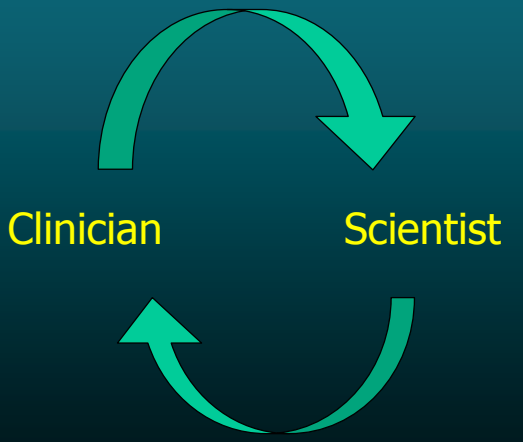
Universitätsspital Basel
Neurologische Klinik
Stroke Unit

Stroke
Focal ischemic brain lesion
Molecular Aspects of Neurological Diseases

Philippe Lyrer
21.04.2009

Aim

- Close the gap !



Overview

- What is a stroke
- Animal models
- The ischemic cascade
- Translation to clinical trials
- Diffuse subcortical ischemic lesions
- Failure of clinical trials
- Outlook

Stroke - Definition

There are two main types of stroke

- **Ischemic stroke** 84%
  - is caused by blockage in an artery that supplies blood to the brain, resulting in a deficiency in blood flow (ischemia)
- **Hemorrhagic stroke** 16%
  - is caused by the bleeding of ruptured blood vessels (hemorrhage) in the brain 10% intracerebral, 6% subarachnoidal.

Stroke – "biologic" Definition

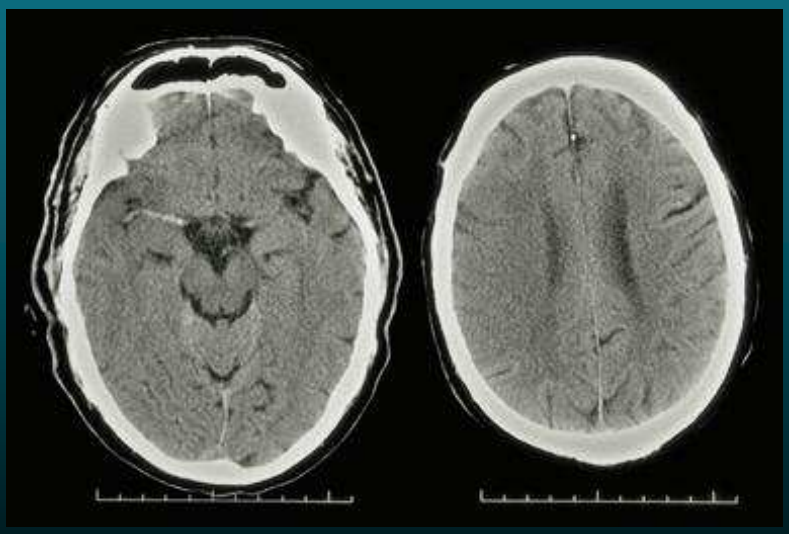
During ischemic stroke, diminished blood flow initiates a series of events (called **ischemic cascade**) that may result in additional, delayed damage to brain cells

Early medical intervention can halt this process and reduce the risk for irreversible complications.

Background Information

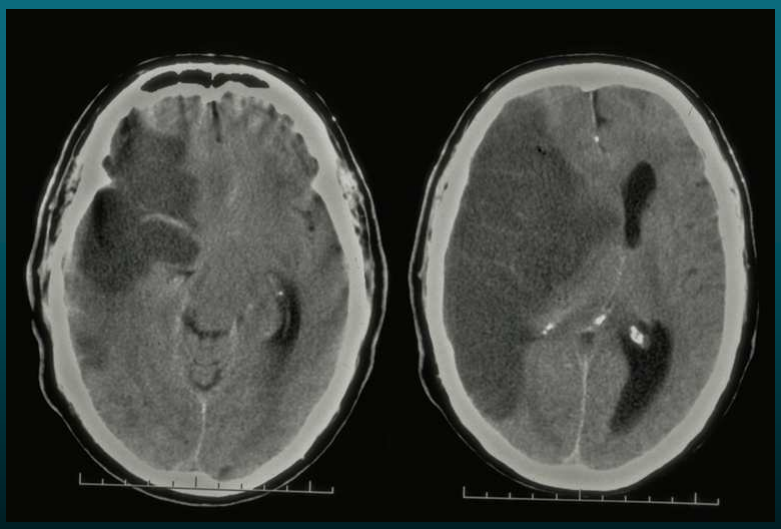
- 3rd most common cause of death
  - after heart attack and cancer
- Higher mortality with increasing age:
  - ≥ 60 years 2nd most common cause of death
- Men and women equally frequent
- Incidence: 150 - 200 / 100 000/year
  - Basel: 170 / 100'000/year (02-03)
  - 45-84 years old: 400 / 100 000/year

Ischemic brain lesion: cranial computer tomography early imaging (2 hours)



Dept. of Neuroradiology, University Hospital Basel, Switzerland

Ischemic brain lesion: delayed cranial computer tomography (48 hours)



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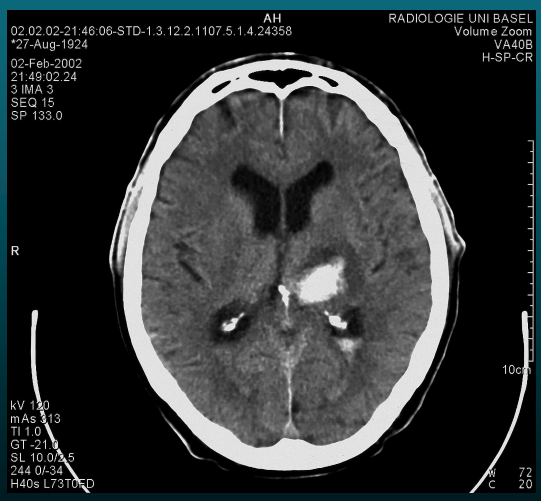
Hemorrhagic brain lesion: Cranial Computer tomography

Exclude intracranial Hemorrhage !



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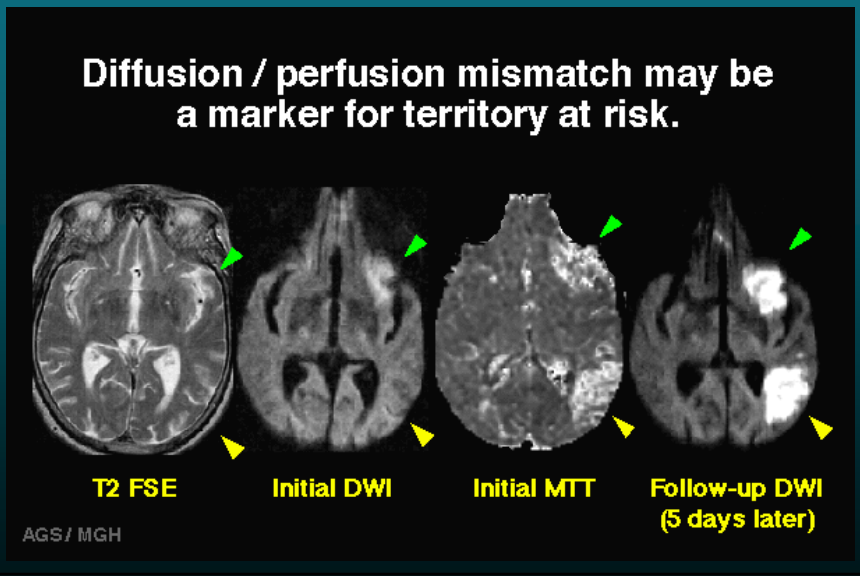
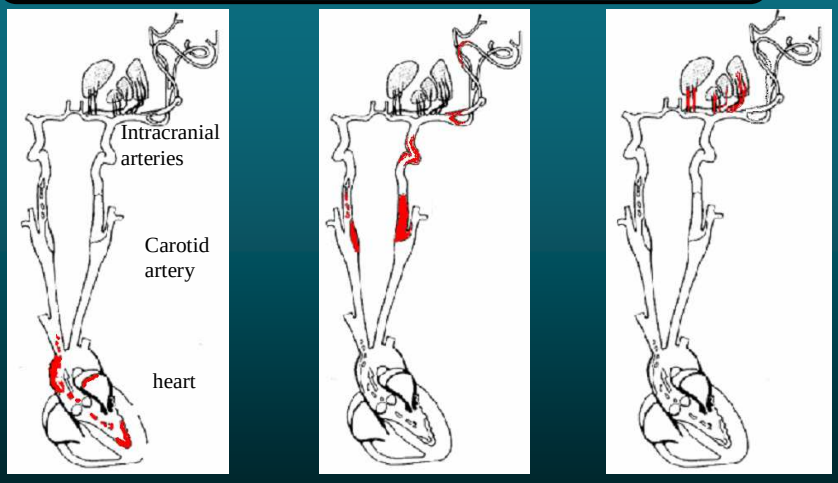
Penumbra: DWI-PWI Mismatch



Mechanism of cerebral ischemia

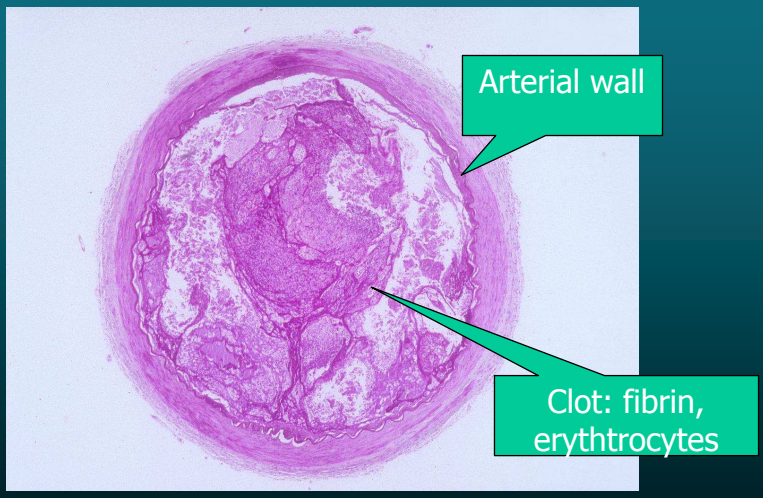


cardiac Emboly
25-35%

cerebral macroangiopathy
15-20 %

cerebral microangiopathy
30%

Embolic artrial occlusion



- Embolic clot occlusion of the middle cerebral artery
  (courtesy of A.Probst, Neuropathology Basel)

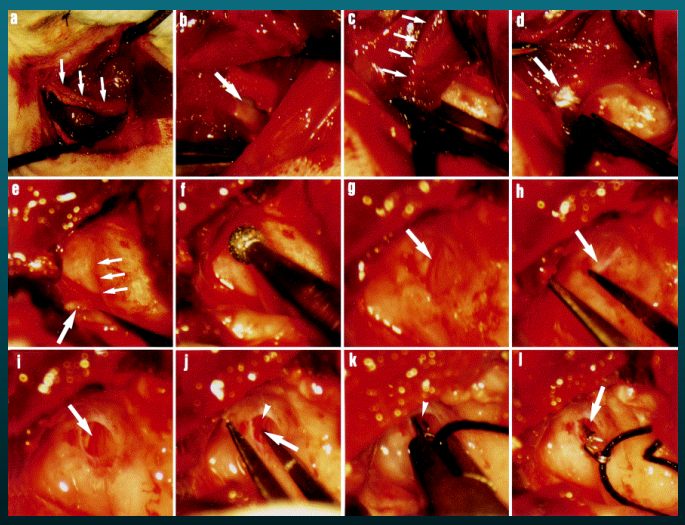
Animal models

- Rat: 4-Vessel occlusion (global)
  MCAO (focal)
- Mouse: MCAO (focal)
- Gerbil CCAO (focal, global)
- Rabbit: clot model (t-PA model)
- Cat: cardiac arrest models
- Dog: cardiac arrest cardiac arrest
- Non-human primates: behavioral models

