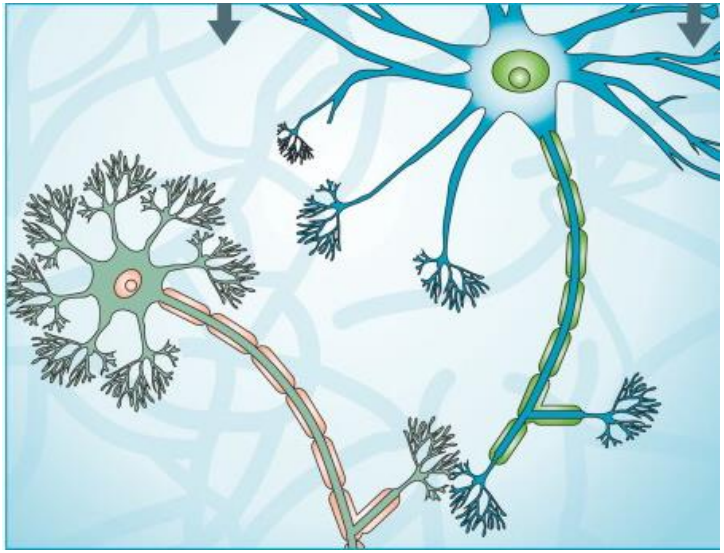
SYMPOSIUM

Local Anaesthetics:

Reappraisal of their Role in RA and Pain Management

Local Anaesthetics (LAs)

NEUROPROTECTION



Eleni Moka, MD, PhD

Consultant Anaesthesiologist

Heraklion, Crete, GREECE

Best Practice & Research Clinical Anaesthesiology 24 (2010) 535–549

Contents lists available at ScienceDirect

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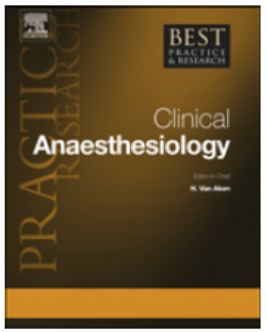
journal homepage: www.elsevier.com/locate/bean



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Perioperative neuroprotection

Klaus Ulrich Klein, MD, Consultant *, Kristin Engelhard, MD, PhD

Department of Anaesthesiology, University Medical Center of the Johannes Gutenberg-University, Langenbeckstr. 1, 55131 Mainz, Germany

Nervous System Ischaemia …

- Brain – Spinal Cord → Perioperative Period
- Pathophysiology → Progress
- Treatment → Challenge

- no Pharmacological Agent
  → Definite Neuroprotection
  → Absolute Indication

- multiple drugs deserve attention !!!

Head BP, Patel P. Curr Opin Anaesthesiol, 2007; 20: 395 – 399
Ginsberg M. Neuropharmacology, 2008; 55: 363 – 389
Klein KU, Engelhardt K. Best Pract Res Clin Anaesthesiol, 2010; 24: 535 – 549
Kunz A et al. Best Pract Res Clin Anaesthesiol, 2010; 24: 535 – 549
Werner C. Best Pract Res Clin Anaesthesiol, 2010; 24: 8 – 10

Novel local anaesthetics and novel indications for local anaesthetics

Markus W. Hollmann[a,b], Marcel E. Durieux[a] and Bernhard M. Graf[b]

Current Opinion in Anaesthesiology 2001, 14:741–749

A brief review of innovative uses for local anesthetics

Jeffrey L. Wright, Marcel E. Durieux and Danja S. Groves

Current Opinion in Anaesthesiology 2008, 21:651–656

Update on local anesthetics

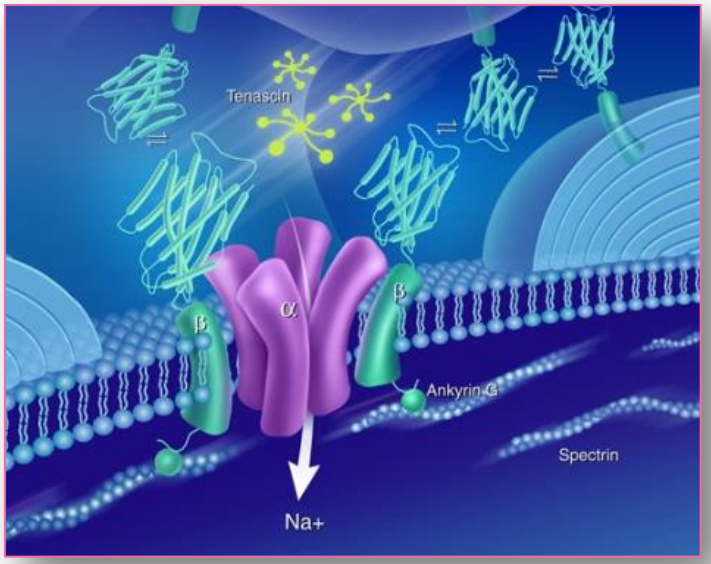
Alain Borgeat and José Aguirre

Current Opinion in Anaesthesiology 2010, 23:466–471

Local Anaesthetics (LAs) …

Traditional – Alternative Cellular Targets

- **Na+ Channels Blockade**
  Anaesthesia – Analgesia
  Antiarrhythmic Action
- **Other Cellular Systems**
  Ca++ / K+ Channels
  TRPV – 1 / NMDA Receptors
  G – Protein Coupled Receptors
  Ligand – Gated Receptors
- **Innovative Actions**
  neuroprotection
  anti – inflammatory effects



