, 1996.*)
- The Second National Acute Spinal Cord Injury Study (NASCIS II) demonstrated that high dose methylprednisolone (30 mg/kg bolus followed by 5.4 mg/kg for 23 hours) was of benefit in spinal cord injury if treatment was instituted within 8 hours of injury.
- Lower doses had proven ineffective in the NASCIS I study. (*Bracken MB, Shephard MJ, Hellenbrand KG et al. Methylprednisolone and neurological function 1 year after spinal cord injury. Results of the National Acute Spinal Cord Injury Study. J Neurosurg 1985; 63: 704-713*)
- The use of glucocorticoids is not recommended for improving outcome or reducing ICP in patients with severe head injury.



**Figure 2.**

Neuroprotective actions of high-dose methylprednisolone therapy in injured spinal cord showing that central mechanism is inhibition of reactive oxygen-induced lipid peroxidation.



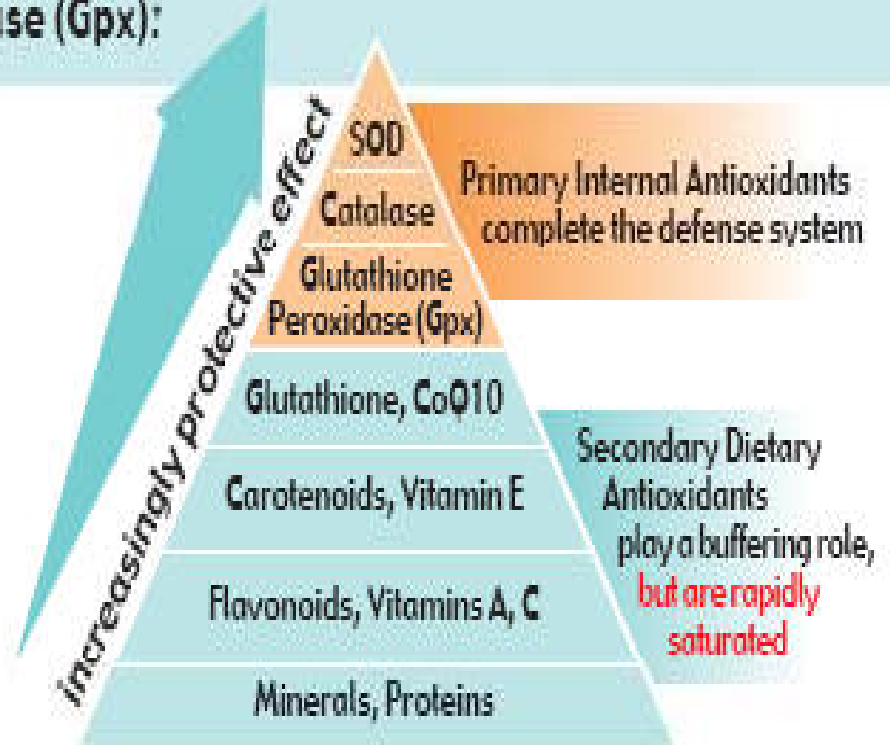
# Tirilazad mesylate- LAZAROIDS

- 21-aminosterid (lazaroid) that was developed specifically to maximize the inhibition of lipid peroxidation by glucocorticoids such as methylprednisolone, but eliminate the unwanted glucocorticoids effects. .( *Andrews RJ, Giffard RG. Clinically useful nonanesthetic agents.*)
- potent antioxidants, 100 times more potent than the corticosteroids
- In animal experiments, TM has been of benefit in both focal and global ischaemia.
- ***Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage. Part I. A cooperative study in Europe, Australia, New Zealand, and South Africa*****Auteur(s) / Author(s)***Lasingo/Kassel et al*  
**Departments of Neurological Surgery and Virginia Neurological Institute, University of Virginia, Charlottesville, Virginia, ETATS-UNIS,Westmead Hospital and University of Sydney, Sydney, AUSTRALIE,Ospedale Civile di Verona, Verona, ITALIE,University Hospital, Lund, SUEDE,Klinikum Mannheim, University of Heidelberg, Heidelberg, ALLEMAGNE****conclude that high-dose tirilazad mesylate is well tolerated in women with aneurysmal SAH. Although a significant reduction in the incidence of symptomatic vasospasm was observed in the treatment group, THE PRIMARY END POINT (MORTALITY RATE AT 3 MONTHS POST-SAH) WAS NOT AFFECTED BY THE STUDY DRUG**