- Note: Transient vs. Permanent vessel occlusion

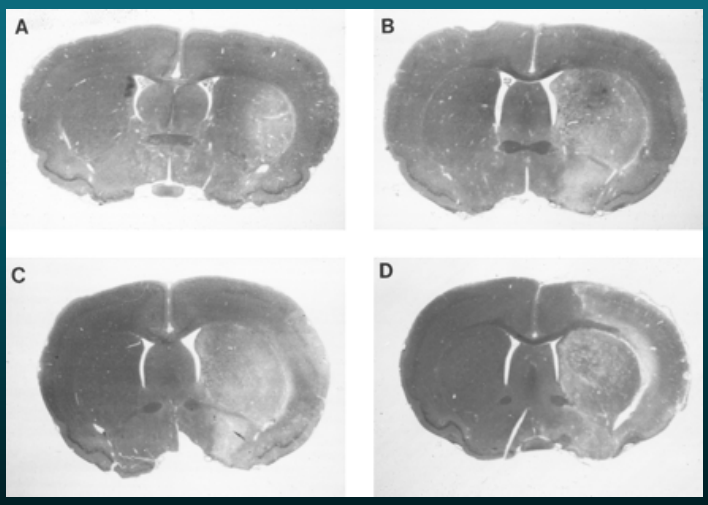
Lit.: Hoyte L. et al.: Exp. Neurology 2004

MCAO: Three-vessel occlusion using a micro-clip for the proximal left middle cerebral artery



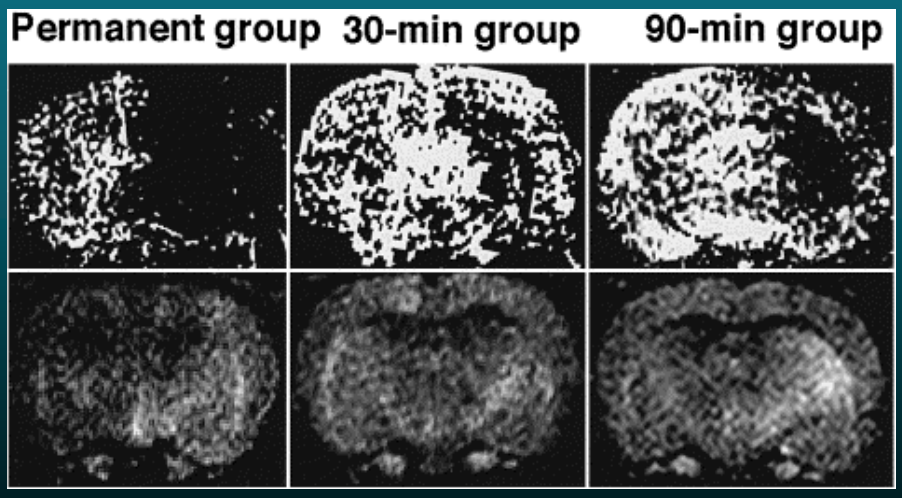
Lit.: Hiroji Yanamoto, Izumi Nagata, Nobuo Hashimoto and Haruhiko Kikuchi

MCA occlusion – permanent (autoradiography)



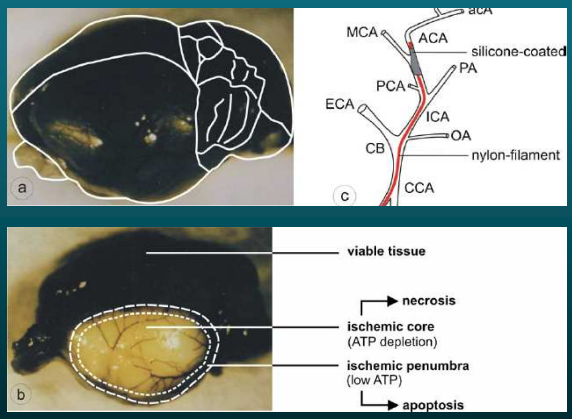
Lit.: Belayev L, et al. Stroke. 1996

MCA occlusion - permanent and temporary



Yasuki Ono[a], Shigehiro Morikawa[b], Toshiro Inubushi[b], Hiroaki Shimizu[a], * and Takashi Yoshimoto[a]

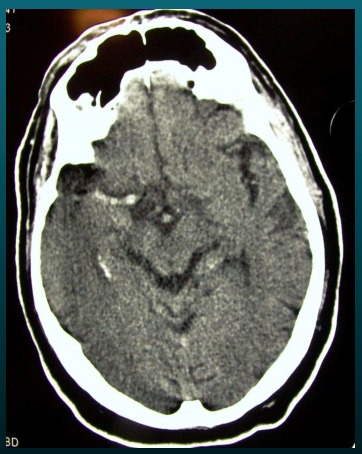
Mouse model of transient cerebral ischemia – temporary MCAO with coated nylon filament



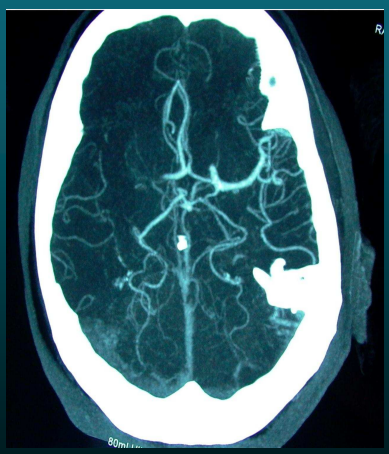
Lit.: Rami A et al., Progress in Neurobiology 85 (2008) 273–296

CT Schädel

Nativ

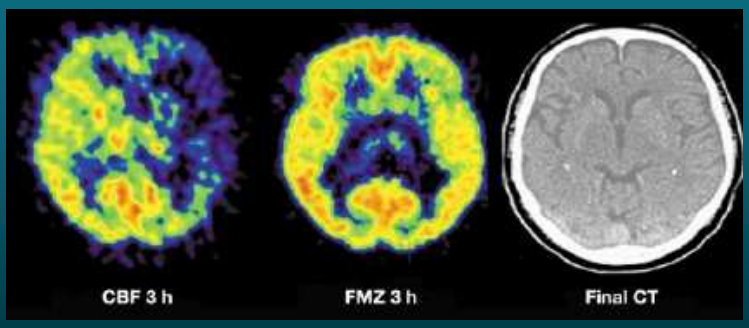


Spiral-CT mit KM



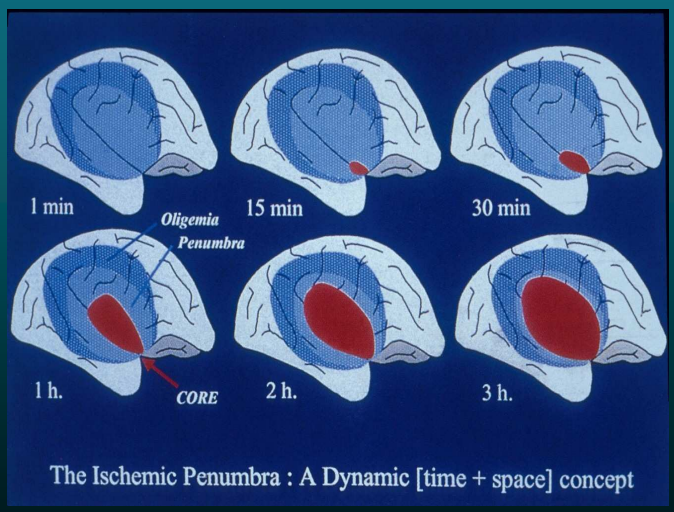
(Aufnahme: Neuroradiologie Universitätskliniken Basel, Prof. F.W. Radü)

PET from patient with acute MCA-occsion



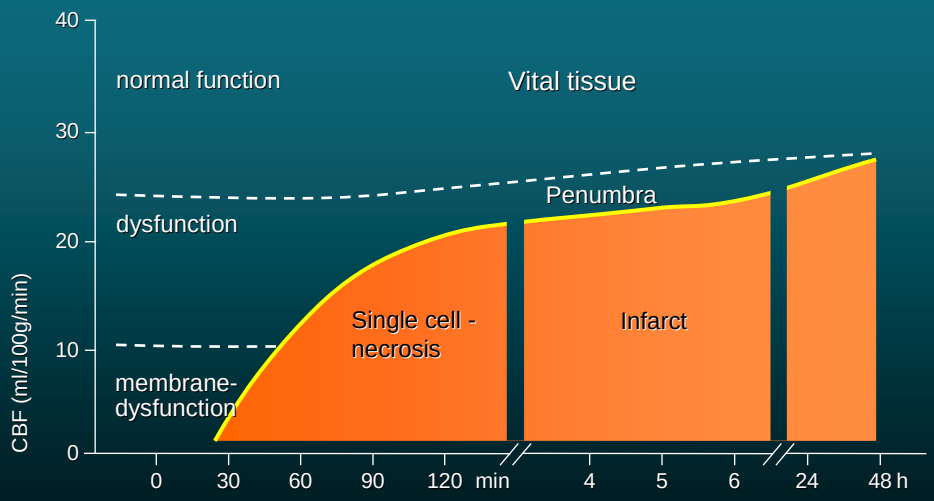
- Regional hypoperfusion at 3 hours after beginning of symptoms
- By reperfusion, no lesion on CT few days later

The penumbra concept



Baron JC Cerebrovascular Diseases 1999;9:193-201.

„Time is Brain“



JCBFM 2000;20:1276-93.

Perfusion Basics

- CBF - Cerebral Blood Flow (ml/100ml/min)
  - Gray matter 45-70 ml/100ml/min
  - White Matter 20-24 ml/100ml/min
- CBV - Cerebral Blood Volume (ml/100ml)
  - Gray matter 4-7 %
  - white matter 2-3%
- MTT - Mean Transit Time (seconds)
  - Mean time to traverse vasculature (NOT pixel!)
  - CBV:CBF ratio

What happens in stroke ?

Blood supply drops suddenly threshold values:

Cerebral blodd flow values:

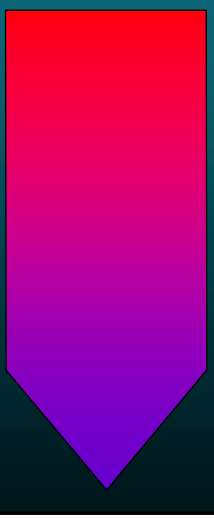
→ 80-60 ml/min/100g:
normal state

→ 37-60 ml/min/100g:
protein syn., selective gene exp.

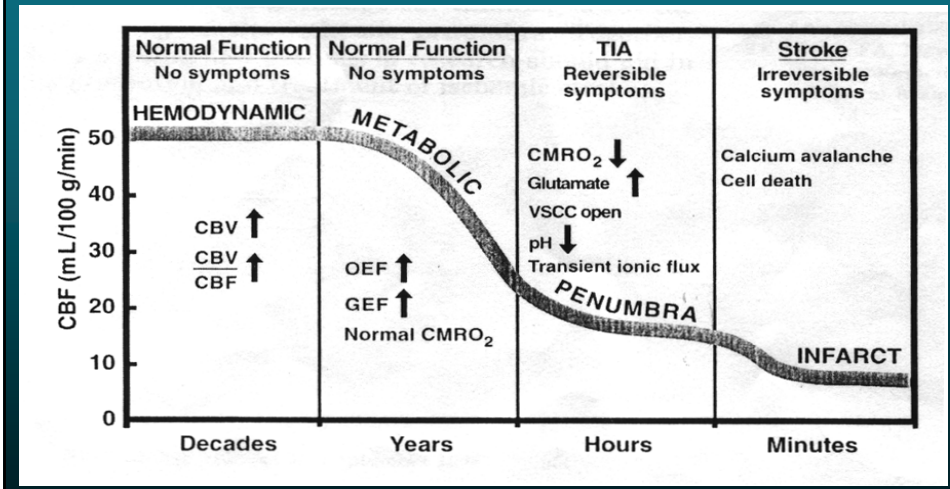
→ 20 –36 ml/min/100g:
lactic acidosis, cytotoxic edema

→ 10-20 ml/min/100g:
energy deficit, glutamate tox.