Kindler CH, Yost CS. Reg Anesth Pain Med, 2005; 30: 260 – 274
Wright JL et al. Curr Opin Anaesthesiol, 2008; 21: 651 – 656
Beloeil H, Mazoit JX. Ann Fr Anesth Reanim, 2009; 28: 231 – 237
Borgeat A, Aguirre J. Curr Opin Anaesthesiol, 2010; 23: 46 – 471

Lecture Outline

- CNS Ischaemia → Pathophysiology
- Recent Progress → LAs Neuroprotection
  - Experimental Data
  - Clinical Data
- Clinical Relevance
- Future Prospects

Nerve Cell Ischaemia – Mechanisms

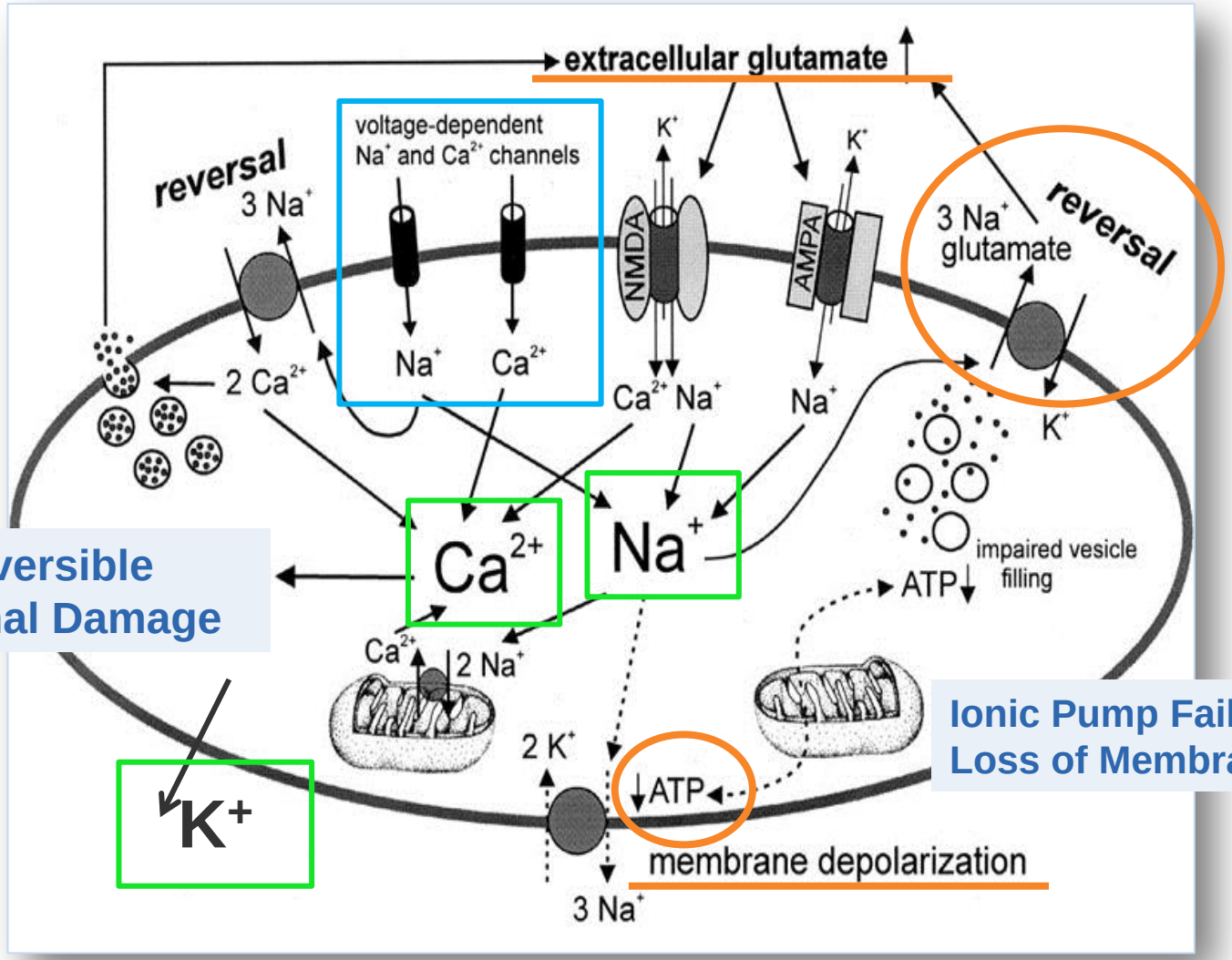
Koerner IP. Curr Opin Anaesthesiol, 2006; 19: 481 – 486
Green AR. Br J Pharmacol, 2008; 153 (Suppl 1): S325 – S338
Galuzzi Z et al. Neuroscience, 2009; 10: 481 – 494
Kunz A, et al. Best Pract Res Clin Anaesth, 2010; 24: 495 – 509