# FREE RADICAL SCAVENGERS

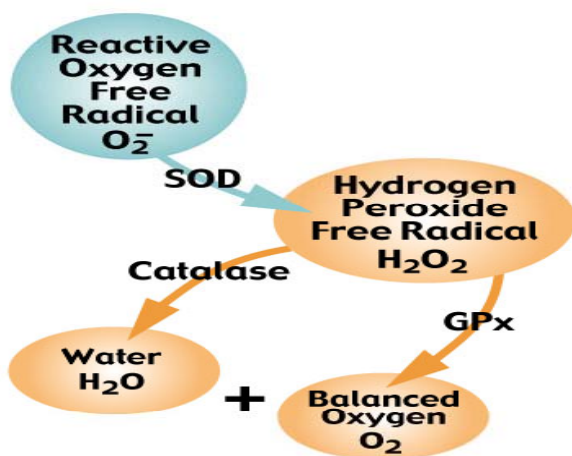
Damage produced by free radicals may be prevented or decreased with the use of free radical scavengers -barbiturates, vitamins C and E, edaravone, mannitol, with enzymes that promote metabolism of free radicals (catalase, superoxide dismutase).

GliSODin activates the most powerful antioxidants known, the body's own internal antioxidant defense system, including Superoxide Dismutase (SOD), Catalase and Glutathione Peroxidase (Gpx):