→ 0-10 ml/min/100g:
anoxic depolarisation, infarction

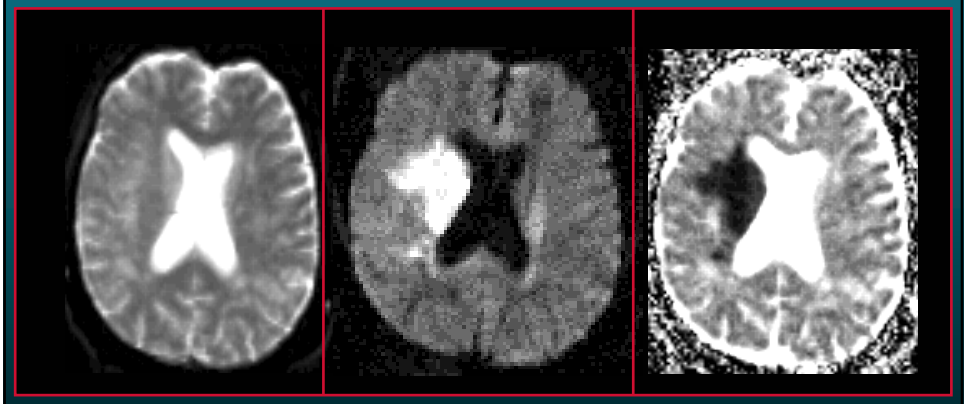


Cerebral blood flow



(from Hakim; Neurology:51(supp3):S44-6)

Magnetic resonance imaging



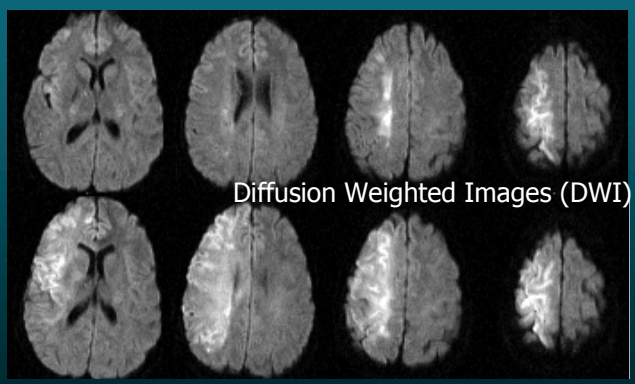
T2 DWI ADC

52 y/o WF with migraines, awoke with right H/A, L hemiparesis

Diagnostic Information in Acute Stroke: Diffusion Weighted Imaging

At 5 hours...

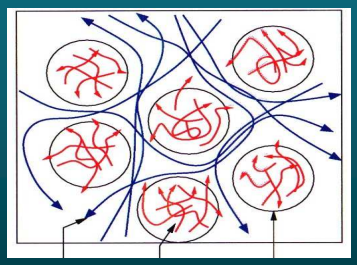
After 5 days...



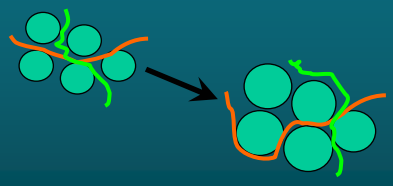
Diffusion Weighted Images (DWI)

- Diagnostic Info: Assess initial infarct by DWI
- Prognostic Info: Predict infarct growth by PWI

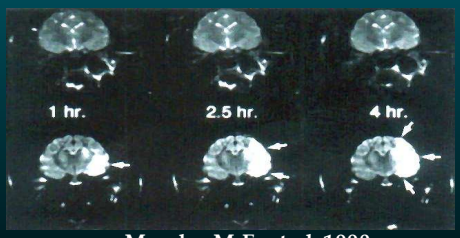
Cytotoxic Edema: Diffusion Weighted Imaging



Hindrance Restriction Barriers



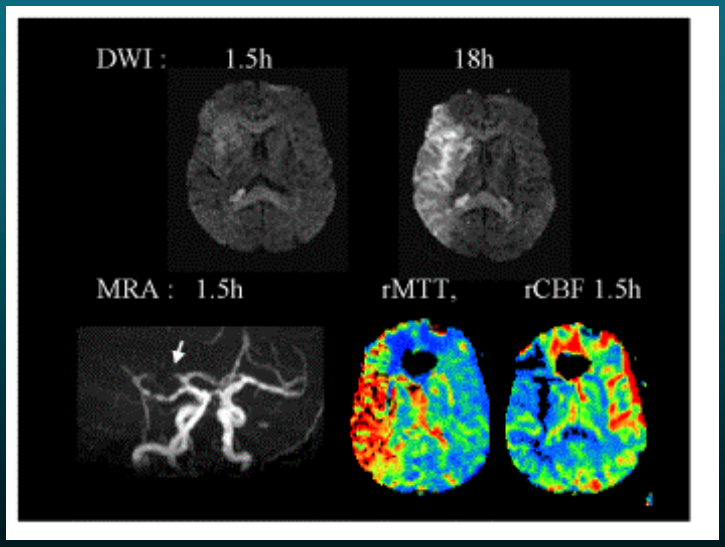
Cat brain - MCA occlusion



Moseley M.E, et al. 1990

ATP-depletion
Na^+-K^+ pump
Cytotoxic edema
Increased extracellular tortuosity
Hindrance of water movement
Diffusion weighted images appear bright

Penumbra: DWI-PWI Mismatch



Patient with acute occlusion of A. cerebri media

What happens in stroke ?

Consequences are disturbence :

- neurons, glial cell, astrocytes – simultaneously
- vessel lesion
- interstitial space
- secondary damages: edema, space occupation, recanalisation injury, bleeding

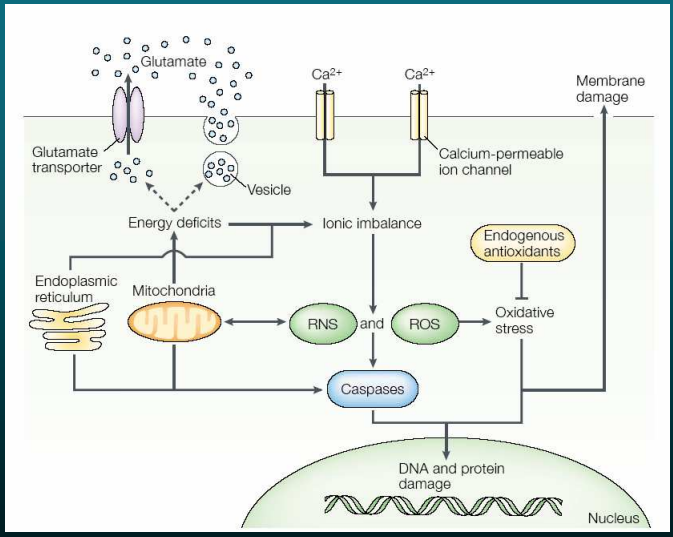
Major pathways implicated in ischaemic cell death

- **excitotoxicity**
- **ionic imbalance**
- **oxidative and nitrosative stresses**
- **apoptotic-like mechanisms**
- **Disturbance of the neurovascular unit:**
  - **Proteolysis**
  - **inflammation**

Lo H., et al. nature rev. 2003

Major pathways implicated in ischemic cell death

RNS reactive nitrogen species



ROS reactive oxygen species

Lo, E.H., T. Dalkara, and M.A. Moskowitz, Nat Rev Neurosci, 2003. **4**(5): p. 399-415.

Major pathways implicated in ischemic cell death

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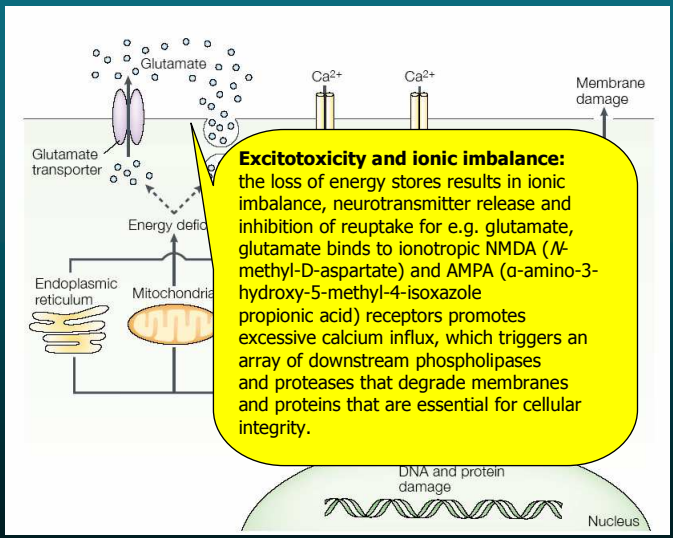
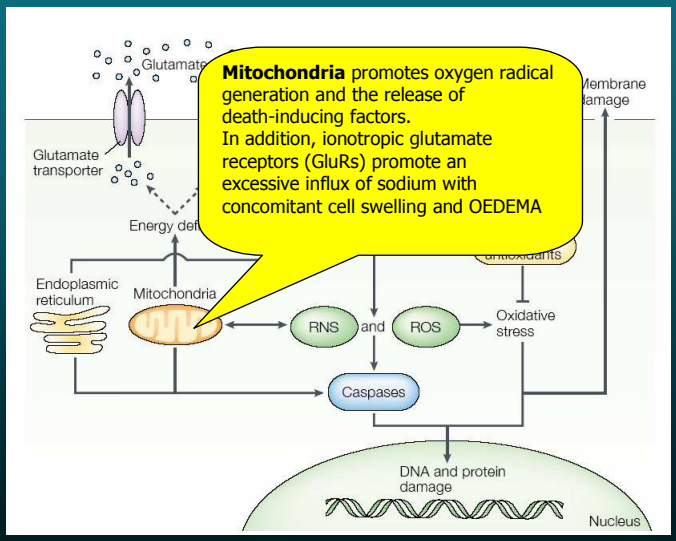


Excitotoxicity and ionic imbalance: the loss of energy stores results in ionic imbalance, neurotransmitter release and inhibition of reuptake for e.g. glutamate, glutamate binds to ionotropic NMDA (*N*-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors promotes excessive calcium influx, which triggers an array of downstream phospholipases and proteases that degrade membranes and proteins that are essential for cellular integrity.

ROS reactive oxygen species

Lo, E.H., T. Dalkara, and M.A. Moskowitz, Nat Rev Neurosci, 2003. **4**(5): p. 399-415.