Ischaemic Nerve Cell Death

Depolarization – Excitotoxicity

Altered Cellular Ion Homeostasis

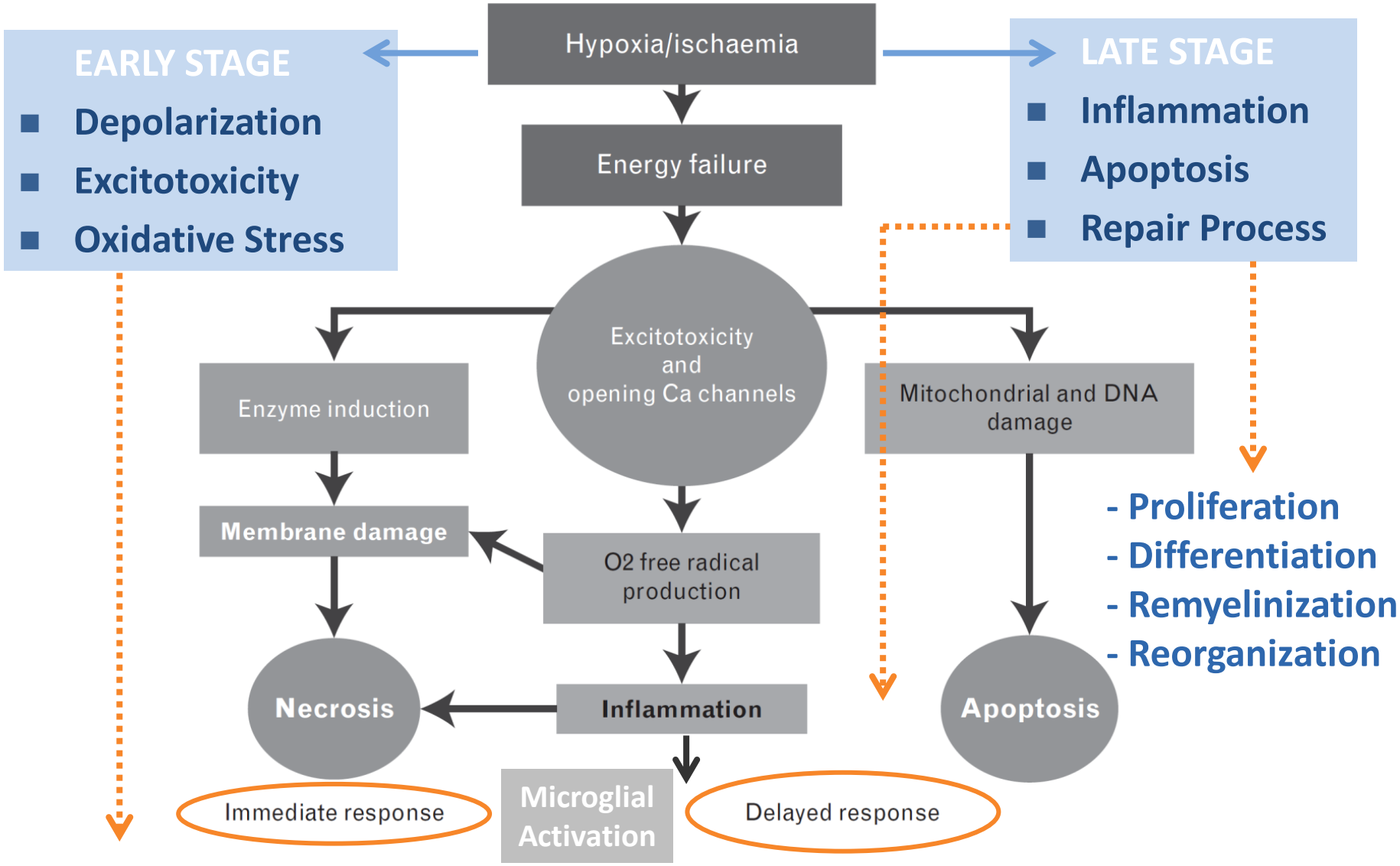
Lo EH et al. Nature Reviews, 2003; 4: 399 – 415
Kass IS. ASA Refresher Course, 2006; 34: 85 – 93
Galuzzi Z et al. Neuroscience, 2009; 10: 481 – 494



Irreversible Neuronal Damage

Ionic Pump Failure
Loss of Membrane Potential

Ischaemic Nerve Cell Death → Major Mechanisms



Mantz J, et al. Eur J Anaesthesiol, 2010; 27: 6 – 10
El Beheiry H. Curr Opin Anaesthesiol, 2012; 25: epub ahead of print

LAs Neuroprotection

Definition

- Every Step in ischaemic cascade → potential target

  → blocking of biochemical, metabolic, cellular cascades

  → prevention of reperfusion – induced secondary insults

- Pretreatment

  - prior / simultaneously with ischaemic insult

  - ↓ tissue damage, ↑ neuronal strength / survival rates

- Resuscitation

  - after ischaemic injury

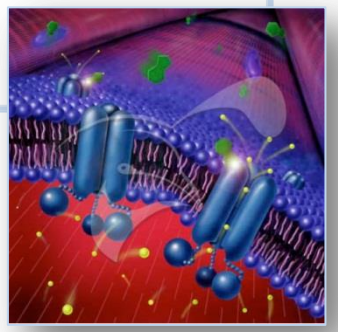
  - attenuation / prevention of later cellular damage

