α-Lipoic acid prevents bupivacaine-induced neuron injury *in vitro* through a PI3K/Akt-dependent mechanism

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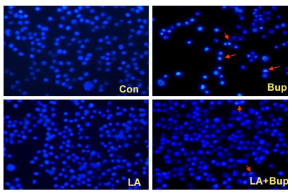
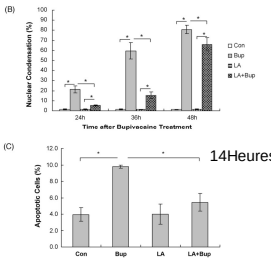
[d] Jiangsu Key Laboratory for Molecular and Medical Biotechnology, Nanjing Normal University, Nanjing 210097, China

NeuroToxicology 31 (2010) 101–112





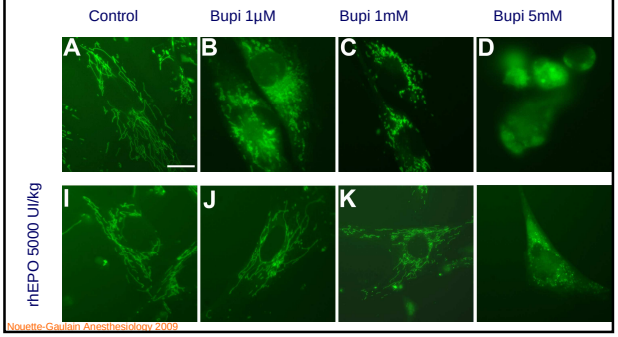
14Heures

Bupivacaine 900 µM
LA 30 min avant la bupivacaine

Le réseau mitochondrial

Effet de la bupivacaïne - Intérêt de rhEPO

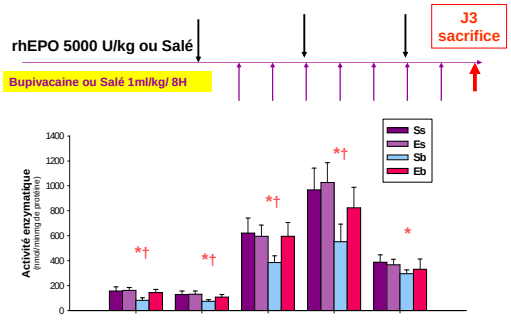
Myoblastes, Mitotracker green



Nouette-Gaulain Anesthesiology 2009

Bupivacaine et rhEPO

Activités enzymatiques des Cx de la CR

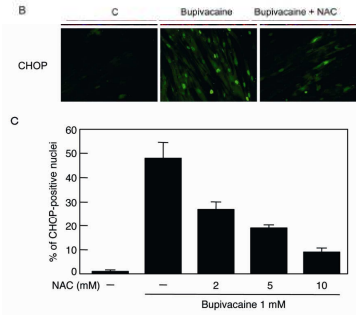


*P<0,02
†P<0,02 vs Eb

Nouette-Gaulain Anesthesiology 2009

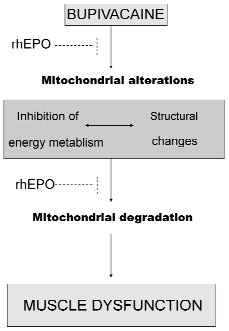
N-acetyl cysteine protects against bupivacaine-induced myotoxicity due to oxidative and sarcoplasmic reticulum stress in human skeletal myotubes

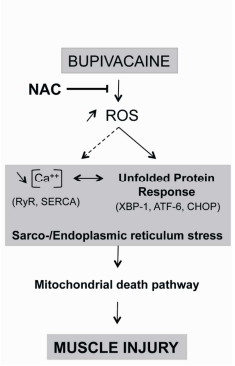
Proteine CHOP
Impliquée dans le stress du RS
Impliquée dans l'apoptose



Galbes Anesthesiology in press

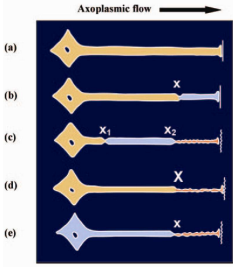
Les mécanismes : nombreux!