Major pathways implicated in ischemic cell death



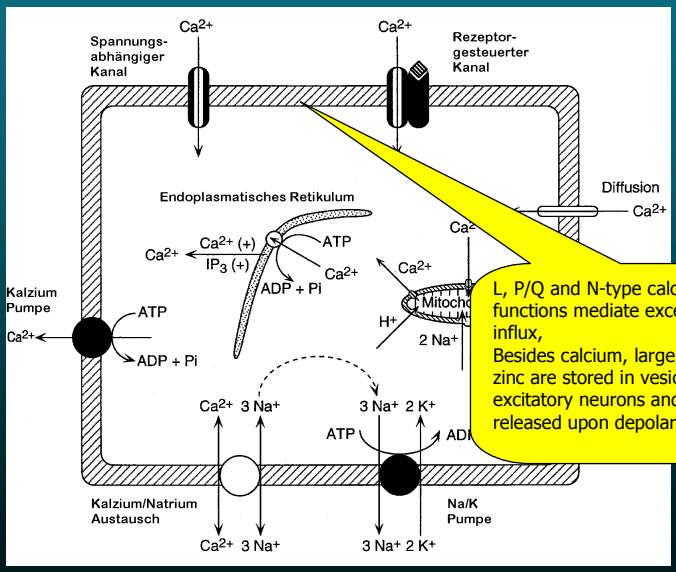
Mitochondria promotes oxygen radical generation and the release of death-inducing factors.
In addition, ionotropic glutamate receptors (GluRs) promote an excessive influx of sodium with concomitant cell swelling and OEDEMA

RNS reactive nitrogen species

ROS reactive oxygen species

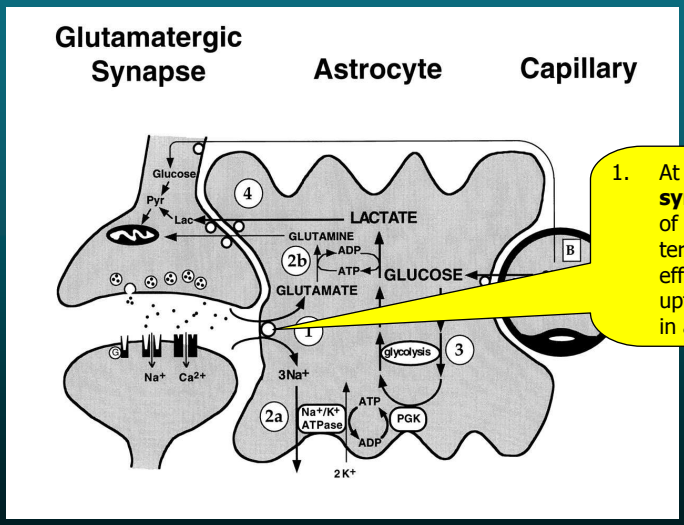
Lo, E.H., T. Dalkara, and M.A. Moskowitz, Nat Rev Neurosci, 2003. **4**(5): p. 399-415.

Ionic imbalance -Calcium metabolism



L, P/Q and N-type calcium channel functions mediate excessive calcium influx,
Besides calcium, large amounts of zinc are stored in vesicles of excitatory neurons and are co-released upon depolarization

Glutamate toxicity - glucose

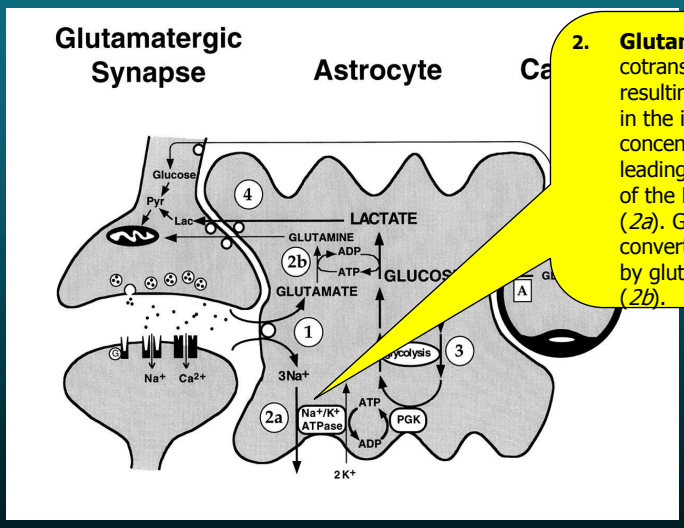


1. At **glutamatergic synapses**, the action of glutamate is terminated by an efficient glutamate uptake system located in astrocytes.

Magistretti P., Pellerin L.;News Physiol Sci. 1999 Oct;14:177-182.

Pyr, pyruvate; Lac, lactate; Gln, glutamine; G, G protein; PGK, phosphoglycerate kinase

Glutamate toxicity - glucose



2. **Glutamate** is cotransported with Na^+, resulting in an increase in the intracellular concentration of Na^+, leading to the activation of the Na^+-K-ATPase (*2a*). Glutamate is converted to glutamine by glutamine synthase (*2b*).

Magistretti P., Pellerin L.;News Physiol Sci. 1999 Oct;14:177-182.

Pyr, pyruvate; Lac, lactate; Gln, glutamine; G, G protein; PGK, phosphoglycerate kinase

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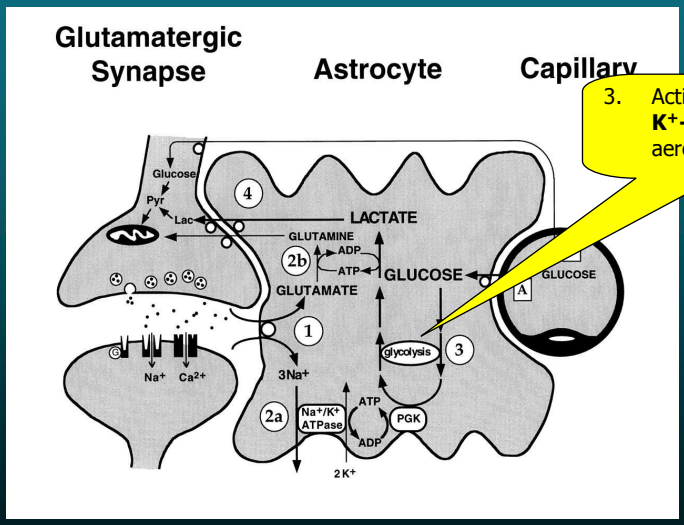
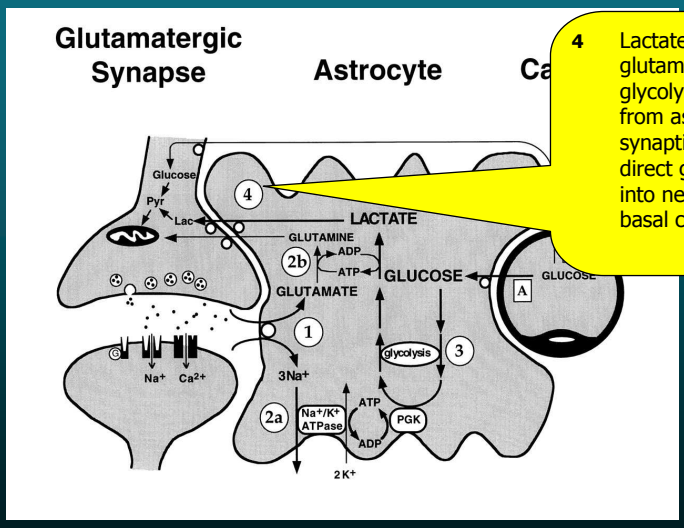


3. Activation of the **Na^+-K^+-ATPase** triggers aerobic glycolysis.

Magistretti P., Pellerin L.;News Physiol Sci. 1999 Oct;14:177-182.

Pyr, pyruvate; Lac, lactate; Gln, glutamine; G, G protein; PGK, phosphoglycerate kinase

Glutamate toxicity - glucose



4 Lactate produced by the glutamate-stimulated glycolysis is released from astrocytes. *A*, synaptic activation; *B*, direct glucose uptake into neurons under basal conditions.

Magistretti P., Pellerin L.;News Physiol Sci. 1999 Oct;14:177-182.

Pyr, pyruvate; Lac, lactate; Gln, glutamine; G, G protein; PGK, phosphoglycerate kinase

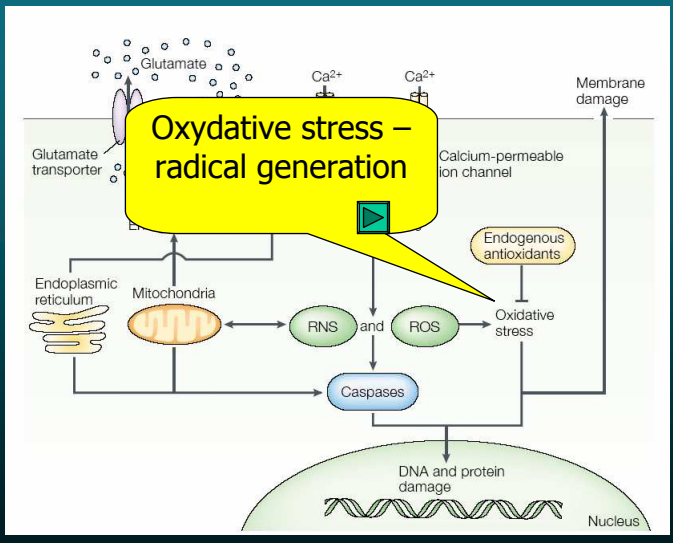
Summary of glutamate-calcium release

- K^+ efflux
- Excesive glutamate release and over excitation of glutamate receptors
- Ca^{2+} release from organelles
- Ca^{2+} influx and sequestration in the cell
- Intracellular accumulation of Ca^{2+} and Zn^{2+}

➢ ends in activation of calmodulin dependent intracellular enzymes (phospholipases, endonucleases and protein kianses)

Major pathways implicated in ischemic cell death

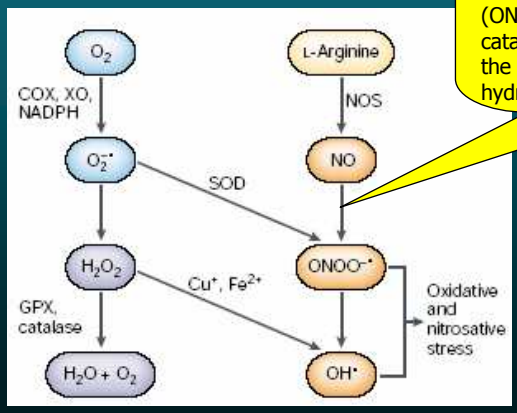
RNS reactive nitrogen species



ROS reactive oxygen species

Lo, E.H., T. Dalkara, and M.A. Moskowitz, Nat Rev Neurosci, 2003. **4**(5): p. 399-415.

Generation of oxygen and nitrogen radicals



Combination of superoxide (O2–•) and nitric oxide (NO) generates the potent radical peroxynitrite anion (ONOO–•). Metal (Cu+ and Fe2+) catalysed pathways can also produce the hydroxyl radical (OH•) from hydrogen peroxide (H2O2).

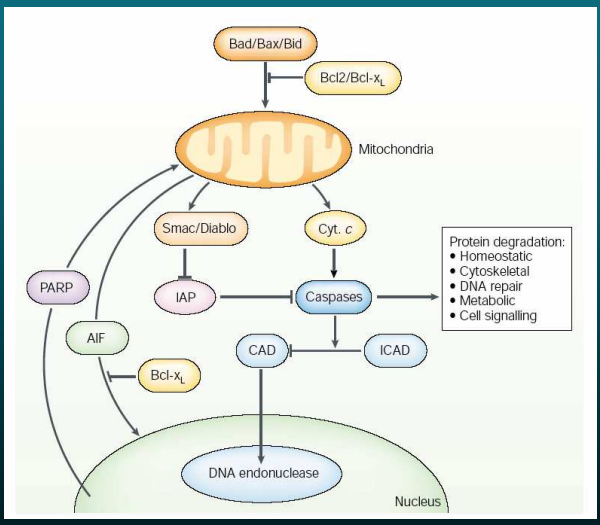
COX - cyclooxygenase
GPX - glutathione peroxidase
NOS - nitric oxide synthase
SOD - superoxide dismutase
XO - xanthine oxidase

apoptotic-like mechanisms Cell death pathways that are relevant to an apoptotic-like mechanism in cerebral ischaemia

IAP inhibitors of apoptosis

PARP poly-(ADP ribose) polymerase

AIF Apoptosis inducing factor



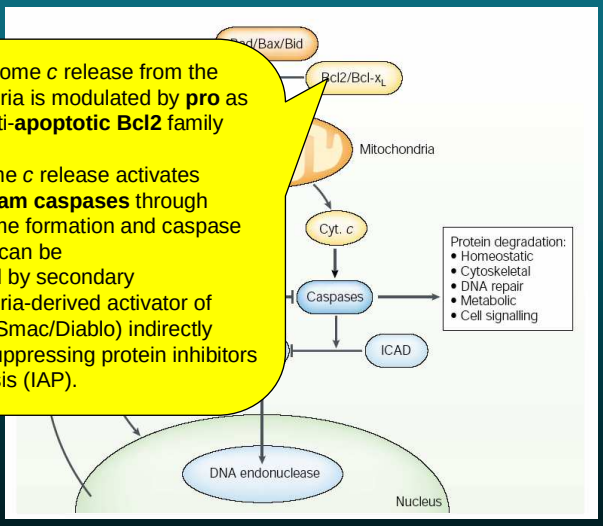
Smac Secondary mitochondria derived activator of caspase

CAD caspase-activated deoxyribo nuclease

Lo, E.H., T. Dalkara, and M.A. Moskowitz, Nat Rev Neurosci, 2003. **4**(5): p. 399-415.

apoptotic-like mechanisms Cell death pathways that are relevant to an apoptotic-like mechanism in cerebral ischaemia

1. Cytochrome *c* release from the mitochondria is modulated by **pro** as well as anti-**apoptotic Bcl2** family members.
Cytochrome *c* release activates **downstream caspases** through apoptosome formation and caspase activation can be modulated by secondary mitochondria-derived activator of caspase (Smac/Diablo) indirectly through suppressing protein inhibitors of apoptosis (IAP).