Hans P, Bonhomme V. Curr Opin Anaesthesiol, 2001; 14: 491 – 496
Hemmings HC. J Neurosurg Anaesthesiol, 2004; 16: 100 – 101
Mantz J, et al. Eur J Anaesthesiol, 2010; 27: 6 – 10

J Neurosurg Anesthesiol • Volume 16, Number 1, January 2004

Neuroprotection by Na^+ Channel Blockade

Hugh C. Hemmings Jr., MD, PhD



LAs ability attenuation of hypoxia – induced alterations

→ voltage – gated Na+ channel blockade or modulation

→ rather than inhibition of action potential propagation

predicts their neuroprotective effects

LOCAL ANAESTHETICS

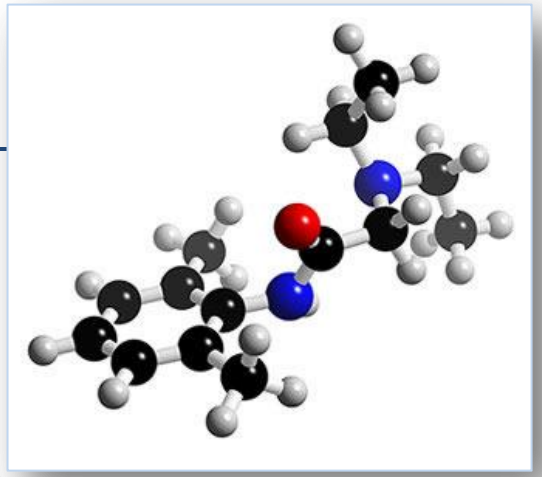
brain protection → ischaemia – trauma

- few clinical investigations
- <u>numerous experimental studies</u>
  - in vitro – in vivo
  - animal models
  - focal and global ischaemia
  - testing LAs doses
  - time – points

Warner DS. J Neurosurg Anaesthesiol, 2004; 16: 95 – 97
Werner C. Best Pract Res Clin Anaesthesiol, 2010; 24: 8 – 10
Mantz J, Degos V, Laigle C. Eur J Anaesthesiol, 2010; 27: 6 – 10
Klein KU, Engelhardt K. Best Pract Res Clin Anaesthesiol, 2010; 24: 535 – 549

Local Anaesthetics

Neuroprotective Mechanisms



LIDOCAINE

- most studied LA
- very promising agent → familiar to clinicians
- easy in pharmacological «manipulation»
- inexpensive – widely available – relatively safe compound
- acts in the early stages of ischaemic cascade (Na+ channels)
- blocks the sequence of pathophysiologic interactions
- especially if given prophylactically
- works at clinically relevant doses (↓ vs antiarrhythmic)

Hans P, Bonhomme V. Curr Opin Anaesthesiol, 2001; 14: 491 – 496
Mitchell SJ, Merry AF. J Extra Corp Technol, 2009; 41: P 37 – P 42
Mantz J, Degos V, Laigle C. Eur J Anaesth, 2010; 27: 6 – 10
Kellermann K et al. Semin Cardiothorac Vasc Anesth, 2010; 14: 95 – 101

LOCAL ANAESTHETICS

BRAIN PROTECTION

Experimental Studies

Lidocaine (canine model – massive iv dose 160 mg/kg)

Astrup J et al. Anesthesiology 1981, Eur Neurol 1981

Global Ischaemia → Prolonged Tolerability Limit – «Dual» Effect

«Barbiturate – Like» Effect

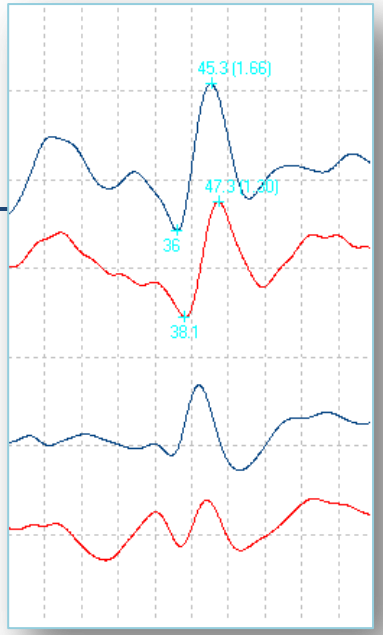
- electrocortical activity abolishment
- ↓ O2 and Glu consumption

Membrane «Sealing» Effect

- ↓ membrane Na+/K+ permeability
- restricts / delays K+ efflux
- ↓ load on associated ion transporters
- ↓ CMRO2 (15 – 20%) below barbiturate min at flat EEG
- similar to hypothermia protection / additive effect

Lidocaine (iv dose 2 or 5 mg/kg)

in vivo: cats – rats



- cerebral ischaemia from air embolism or trauma

Neuroprotective Effects over a 2 – hour Period

- preservation of SEPs 2h post embolism
- attenuation of Acute Hypertension & ↑ ICP
- ↑ recovery of neuronal function

Evans DE et al. J Neurosurg 1984, Neurosurgery 1987, J Neurosurg 1989

- ↓ post – traumatic motor deficits brain injury
- ↓ cortical hypoperfusion and CBF preservation
- Pegorgotein (Dismutec) → same beneficial action
- free radical scavenging effect – antiinflammatory actions

Muir JK et al. Am J Physiol 1995, J Neurotrauma 1995
Hamm RJ et al. J Neurotrauma 1996