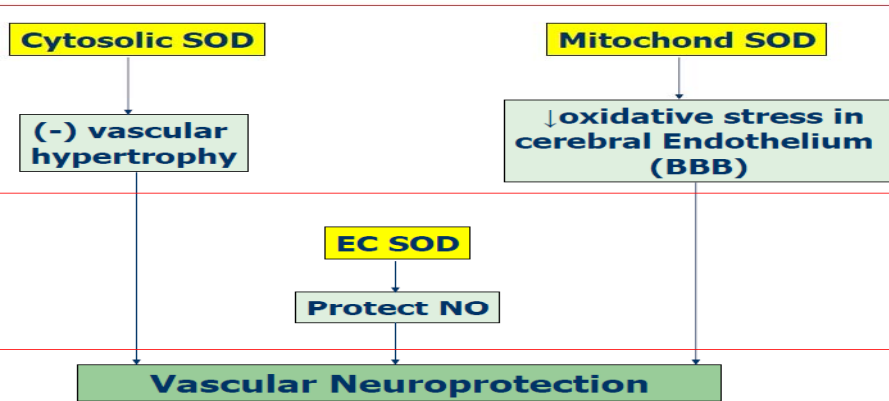




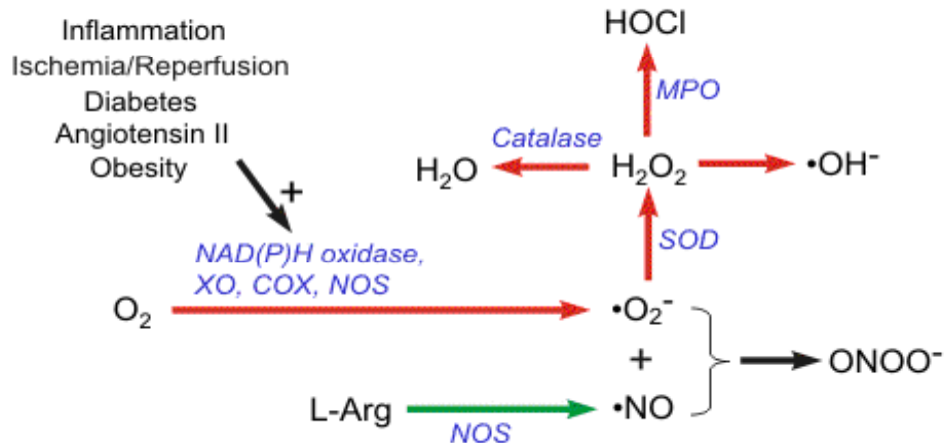
# Superoxide dismutase



## Vascular Protective Effects of SODs



- REPERFUSION INJURY
- SOD- specific scavenger of superoxide anion
- Biological half-life of only 5 minutes, it has been conjugated with polyethylene glycol (PEG-SOD) for use in humans.
- *Patients with severe closed head injury treated with the free-radical scavenger PEG-SOD (polyethylene glycol-superoxide dismutase) showed an 18% relative improvement in favourable outcome compared to placebo, according to results of a Phase III trial presented by Paul Muizelaar of Wayne State University at the 44th annual meeting of the Congress of Neurological Surgeons in Chicago, USA*



# CALCIUM CHANNEL BLOCKERS

**TABLE III Mechanisms by which calcium entry blocking agents may exert a cerebral protectant effect<sup>1</sup>.**

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Prevention of Ca<sup>++</sup> entry into cells

Prevention of Ca<sup>++</sup> sequestration by mitochondria

Alteration in fatty acid metabolism

Vasodilation

Free radical scavenging

Prevention of platelet aggregation

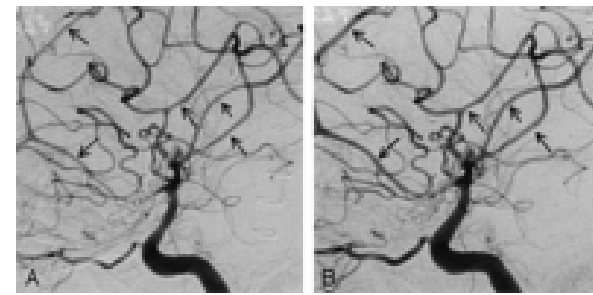
Prevention of increases in blood viscosity

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## **LIDOFLAZINE AND FLUNARIZINE**

- The results of studies :inconclusive

# Nimodipine



- Blocks the L-type of voltage-sensitive Ca channels.
- Nimodipine has an effect on CBF particularly after complete ischaemia where it ameliorates post-ischaemic hypoperfusion thus increasing CBF once reperfusion has been established.
- Even in the non-traumatized brain, nimodipine increases the CBF without increasing the cerebral metabolic rate *Harper AM, et al. J Cereb Blood Flow Metab 1981; 1: 349-56.*
- *Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial.: J. D. Pickard, G. D. Murray, R. Illingworth, M. D. Shaw, G. M. Teasdale, P. M. Foy, P. R. Humphrey, D. A. Lang, R. Nelson, P. Richards et al. Wessex Neurological Centre, Southampton General Hospital.*

### *Nimodipine in Sub-arachnoid haemorrhage*

- The protective effect was attributed to the inhibition of cerebral arterial spasm by nimodipine.
- Allen *et al.* demonstrated a beneficial effect due to nimodipine as the occurrence of neurologic deficits and death were significantly reduced in treated patients.

*Allen GS, et al. N Engl J Med ; 308: 619-24.*

### *Nimodipine in head injury*

- Nimodipine is efficacious in treating patients with severe head trauma but without producing adverse changes in ICP or systemic blood pressure.

*Kostron H, et al. Neurol Res 1984; 6: 29-32.*

### *Nimodipine in stroke*

- In a double-blind, placebo-controlled prospective study, nimodipine significantly reduced mortality from all causes during acute ischaemic stroke in man.
- During a six-month follow-up, patients in the nimodipine group continued to show significant improvement when compared with the placebo group.