AIF
Apoptosis inducing factor

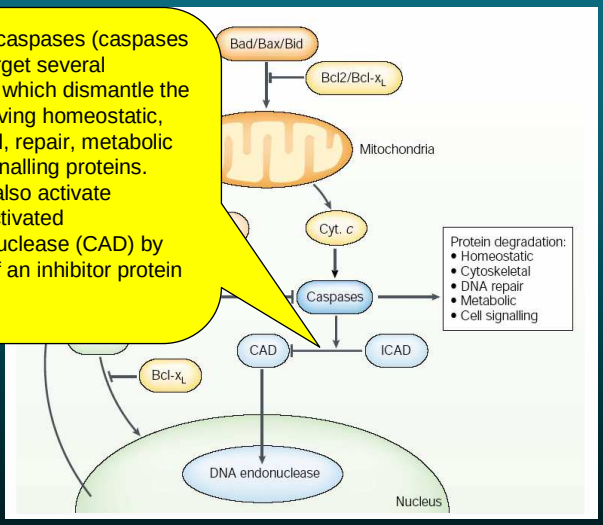
Smac
Secondary mitochondria derived activator of caspase

CAD
caspase-activated deoxyribo nuclease

Lo, E.H., T. Dalkara, and M.A. Moskowitz, Nat Rev Neurosci, 2003. **4**(5): p. 399-415.

apoptotic-like mechanisms Cell death pathways that are relevant to an apoptotic-like mechanism in cerebral ischaemia

2. Effector caspases (caspases 3 and 7) target several substrates, which dismantle the cell by cleaving homeostatic, cytoskeletal, repair, metabolic and cell signalling proteins. Caspases also activate caspase-activated deoxyribonuclease (CAD) by cleavage of an inhibitor protein (ICAD)..



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Smac
Secondary mitochondria derived activator of caspase

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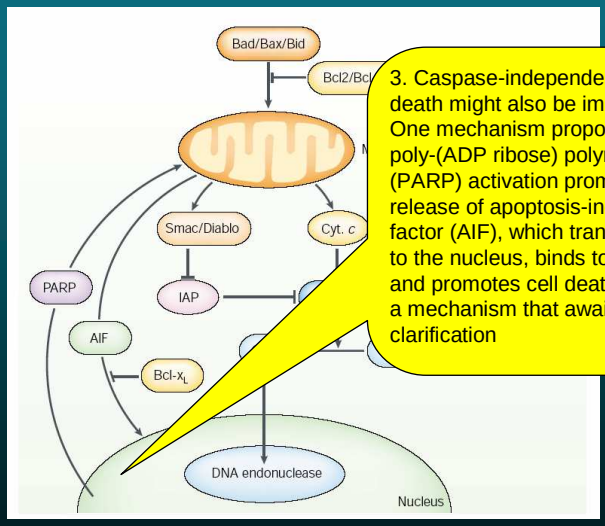
PARP poly-(ADP ribose) polymerase

AIF Apoptosis inducing factor



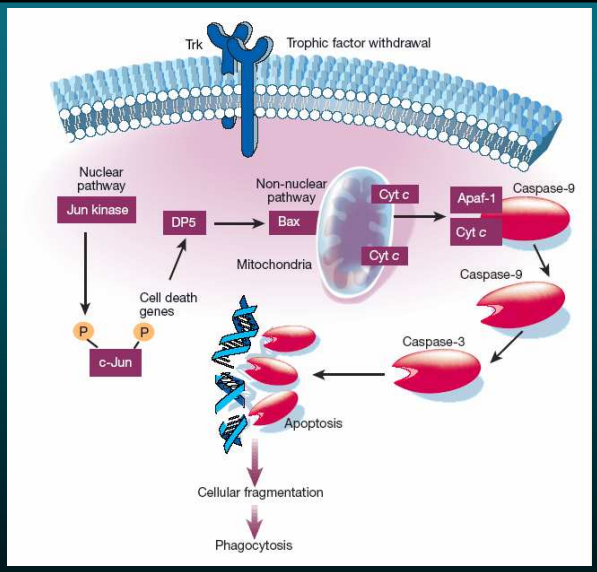
3. Caspase-independent cell death might also be important. One mechanism proposes that poly-(ADP ribose) polymerase (PARP) activation promotes the release of apoptosis-inducing factor (AIF), which translocates to the nucleus, binds to DNA and promotes cell death through a mechanism that awaits clarification

dria

activated deoxyribo nuclease

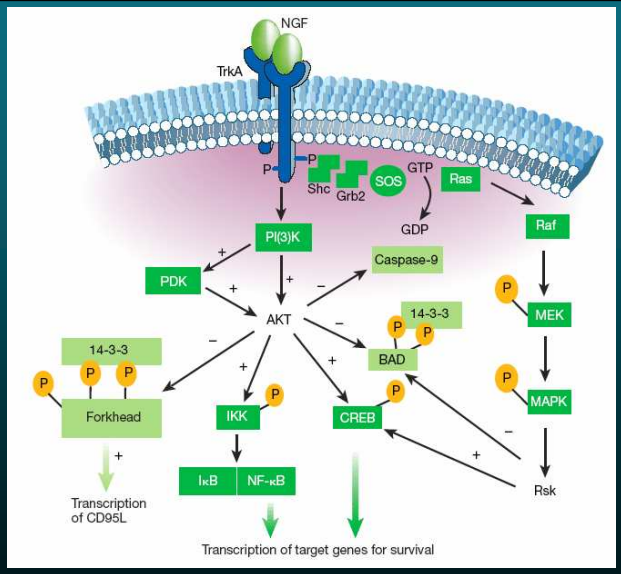
Lo, E.H., T. Dalkara, and M.A. Moskowitz, Nat Rev Neurosci, 2003. **4**(5): p. 399-415.

Apoptosis



Yuang & Yankner, Nature 2000

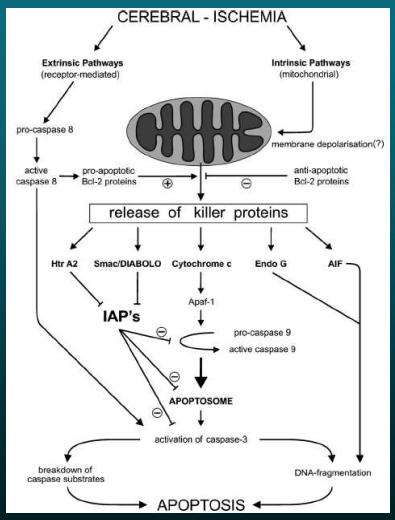
Apoptosis



Yuang & Yankner, Nature 2000

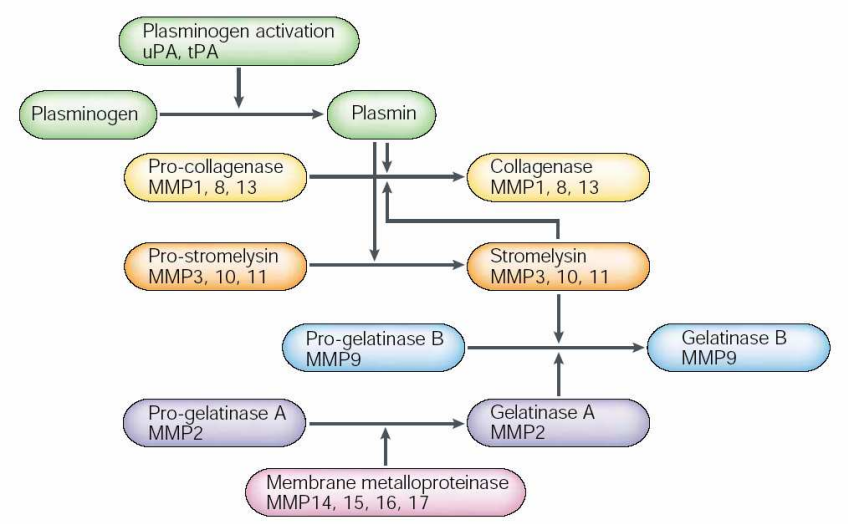
Central role of mitochondria in neuronal apoptosis

IAP: inhibitor of apoptosis proteins



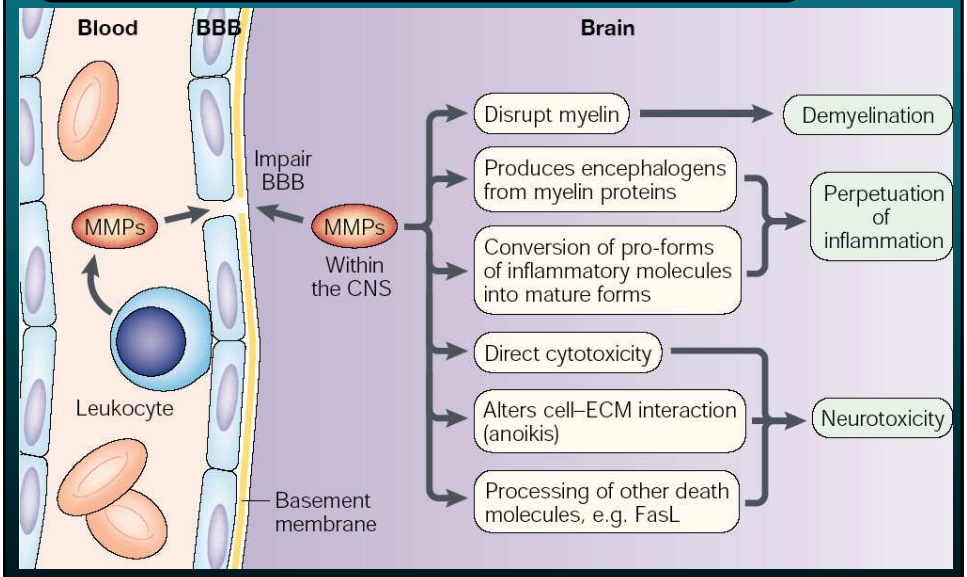
Lit.: Rami A et al., Progress in Neurobiology 85 (2008) 273–296

protease cascade involving members of the matrixmetalloproteinase



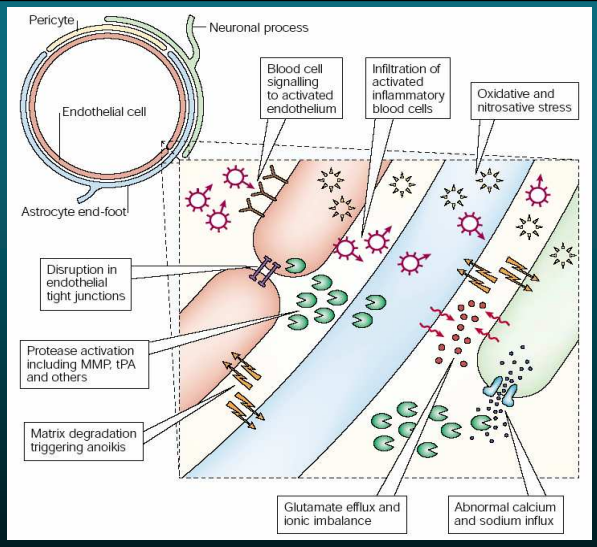
Lo, E.H., T. Dalkara, and M.A. Moskowitz, Nat Rev Neurosci, 2003. **4**(5): p. 399-415.