Laboratory Report

Lidocaine prolongs the safe duration of circulatory arrest during deep hypothermia in dogs

CAN J ANAESTH 1998
45: 7 / pp 692–698

Yuan Zhou MD, Dongxin Wang MD PhD,
Minyi Du MB, Jianghua Zhu ChB,
Guojin Shan PhARB, Daqing Ma MD,
Dajian Xie ChB, Qiong Ma,
Xiaohua Hu, Jun Li

Effect of Lidocaine on Improving Cerebral Protection Provided by Retrograde Cerebral Perfusion: A Neuropathologic Study

Dongxin Wang, MD, PhD, Xinmin Wu, MD, Yanfeng Zhong, MD, Yuan Zhou, MD, Guojin Shan, Xiaohua Hu, Jun Li, Yong Liu, MD, Xiang Qin, MD, and Zhunan Xia, MD

Journal of Cardiothoracic and Vascular Anesthesia, Vol 13, No 2 (April), 1999: pp 176-180

Lidocaine – Pretreatment at various doses

Experimental Studies – In Vitro Ischaemia

Rat Hippocampal Slices

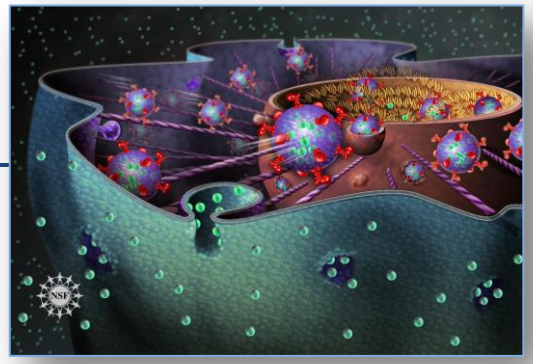
- delayed / ↓ hypoxic depolarization
- ↓ transmembrane ion fluxes
- recovery of resting action potential
- glutamate transporter → reversed operation
- presynaptic modulation of fPSP
- ↓ ischaemic excitotoxin release, ↓ NMDA activation
- modulation of inflammatory mediators

Sakabe T et al. Anesthesiology, 1974
Weber ML et al. Brain Research, 1994
Ayad M et al. J Neurosurg Anesthesiol, 1994

Fried E et al. J Physiol, 1995
Taylor CP et al. J Neurosci Methods, 1995
Raley Susman KM et al. J Neurophysiol, 2001

Lidocaine

Cerebroprotective Mechanisms



in vitro studies

- ATP content preservation
- mitochondria – intracellular organelles protection
- ↓ glutamate excitotoxicity
- inhibition
  - Ca++ release from intracellular stores
  - Ca++ influx from extracellular space
- probably inhibition of IP3 receptor – mediated Ca++ release

↓ intracellular Ca++ concentration

Shoshan V et al. J Membr Biol, 1993; 133: 171 – 181
Fujitani T et al. Neuroscience Letters, 1994; 179: 91 – 94
Liu K et al. Anesthesiology, 1997; 87: 1470 – 1478
Yamada A et al. Neuroscience Research, 2004; 50: 291 – 298
Niiyama S et al. Neuroscience Research, 2005; 53: 271 – 278
Martinez Sanchez M et al. Neuroscience, 2004; 128: 729 – 740

Local Anaesthetics – Pretreatment

Experimental Studies – In Vitro Ischaemia

Rat Hippocampal Slices

- synaptic potentials recovery

↓

- ↓ injury in hippocampus
- ↓ No of morphologically damaged pyramidal cells
- improved recovery
- ↑ protein synthesis of CA1 cells

Suttherland G et al. Stroke, 1989; 20: 119 – 122
Weber ML et al. Brain Research, 1994; 664: 167 – 177
Liu K et al. Anesthesiology, 1997; 87: 1470 – 1478
Zhou Y et al. Can J Anaesth, 1998; 45: 692 – 698
Wang D et al. J Cardiothorac Vasc Surg, 1999; 13: 176 – 180

The Effect of Intravenous or Subarachnoid Lidocaine on Glutamate Accumulation During Transient Forebrain Ischemia in Rats

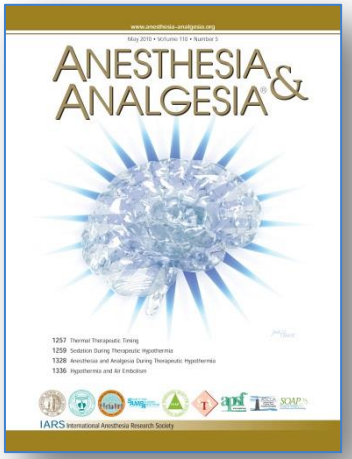
Hiromichi Terada, MD*, Sukejuro Ohta, MD†, Toshiaki Nishikawa, MD*, Takahide Mizunuma, MD*, Yoichi Iwasaki, MD*, and Yoko Masaki, PhD*

*Department of Anesthesiology, Akita University School of Medicine; and †Division of Anesthesiology, Akita Medical Center, Akita, Japan

(Anesth Analg 1999;89:957–61)

- 10 min forebrain ischaemia in rats
- iv – subarachnoid LIDO vs NS 0.9% (before ischaemia)
- 5 or 10 mg/kg
- Dialysis Electrode Method