*Gelmers H J, et al. N Engl J Med 1988; 318: 203-7.*

# Lidocaine

Possible mechanisms for cerebral protection by lidocaine include

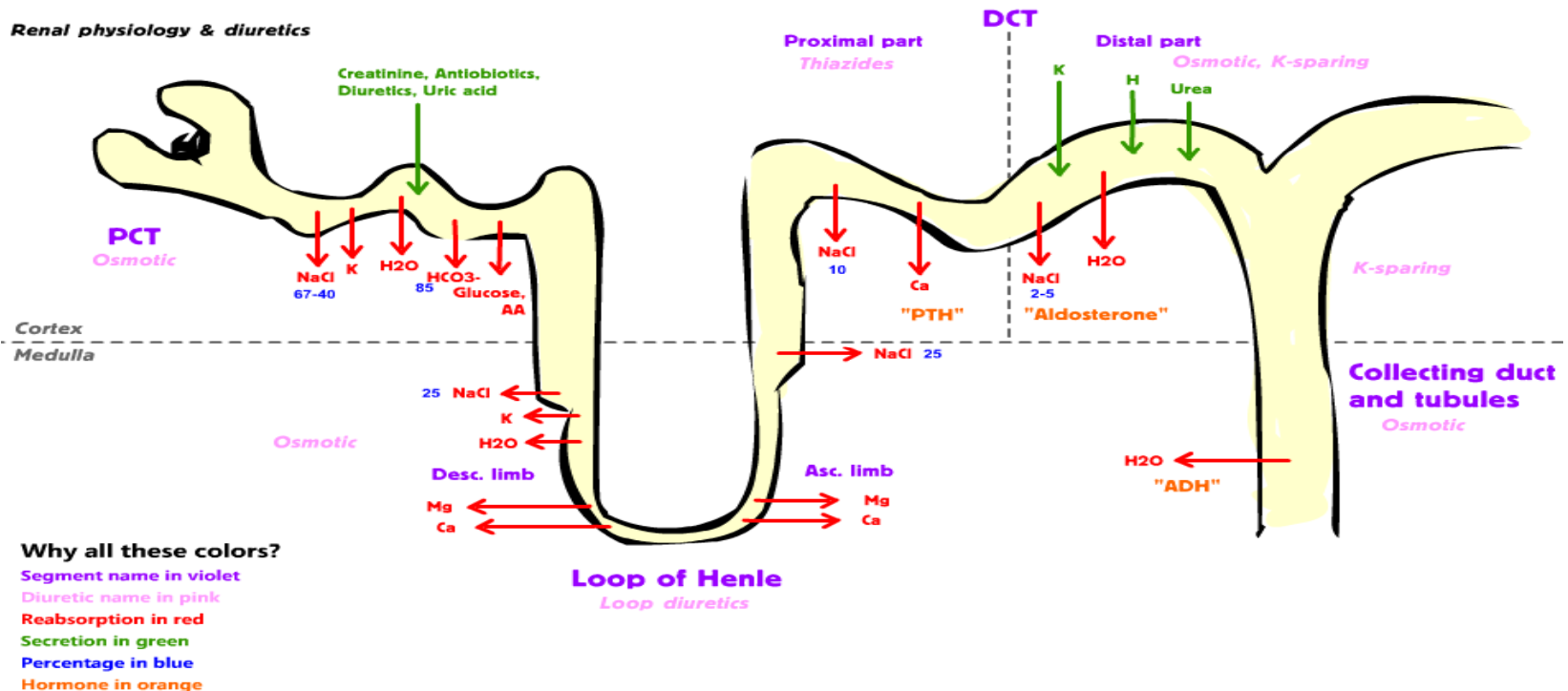
- 1. deceleration of ischaemic transmembrane ion shifts**
- 2. reduction in CMR**
- 3. modulation of leukocyte activity**
- 4. reduction of ischaemic excitotoxin release**
- 5. reduces intracranial hypertension**