Metalloproteinases



Yong et al. Nature Reviews 2001

Schematic view of the neurovascular unit or module, and some of its components



Lo, E.H., T. Dalkara, and M.A. Moskowitz, Nat Rev Neurosci, 2003. **4**(5): p. 399-415.

Cause: Perfusion deficit, CBF <20ml/100g/min, complete, partial, time-dependent

Stop of metabolism, depletion of ATP, accumulation of lactate

Breakdown of the ATP-dependent Na-K-pump, loss of electric gradient, missing re-uptake and loss of glutamate, excitotoxicity

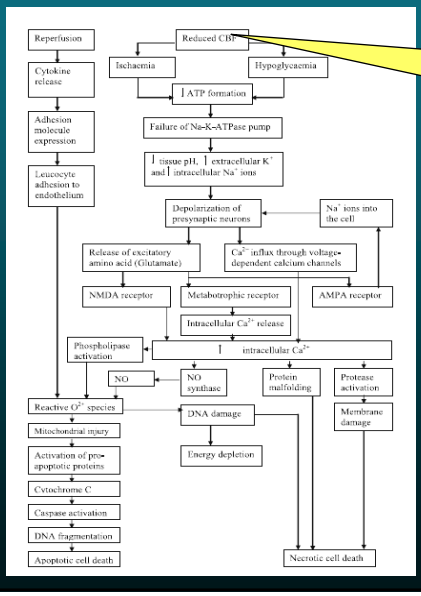
Increase of intracellular Ca^{2+}-due to inflow of Ca^{2+} from extracellular space and release of Ca^{2+} from endoplasmatic reticulum and mitochondria

Activation of proteases, early gene expression, phospholipidase A2 triggers production of arachidonic acid → cell mediators: leucotriens, adhesion molecules, platelet aggregation factor

Generation of free radicals, arachidonic acid -> prostaglandin, oxidation of lipids, release of iron

Cellular edema, irreversible cellular destruction, apoptosis via programmed metabolism due to proteases and endonucleases

Overview of the ischemic cascade



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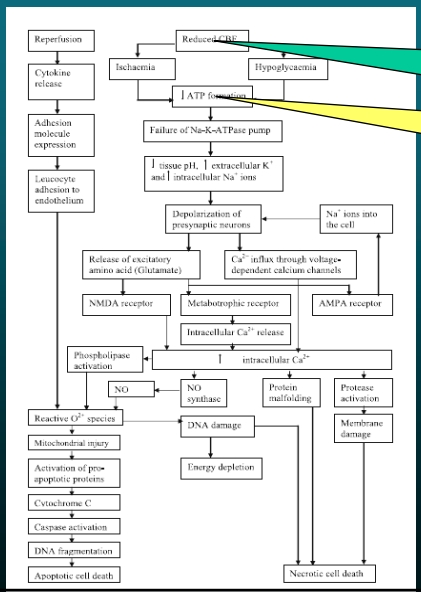

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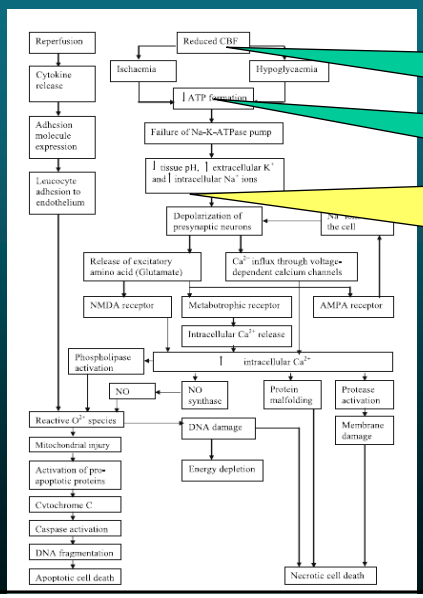

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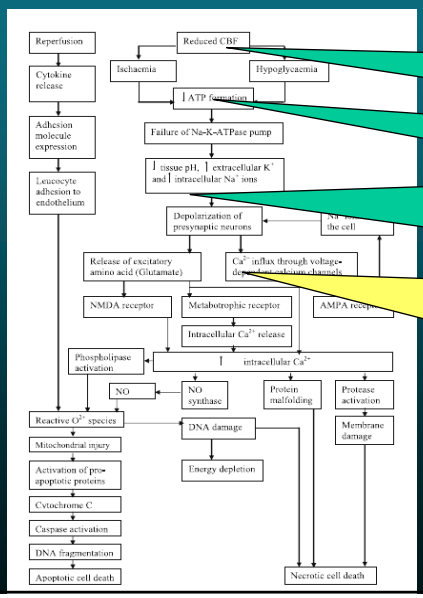

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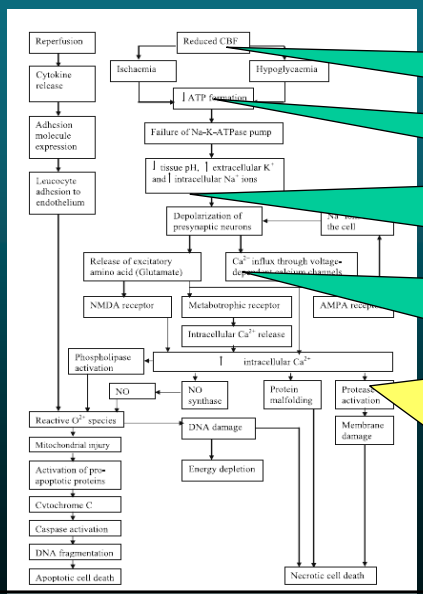

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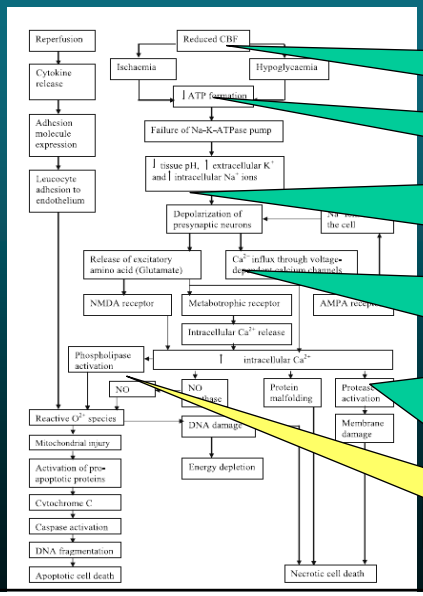

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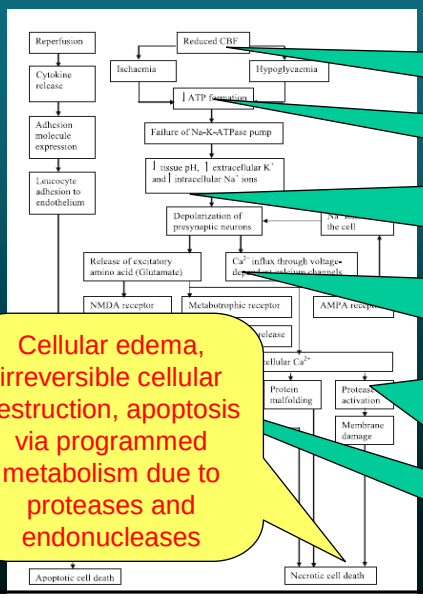

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Dynamics in cerebral ischemia - Schematic overview of dynamics in neuronal ischemic cell death

DYNAMICS	*minutes to hours*	*minutes, hours to days*	*hours to days*	*days, weeks to months*
systemic/ cellular events	Necrosis, Apoptosis, Inflammation, Repair Remodeling, Plasticity			
molecular events	ATP↓ Ca^{2+}↑ glut↑ NO↑ ROS↑ TF↑ IEGs↑ µ-calpain	caspase AIF-accumulation IAPs-breakdown mitochondria-collapse cytoskeleton-breakdown	microglia cytokines (IL-1ß, TNFα)↑ adhesion molecules (ICAM, selectin)↑	angiogenesis MMP-13↑ aggregan↑ ECM-reorganisation cell-cycle proteins (cyclines)	axonal sprouting glial scar formation
systemic intervention	acute therapies thrombolysis recanalisation	anti-necrotic agents anti-inflammatory agents	anti-apoptotic agents combined therapy (anti-apoptotic agents +thrombolysis	growth factors stem cell therapy gene therapy
molecular intervention	rTPA DSPA	DP-b99 (calcium chelator) NXY-059 (antioxidant) YM-872 (AMPA antagonist) µ-calpain-inhibitors	caspase-inhibitors HtrA2-inhibitors Smac-inhibitors IAP-inducers calpain-inhibitors Bcl-2-inducers	GNDF CNTF NGF BDNF

Lit.: Rami A et al., Progress in Neurobiology 85 (2008) 273–296

The concept of so-called neuroprotection

- Neuroprotective treatment
  - Glutamat-Antagonist
    - NMDA-Receptor-Antagonist (e.g. Magnesium, Lubeluzole)
    - AMPA-Receptor-Antagonist (e.g. ZK200775)
    - Glycin-Antagonist (e.g. GV-150526A)
  - GABA-Agonist (e.g. Clomethiazol)
  - GABA-Analoga (e.g. Pirazetam)
  - Calcium antagonist (e.g. Nimodipin)
  - calcium channel blockers (e.g. BMS-204352)
  - Adenosin agonist (e.g. Acadesin, Propentofyllin, Pentoxifyllin)
  - 5-HT_{1A} -Agonist (e.g. Ipsapiron, BAY X 3702)
  - growth factors (e.g. Trafermin)
  - Membrane-stabilizer (e.g. Citicholin, Tirilazad)
- Anti-inflammatory treatment
  - Cytokin inhibitors (e.g. IL-1-Rezeptor-Antagonisten)
  - Immune modulation (e.g. Tacrolimus, Cyclosporin)
- free radical scavengers
- barbiturates

Hoyte, L., J. Kaur, and A.M. Buchan, Lost in translation: taking neuroprotection from animal models to clinical trials. Exp Neurol, 2004. 188(2): p. 200-4.