- ↓ extracellular glutamate concentration hippocampal CA1 area & cortex



Neuroprotective Effect of Low-dose Lidocaine in a Rat Model of Transient Focal Cerebral Ischemia

Baiping Lei, M.D., Ph.D., James E. Cottrell, M.D.,† Ira S. Kass, Ph.D.‡*

Anesthesiology 2001; 95:445-51

LIDOCAINE ATTENUATES APOPTOSIS IN THE ISCHEMIC PENUMBRA AND REDUCES INFARCT SIZE AFTER TRANSIENT FOCAL CEREBRAL ISCHEMIA IN RATS

B. LEI,[a] S. POPP,[b] C. CAPUANO-WATERS,[a]
J. E. COTTRELL[a] AND I. S. KASS[a,b,c*]

Neuroscience 125 (2004) 691–701

- ↓ infarct size
- improved neurologic outcome over time
- attenuation of apoptosis in penumbra
  - ↓ cytochrome – C release and ↓ caspase – 3 activation at 4h
  - ↓ DNA fragmentation at 24h
- no effects on CBF

NEUROSURGICAL ANESTHESIA
SECTION EDITOR
DAVID S. WARNER

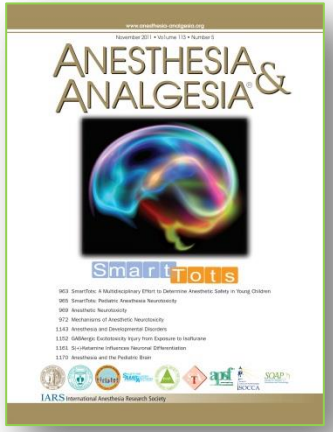
ANESTH ANALG
2005;101:1163–9

Pre- or Postinsult Administration of Lidocaine or Thiopental Attenuates Cell Death in Rat Hippocampal Slice Cultures Caused by Oxygen-Glucose Deprivation

Hong Cao, MD*‡§, Ira S. Kass, PhD*†‡, James E. Cottrell, MD*, and Peter J. Bergold, PhD†

- In Vitro Experimental Model of Ischaemia
- Lidocaine → before or after ischaemic insult
- 10 min of Oxygen – Glucose Deprivation (OGD)

- cerebroprotectants
- ↓ cell death, ↓ neuronal damage



Lidocaine

Cerebral Protection

global brain ischemia in rats

iv Lidocaine 2 or 4mg/kg – 0.75 or 1.5 mg/kg

before, during and after ischaemic insult

- **↑ No of surviving CA1 pyramidal neurons at 4 wks**
- **preserved cognitive function associated with that area**
- **↓ cerebral impedance, strong early anti – oedema effect**

Popp SS et al. Neuroscience, 2011; 192: 537 – 549
Wix – Ramos R et al. Pharmacology, 2011; 88: 316 – 321

Lidocaine 10 mg/kg + Dexmedetomidine 3 µg/kg sc

- **↑ neurologic & histopathologic recovery**
- **no alteration in extracellular Glutamate or Epinephrine C**

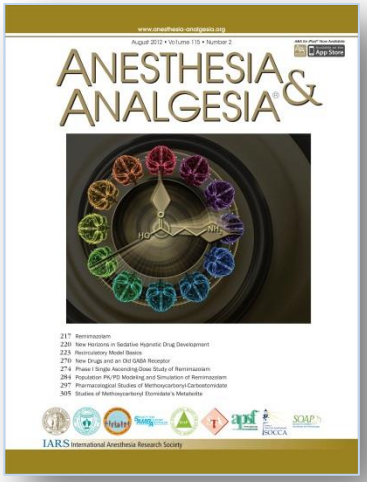
Goyagi T et al. Acta Anaesthesiol Scand, 2009; 53: 1176 – 1183

Inhibition of Acid Sensing Ion Channel Currents by Lidocaine in Cultured Mouse Cortical Neurons

Jun Lin, MD, PhD,* Xiangping Chu, MD, PhD,† Samaneh Maysami, MD, PhD,† Minghua Li, PhD,† Hongfang Si, PhD,† James E. Cottrell, MD,* Roger P. Simon, MD,† and Zhigang Xiong, MD, PhD†

(Anesth Analg 2011;112:977–81)

- in vitro experimental study
- Acid Sensing Ion Channels (ASICs)
  - proton – gated cation channels
  - Na+, Ca++ influx
  - acidosis – mediated neuron injury



LIDO at different concentrations

- rapid, reversible, dose – dependent inhibition
- approximately by 90% – ASIC2a current

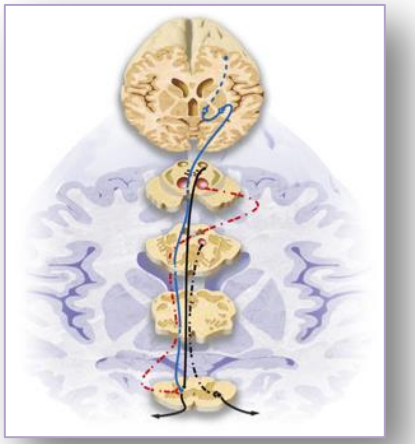
Delayed Treatment with Lidocaine Reduces Mouse Microglial Cell Injury and Cytokine Production After Stimulation with Lipopolysaccharide and Interferon γ

Hae-Jeong Jeong, MD, PhD, Daowei Lin, MD, Liaoliao Li, PhD, and Zhiyi Zuo, MD, PhD

Anesth Analg, 2012; 114: 856 – 861

Lidocaine

Protection from Neuroinflammation



- ↓ mouse microglial cell injury
- ↓ cytokine production
- mediated by cell surface targets
- neurovascular & anti – neuroinflammatory effect versus simple membrane stabilizing action

What is the Clinical Evidence ???