**This effects of lidocaine (i.e., metabolic inhibition beyond that achievable with an isoelectric EEG alone and a delay in the ischaemic potassium efflux) resemble those of hypothermia.**

**It was demonstrated by Astrup *et al.* in a canine global ischaemia model that in the functionally arrested brain (i.e., an isoelectric EEG induced by barbiturates), lidocaine can further reduce the metabolic rate by 15-20 per cent.**

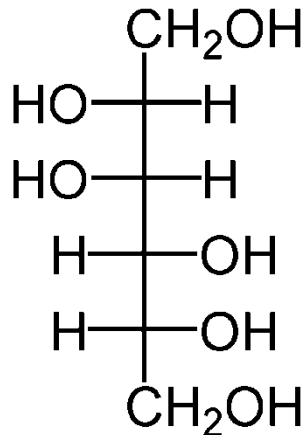
# Furosemide

- Sulfonamide that inhibits distal tubular reabsorption.
- Decrease ICP effectively without the transient ICP increase that can be seen with mannitol.
- Reduction of cerebrospinal fluid formation.
- Dose: upto 1 mg/kg



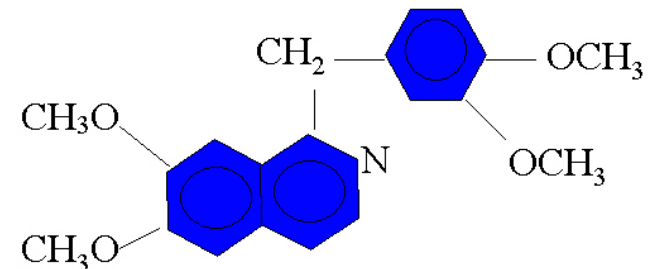
# Mannitol

- Mannitol can also scavenge free radicals & thus reduce tissue damage caused by superoxide radicals
- Osmotic diuresis, increased blood viscosity & free radical scavenging.
- Bolus intravenous infusion, over 10 to 30 minutes, in doses ranging from 0.25 to 1g kg<sup>-1</sup> body weight.
- It is more effective and safer when administered in bolus infusion doses than as a continuous infusion.
- Reduce cerebral edema after ischaemia.



# Papaverine

- Smooth muscle relaxant -blocking calcium channels.
- Topical application on arteries to reverse vasoconstriction resulting from manipulation (mechanical ‘vasospasm’).
- Intra-arterial injection.
- Concentration used is 30mg in 9cc saline
- Applied on to vessels with gelfoam or cotton pledget soaked in this mixture & left in contact with vessels for 2 minutes.
- Local application of controlled-release papaverine drug pellets have been safely used in preventing vasospasm.
- During cerebral aneurysm surgery, drug pellets were placed in cisterns over arterial segments.





# MAGNESIUM SULFATE

1. **Maintains of cellular ATP levels through Ca ++ channels blockade**
  2. **NMDA receptor antagonist**
  3. **Inhibition of neuronal transmission**
  4. **Free radical scavenger**
  5. **Membrane stabilizer**
- **Magnesium sulfate for neuroprotection after traumatic brain injury: randomised controlled trial** -*Nancy Temkin PhD et al: The Lancet Neurology, Volume 6, Issue 1, Pages 29 - 38, January 2007* :Continuous infusions of magnesium for 5 days given to patients within 8 h of moderate or severe traumatic brain injury were not neuroprotective and might even have a negative effect in the treatment of significant head injury.
  - **Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage: A Randomized Controlled Trial** *Walter M. van den Bergh on behalf of the MASH Study Group*  
*Correspondence to W.M. van den Bergh, MD, Department of Neurology, Room G03.124 University Medical Center Utrecht, This study suggests that magnesium reduces DCI and subsequent poor outcome, but the results are not yet definitive.*