Treatment with thrombolysis and its therapeutic effect

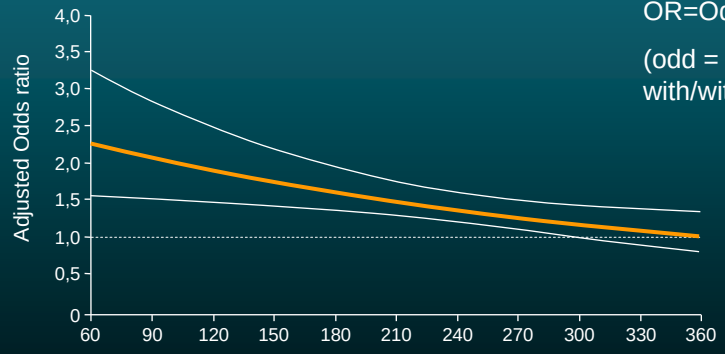
OR/NNT combined endpoints (mRS1, NIHSS 1, BI³95)

0–90 min: OR 2,8; NNT»4

91-180 min: OR 1,5; NNT»9

181-270 min: OR 1,4; NNT»21

271-360 min: OR 1,2; NNT»45



OR=Odds ratio

(odd = ratio of number with/without event)

From RCT:

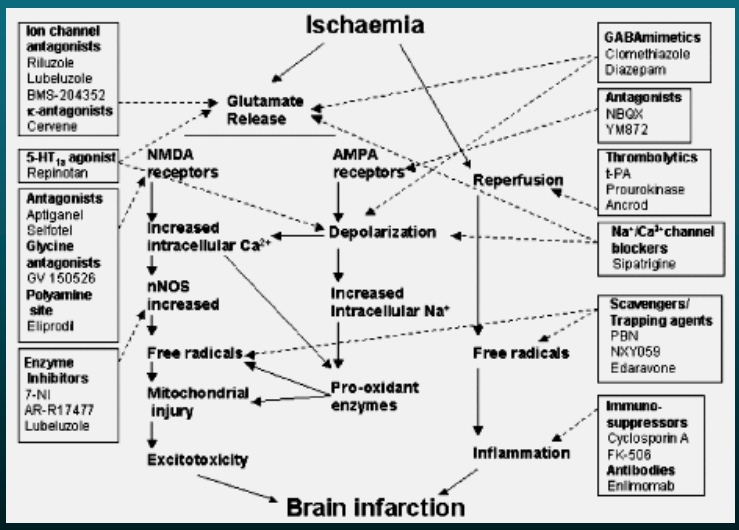
NINDS

ECASS I + II

ATLANTIS

Brott et al., 2003

The concept of so-called neuroprotection



A. Richard Green, Tim Ashwood, Tomas Odergren, David M. Jackson; Pharmacology & Therapeutics 100 (2003) 195– 214

Mechanism of action	Drugs	Number of clinical trials	Result
Calcium channel blockers	Nimodipine (voltage-dependent Ca^{2+} channels)	15	No benefit
	Flunarizine	2 (1 pilot)	No benefit
	Isradipine	2 (1 pilot, 1 discontinued)	No benefit
	Nicardipine	1 (phase II)	No benefit
	PY 108-068	1	No benefit
Calcium chelator	DP-b99	1 phase II completed	Safe
Free radical scavengers (antioxidants)	Ebselen	2 completed, 1 re	mpleted No benefit on primary endpoint
	Tirilazad	1 completed, 1 t	maturely No benefit
	NXY-059 (CPI-22)	phase II co	Well tolerated
		hase III	
GABA agonists	Cl	nzole	efit
	Di		sing
Glutamate antagonists			
AMPA antagonists	YM8		ngoing
	ZK-2		Abandoned due to side-effects
Competitive NMDA antagonists	CGS 1		
Non-competitive NMDA antagonists (NMDA ch blockers)	Aptigan		ng
			ndoned
			side-effects
Glycine site antagonists			efit
			low dose
Polyamine site antagonists			ot published
Growth factors			High mortality
Leucocyte			Treatment worsened outcome
			benefit
Phosphatidylcholi			results
Sodium channel blocke			
Potassium channel opener			No benefit, weather is considered
Mechanism unknown or up		stopped	No benefit on primary endpoint
Adenosine transport in		T	Tend but non-significant
Other ionic channel		completed, 1 phase III ongoing	Beneficial outcome in phase II
			No benefit
Opioid antagonists	Nalt	2 trials (1 phase II, 1 phase III)	No benefit
Multiple action sites	Lube	c oxide inhibitor,	No benefit
	sodiu	l blockers, presynaptic	
	gluta	lease inhibitor, unknown	
	mech	n	

EGASIS = Early GABAergic Activation Study in Stroke; AMPA = *D*-amino-3-hydroxyl-5-ethyl-4-isoxazole propionate; NMDA = *N*-methyl-*D*-aspartate; RCT = randomized controlled trial; CNS = central nervous system; ICH = intracranial haemorrhage.

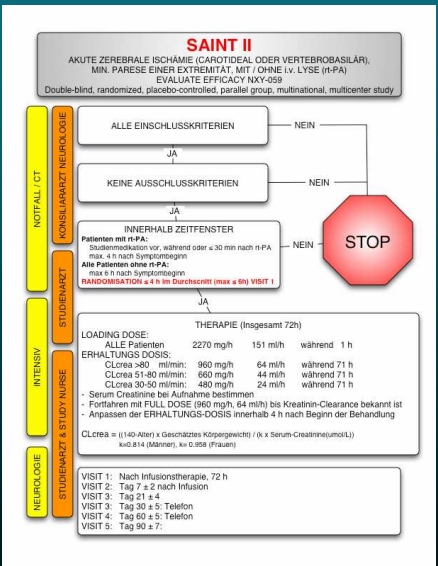
Total of 71 identified trials
Mostly RCT
Result: no benefit at all
Compounds are
safe to harmful

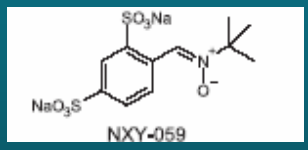
Lit.:Wahlgren NG; Cerebrovasc Dis 2004

Neuroprotective clininal trials in UHBS

N patients	Trial; years	Drug	Result
3	TESS; 94-95	Tirilazad	Negative - harmful
4	TEAST; 97-98	Trafermin (fibroblast growth factor)	harmful
20	POST 010; 00-01	BMS 204352	Negative safe

SAINT-2 a recent trial





Investigational compound

Nitron, traps free radicals

i.v. therapy starts within 6 hours of stroke onset

Infarct size reduction in rat MCAO 62-69 %

What is wrong with neuroprotection ?

„Is it not erroneous to lump together infarcts of all shapes, sizes, times, severities, and locations due to various occlusions (or no occlusions or site of occlusion unknown) and trust the statisticians to make sense of it all through randomization into underpowered trials?“

Furlan AJ, Stroke 2002;33:1450-501.

Reasons for neuroprotectants failure

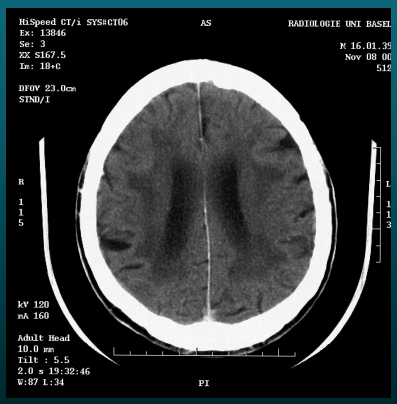
- Pharmacologic reasons
  - pharmacologic target not relevant to humans
  - wrong dose
  - wrong treatment duration
  - unsuitable pahrmacokinetics
- Unsuitable study design
  - Use of wrong measurements (outcomes)
  - delayed treatment
- Statistical Power[1]
  - overestimation of therapeutic effect (>10%)
  - underestimation of clinical relevant effects
- Pathophysiological heterogeneity[2] of the disease
  - no biological substrate to salvage
  - no penumbra
  - lack of reperfusion

[1]Stroke 2001;32:669-74; [2]Stroke 2002;33:1545-50.

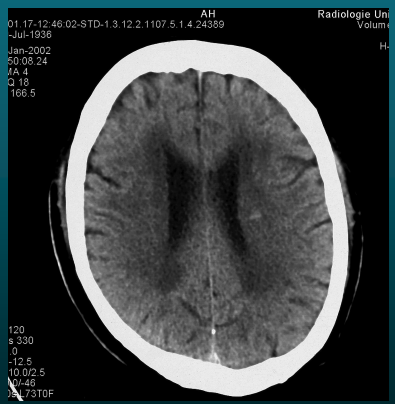
Future design for neuroprotective trials

- More standardized stroke syndromes for inclusion in trials
- Animal models should be standardized
- Short time window
- Salvageable tissue in the DWI/PWI MRI
- Molecule that passes BBB
- Co-administration of thrombolytic therapy

Leucoaraiosis

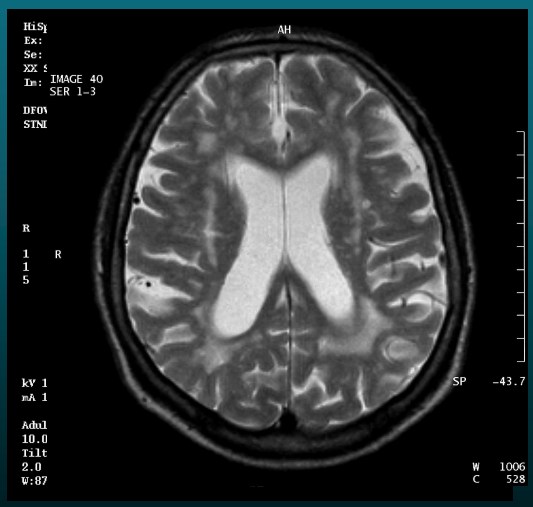


JJ160139, m 61 yrs
Hypertension



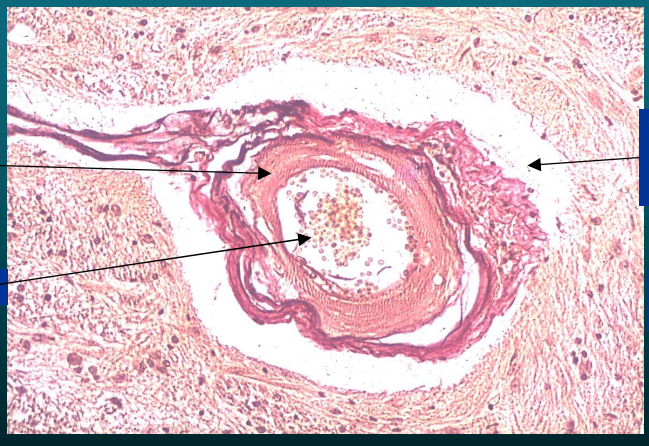
RE030736, m 66-years,
no hypertension

Subcortical hypertensive arteriosclerotic enzephalopathy



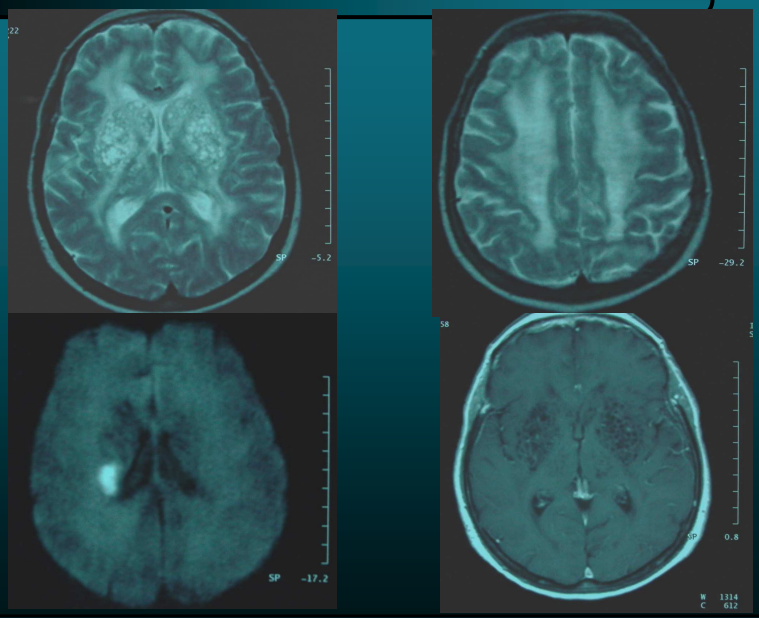
JJ160139, m 61 yrs, hypertension

Pathology – miccroscopic appearence of affected vessels (arterioles)



from A. Probst, Neuropathology, Basel

FM, 020136, f



Vascular Dementia - Epidemiology

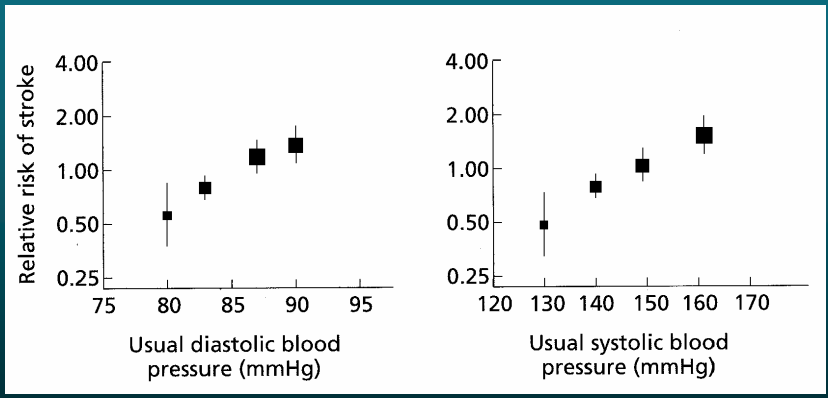
- Prevalence (%) in Europe/USA:

1989 Boston	AD	8.7	VaD	0.9
1990 London		3.1		0.1
1991 Stockholm		6.0		3.0
1995 Rotterdam		4.5		1.0
1997 Odense		4.7		1.3

- Ratio AD/VaD: <0.1-0.5 !