Cerebral Protection by Lidocaine During Cardiac Operations

Simon J. Mitchell, MB, ChB, Ora Pellett, MSc, and Des F. Gorman, PhD

Royal New Zealand Navy Hospital, Cardiothoracic Surgical Unit and Department of Anesthesia, Green Lane Hospital, and the Faculty of Medicine and Health Sciences, University of Auckland, Auckland, New Zealand

Ann Thorac Surg 1999;67;1117–24

- 55 pts – valve surgery
- Double – Blind RCT
- Lidocaine or Placebo for 48h

LIDO Dosage Scheme

- bolus

  1mg/kg at anaesthesia induction

- infusion

  240 mg 1st hour → 120 mg 2nd hour → 60 mg/h

Cerebral Protection by Lidocaine During Cardiac Operations

Simon J. Mitchell, MB, ChB, Ora Pellett, MSc, and Des F. Gorman, PhD

Royal New Zealand Navy Hospital, Cardiothoracic Surgical Unit and Department of Anesthesia, Green Lane Hospital, and the Faculty of Medicine and Health Sciences, University of Auckland, Auckland, New Zealand

Ann Thorac Surg 1999;67;1117–24

- **Neuropsychological (NP) Tests**
- **10 days, 10 weeks, 6 months post – surgery**
- **cognitive function → improvement pts LIDO Group vs Placebo**

CARDIOVASCULAR ANESTHESIA
SECTION EDITOR
KENNETH J. TUMAN

SOCIETY OF CARDIOVASCULAR ANESTHESIOLOGISTS

Anesth Analg 2002;95:1134–41

The Effect of Lidocaine on Early Postoperative Cognitive Dysfunction After Coronary Artery Bypass Surgery

Dongxin Wang, MD, PhD*, Xinmin Wu, MD*, Jun Li, MD*, Feng Xiao, MD†, Xiaoying Liu, MD*, and Meijin Meng, MD*

Departments of *Anesthesiology and †Cardiac Surgery, First Hospital, Peking University, Beijing, China

- **double – blind RCT, 118 CABG pts**
- **LIDO → intraoperatively**
  - **bolus 1.5 mg/kg**
  - **infusion 4 mg/kg + 4mg/kg CPB Prime**
- **↓ early postop cognitive dysfunction (9 days)**

  LIDO → 18.6% / Placebo → 40%

Cerebral Protection by Lidocaine During Cardiac Operations: A Follow-Up Study

Simon J. Mitchell, FANZCA, PhD, Alan F. Merry, FANZCA, Christopher Frampton, PhD, Elaine Davies, Diana Grieve, MA, Brigid P. Mills, MHSc(Hons), Craig S. Webster, PhD, F. Paget Milsom, FRACS, Timothy W. Willcox, CCP, and Desmond F. Gorman, MD, PhD

Department of Anaesthesiology, University of Auckland, StatistEcol, Mount Eden, and Departments of Anaesthesia, Surgery, and Clinical Perfusion, Auckland City Hospital, Auckland, New Zealand

Ann Thorac Surg 2009;87:820–5

- double – blind, randomized
- intention – to – treat, follow – up study
- appropriately powered design
- 158 pts – typical mix of procedures
- LIDO → 12 hours versus Placebo
  - bolus 1 mg/kg
  - infusion 2 mg/min 2h + 1 mg/min thereafter
- similar cognitive decline + LOS in both groups

Randomized, Double-Blinded, Placebo Controlled Study of Neuroprotection With Lidocaine in Cardiac Surgery

Joseph P. Mathew, MD; G. Burkhard Mackensen, MD, PhD; Barbara Phillips-Bute, PhD; Hilary P. Grocott, MD; Donald D. Glower, MD; Daniel T. Laskowitz, MD; James A. Blumenthal, PhD; Mark F. Newman, MD; for the Neurologic Outcome Research Group (NORG) of the Duke Heart Center*

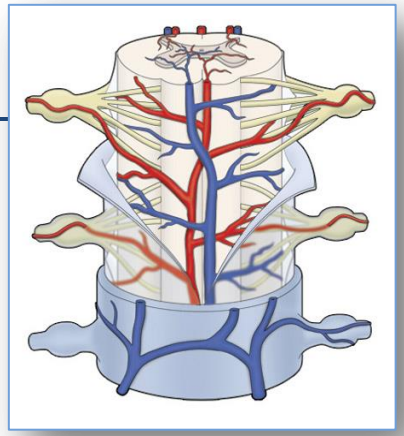
Stroke. 2009;40:880-887

- 241 pts – all types of heart surgery
- LIDO – Placebo (48h)

- no ↓ postop cognitive dysfunction
- ↑ LIDO dose + DM: independent predictors of cognitive decline
- protective effect in non – diabetic pts, 1 year post – surgery