- **Prophylactic intravenous magnesium sulfate for treatment of aneurysmal subarachnoid hemorrhage: A randomized, placebo-controlled, clinical study**(*Crit Care Med* 2010; 38:1284 –1290) The high-dose intravenous magnesium can reduce cerebral ischemic events after aneurysmal subarachnoid hemorrhage by attenuating vasospasm and increasing the ischemic tolerance during critical hypoperfusion.
- **Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial**
  - **Continuous infusions of magnesium for 5 days given to patients within 8 h of moderate or severe traumatic brain injury were not neuroprotective and might even have a negative effect in the treatment of significant head injury.**

**Lancet , Volume 6, Issue 1, January 2007**

- **Mg in stroke**
  - early administration of intravenous magnesium does not reduce mortality or disability in the 90 days following onset of acute stroke.**

**IMAGES Trial, *Lancet*. 2004;363:439–45.**

# Phenytoin

- **Two separate studies, by Aldrete *et al.* and Cullen *et al.*, demonstrated that treatment with phenytoin improved neurological recovery and reversed histopathological changes in animals subjected to complete global ischaemia.**

*Aldrete JA, et al. Crit Care Med 1979; 7: 466-7 I.*  
*Cullen JP, et al. Anesth 1979; 58: 165-9 Anesth.*

*Artru et al.* proposed that phenytoin exerts its protective effects through slowing the release of  $K^+$  from ischaemic neurons, and by stabilization of cellular membranes.

- **Phenytoin limit cerebral extracellular  $K^+$  accumulation, improving the distribution of CBF, energy/substrate delivery, and prevent the accumulation of metabolites and toxic substances**

## **GROWTH FACTORS**

- **Endogenous nerve growth factor (NGF) and BDNF are upregulated in neurons after cerebral ischemia and have antiapoptotic effect**
- **The expression of BDNF is even enhanced by therapeutic hypothermia**
- **RESULT:INCONCLUSIVE**

## **PROSTAGLANDIN INHIBITORS**

- **Indomethacin is a cyclo-oxygenase inhibitor that has been shown to inhibit the increase in prostaglandins that accompanies post-ischaemic reperfusion and to improve post-ischaemic CBF in experimental models of ischaemia.**

## **IRON CHELATORS**

**Fe<sup>2+</sup> as a catalyst in oxygen-free radical mechanisms that lead to lipid peroxidation which in turn leads to cell damage,**

- **By eliminating iron as a catalyst, lipid peroxidation and cell damage may be prevented.**
- **The iron chelator deferoxamine has been shown to inhibit post-ischaemic lipid peroxidation and thus may help to prevent reperfusion injury due to membrane injury by lipid peroxidation.**

## **ERYTHROPOEITIN**

- **Stimulates neurogenesis,angiogenesis**
- **Inhibits excitotoxicity,neuronal apoptosis**
- **Reduces inflammation**

**Grasso G.et al, JNA 2006;18:91**

# xenon

- NMDA antagonist
- Upregulation of genes and synthesis of the CREB-dependent survival proteins Bcl-2, BDNF, Ras protein).

D Ma et al, *Journal of Cerebral Blood Flow & Metabolism* (2006) 26, 199–208

# Gene therapy for neuroprotection

- **Direct application of neurotropic factors (VEGF,GDNF,ILGF-1 )through adenoviral construct(Ad-p65).**
- **ZFP transcription factor gene therapy to increase expression of the full complement of VEGF-A splice variants is a promising avenue for the treatment of nerve injury and neuro degeneration.**

**Gene Therapy (2009) 16, 1292–1299**

- **Topical application of GDNF protein greatly reduced the infarct size and brain edema at 24 hr of continuous MCAO in rats. GDNF protein showed a direct protective effect against ischemic brain damage, but not secondary by improving CBF.**

**Clinical Neurology.43;11;894-896(2003)**

**THANK YOU**