Review, Acta Psych Scand 2001;104:4-11

Blood pressure and risk of stroke



per 5-6mmHg diastolic or 10-12 systolic BP-elevation: 38% relative Risk increase

(Lit.: Journal of Neurology, Neurosurgery and Psychiatry. 1991; 54: 1044-1054)

Animal models: **Genetically predisposed rats**

Spontaneously Hypertensive rats (SHR)

Origine:

Okamoto at the Kyoto School of Medicine in 1963 from an outbred Wistar Kyoto male with marked elevation of blood pressure mated to female with slightly elevated blood pressure

Characteristics:

Hypertension, insulin resistance, hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia.

Spontaneously Hypertensive Stroke Prone rats (SHR-SP)

Characteristics:

82 % of males will develop cerebrovascular lesions (cerebral hemorrhage or infarction) over 100 days of age.
Hypertension,nephropahy, insulin resistance, hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia.

Animal models: **Genetically predisposed rats**

Anatomical abnormalities:

- Variable branching pattern of the distal MCA
- Morphological arrangement of vascular smooth muscle cells are disorganized in the basilar artery of the SHR-SP: influence collateral circulation, rheological changes of blood flow, or vulnerability of the arterial wall to high blood pressure,
- Abnormalities in the BBB: plasma components leakage through arteriols: induce fibrinoid necrosis of small arteries, severe brain edema and lacunar infarction.
- No atheromatous lesions.

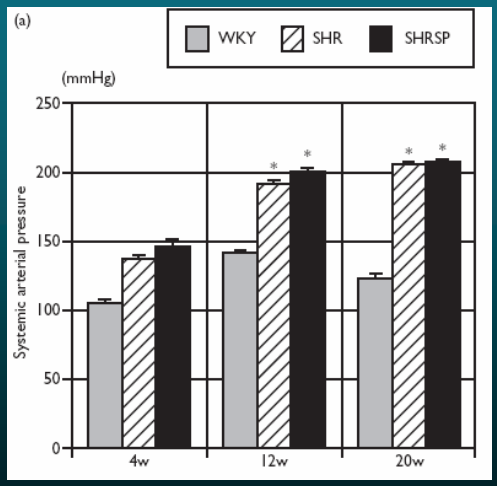
Vascular physiology:

- Response of the cerebral artery to substances causing endothel-dependent vasodilatation impaired in SHR-SP.

Genetic loci involved:

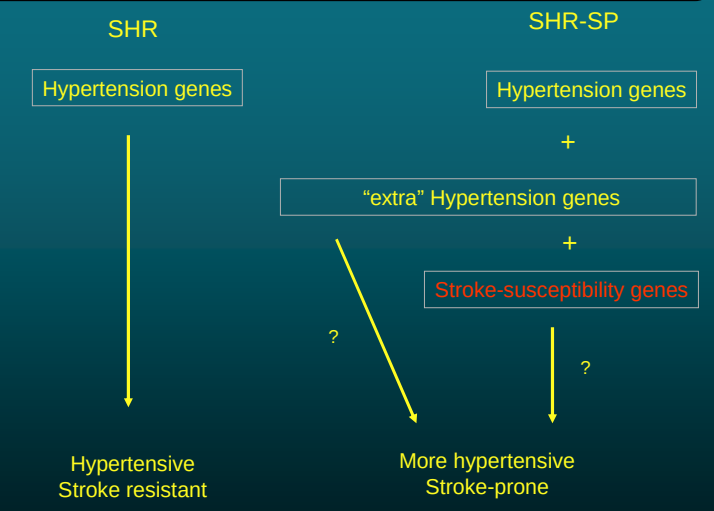
- Chromosomes 1 and 18: genes involved in blood pressure
- Chromosome 5: blood pressure independent, co-localized with genes encoding atrial and brain natriuretic factor

Blood pressure according to different strains



Lin J.-X. et al., Neuroreport 2001;12:1835-1839

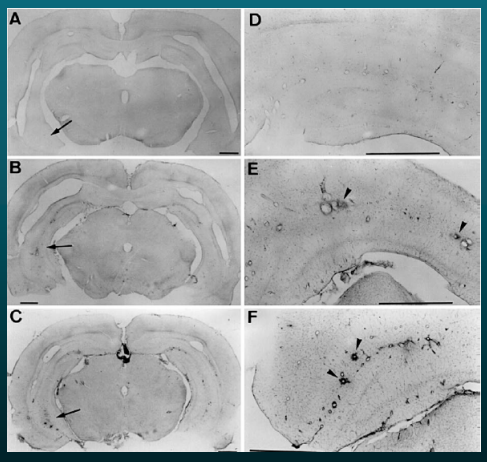
Hypothetical hypertension genes of SHR and SHR-SP



Nabika T. et al., Cellular and Molecular Neurobiology 2004;24:639-646

Vascular permeability in WKY, SHR and SHR-SP

Horse-radish peroxidase accumu-lation



Normotensive
Stroke-resistant WKY

Hypertensive
Stroke-resistant SHR

Hypertensive
Stroke-prone SHR-SP

Ueno M. et al. Acta Neuropathol 2004;107:532-538

Differences between SHR and SHR-SP strains

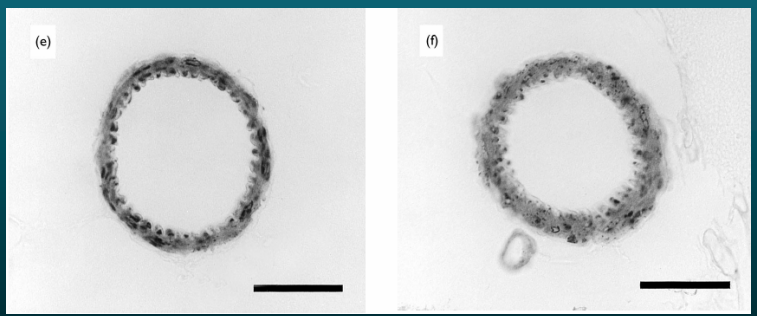
Collagen staining reveals significant differences in the distribution of collagen in MCA from SHR-SP compared with SHR:

SHR-SP SHR

Izzard A.S. et al., Am J Physiol Heart Circl Physiol 2003;285 H1489-1494

Differences between Wistar and stroke prone SHR

Smooth muscle actin staining, increased in SHR-SP with hypertrophic arteries (Anterior cerebral artery)

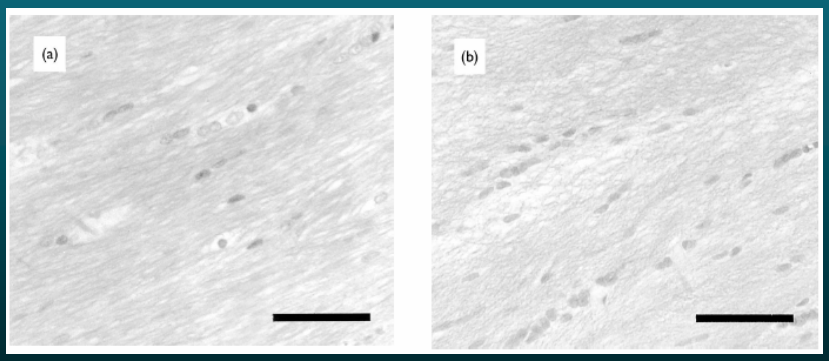


WKY SHR-SP

Lin J.-X. et al., Neuroreport 2001;12:1835-1839

Klüver-Barrera staining of white matter in corpus callosum

Disturbed structure of the white matter im CC from SHR-SP: disarrangement of nerve fiber, marked vacuoles und disappearence of myelinated fibers



WKY SHR-SP

Lin J.-X. et al., Neuroreport 2001;12:1835-1839

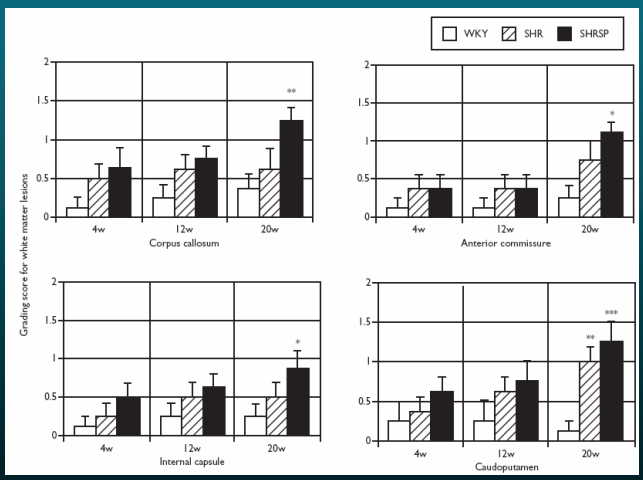
Appearance of white matter lesions in the brain of SHR, SHR-SP

Normal
(grade 0)

disarrangement
of the nerve
fibers
(grade 1)

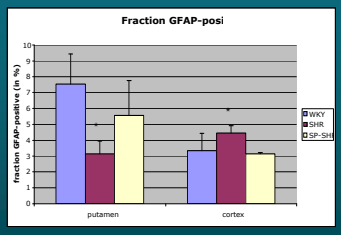
formation of
marked vacuoles
(grade 2)

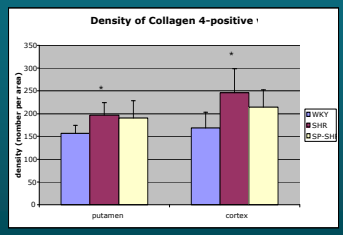
disappearance
of myelinated
fibers
(grade 3)

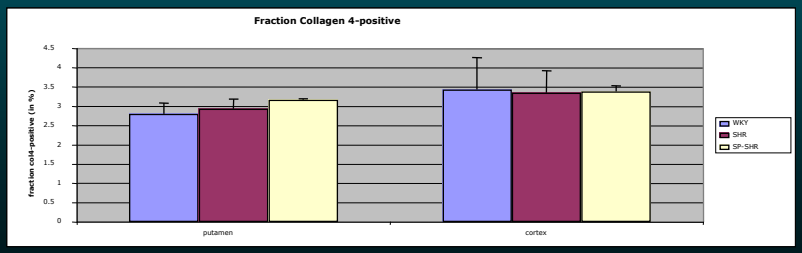


Lin J.-X. et al., Neuroreport 2001;12:1835-1839

Col4 and GFAP in normotensive and hypertensive rats







The End