Local Anaesthetics

SPINAL CORD (SC) Neuronal Protection



- LAs Cerebral Protection
- plasma C < ED50 for Na+ channels blockade

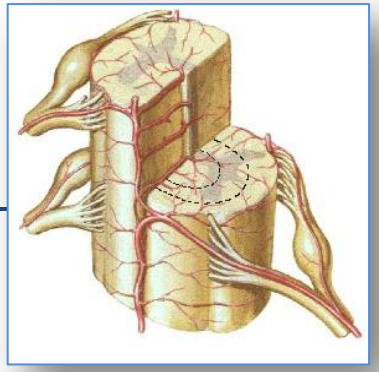
SC Neuroprotection from Ischaemia

- ↓ LAs concentrations
- yet to be established
- few experimental literature reports

Johnson ME. J Neurosurg Anesthesiol, 2004; 16: 80 – 83
Fu ES, Tummala RP. Curr Opin Anesthesiol, 2005; 18: 181 – 187
Sinha AC, Cheung AT. Curr Opin Anesthesiol, 2010; 23: 95 – 102

Local Anaesthetics

SPINAL CORD (SC) Protection



iv LIDO 0.5 mg/kg – porcine model

- ↓ spinal motor – evoked potential amplitude loss
- did not alter neurological deficit rate

Kobrine AI et al. J Neurosurg, 1984; 60: 595 – 601
Svensson LG et al. Ann Thorac Surg, 1992; 54: 74 – 79

Regional LIDO Infusion – rabbit model

- ↓ post – ischaemic SC injury

Apaydin A, Bucket S. Tex Heart Inst J, 2001; 28: 172 – 176

IT tetracaine in rabits

- SC injury prevention after 30 min AoX
- no ↓ glutamate release
- no neurologic – histopathologic outcome alteration

Breckwoldt WL et al. Ann Thorac Surg, 1991; 51: 959 – 963
Wakamatsu H et al. Anesth Analg, 1999; 88: 56 – 62

*Acta Anaesthesiol Scand 2007; **51**: 60–67*

Effects of intrathecal bupivacaine in conjunction with hypothermia on neuronal protection against transient spinal cord ischemia in rats

J – R Lee, S – M Han, J – G Leem and S – J Hwang

Intrathecal BUPIVACAINE

- no neuroprotective effects
- ↑ hypothermia neuroprotection
  - sensory deficit scores
  - neuronal cell death
  - HSP70

Do LAs neuroprotective benefits outweigh risks?

Johnson ME. J Neurosurg Anesthesiol, 2004; 16: 80 – 83
Zink W, Graf BM. Curr Opin Anesthesiol, 2008; 21: 645 – 650
Takenami T et al. Can J Anaesth , 2012; 59: 456 – 465
Gaulain – Nouette K, Capdevilla X, Rossignol R. Curr Opin Anesthesiol, 2012, epub ahead of print

PERIOPERATIVE NEUROPROTECTION SYMPOSIUM

J Neurosurg Anesthesiol 2004;16:80–83

Neurotoxicity of Lidocaine: Implications for Spinal Anesthesia and Neuroprotection

Michael E. Johnson, MD, PhD

- **experimental reports → LAs protection against SC ischaemia**

  BUT
- **intrathecal LAs for spinal anaesthesia → direct neurotoxicity**

- **LIDO more neurotoxic vs BUPI - Tetracaine**
- **narrow therapeutic index**
- **implications**

  spinal anaesthesia + attempts for neuroprotection

Local anesthetic 'in-situ' toxicity during peripheral nerve blocks: update on mechanisms and prevention

Curr Opin Anesthesiol 2012, 25:000–000

Karine Nouette-Gaulain[a,b], *Xavier Capdevila*[c,d], *and Rodrigue Rossignol*[a]

- cellular mechanisms → not fully elucidated
- pleiotropic effects on cell metabolism
- tissue ultrastructure alterations in neurons

- not mediated by Na+ channels blockade
- ≠ global CNS toxicity after systemic LAs overdose
- altered Ca++ homeostasis – biphasic response
- mitochondrial energy metabolism inhibition

Local Anaesthetics

Dose – Time – Concentration Dependent Action

Neuroprotection or Neurotoxicity

Impact of Discontinuous Dose-Response Curves on Risk Assessment

WILLIAM SLIKKER, JR., HELEN DUHART, DAVID GAYLOR, AND SYED IMAM

Ann. N.Y. Acad. Sci. 993: 158 (2003)

- multiple mechanisms of action may exist
  when full dose response curve is explored
- dose – dependent transitions in principal mechanisms
  opportunity → possible LAs neuroprotective properties

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Commentary

Lost in translation: taking neuroprotection from animal models to clinical trials☆

L. Hoyte,[a] J. Kaur,[a] and A.M. Buchan[b,*]

[a] *Calgary Stroke Program, Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada T2N 2T8*
[b] *Calgary Stroke Program, Department of Clinical Neurosciences, University of Calgary, Calgary AB, Canada T2N 2T9*

- **experimental data → support LAs neuroprotective effects**
- **clinical evidence → less convincing**
- **translational failure in search of clinical neuroprotection**

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- **methodological factors**
- **misconception of experimental studies**

- basic research → still necessary
- more sophisticated study designs → required

Local Anaesthetics

Neuroprotective or Wishful Thinking ???

Mitchell SJ. J Extra Corp Technol, 2009; 41: P37 – P42