Neurologic Complications After Neuraxial Anesthesia or Analgesia in Patients with Preexisting Peripheral Sensorimotor Neuropathy or Diabetic Polyneuropathy

Hebl et col. Anesth Analg 2006;103:1294 –9



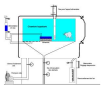
Complications neurologiques permanentes:

Moen 127 (0,008%) pour 1 510 000

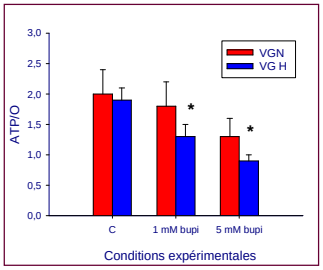
Auroy 12 (0,03%) pour 35439 RachiA et 5561 Péri

Hebl 2 patients (0,4%) pour 567 patients avec neuropathie périphérique préexistante

Hypoxie chronique et Bupivacaïne: Effet potentialisé sur les mitochondries de cœur in vitro



P= 0,5 atm, Durée HC:14j, HTAP+

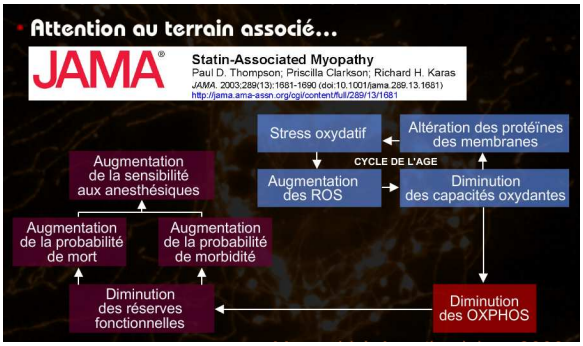


Altération du rendement des oxydations phosphorylantes

Diminution de la synthèse d'ATP

Titrer les doses chez les BPCO ?

Nouette-Gaulain et al. *Anesthesiology 2002; 97:1507–11*

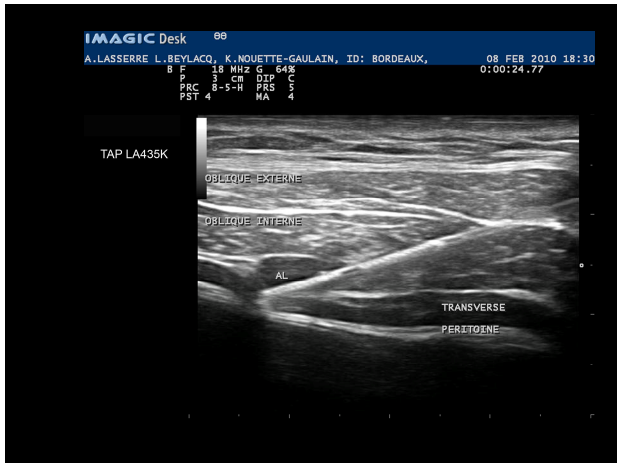


Muravchick Anesthesiology 2006

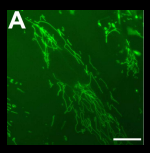
Toxicité locale des AL et Echographie

Pas de preuve, incidence des complications trop faible

- Réduire les doses d'AL….
- Favoriser les techniques ALR nerveuses périphériques
- Éviter les injections intraneurales
- Éviter les injections intramusculaires

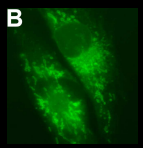


Conclusion

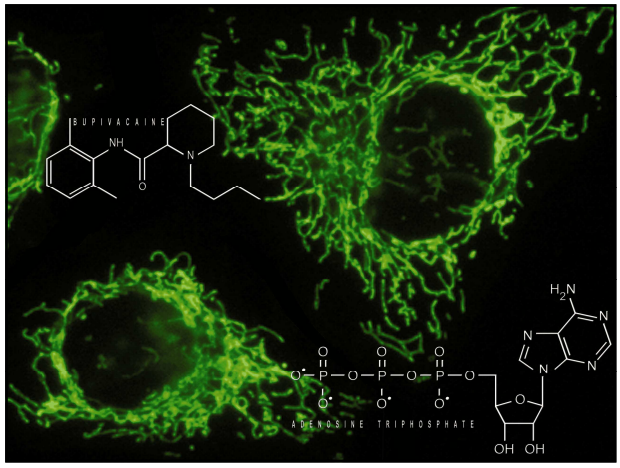


- Toxicité locale des AL
  - Effets cliniques
  - Altérations histologiques et métaboliques associées
  - Effets temps et effet concentration
  - Propriétés pharmacologiques des agents

+

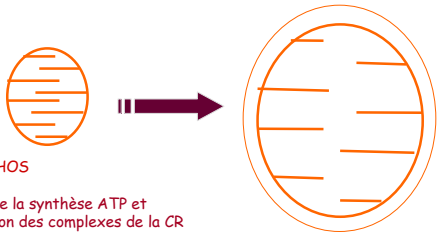


- Particularités du patient et environnement de l'ALR
  - Âge: enfant, *vieillard?*
  - Traitement
    - protection par les anti –oxydants
    - Aggravation par les *statines?*
  - *Altérations physiopathologiques*
    - *Hypoxie chronique, diabète, AOMI, myopathie…*



Mécanismes de toxicité

Bupivacaïne +



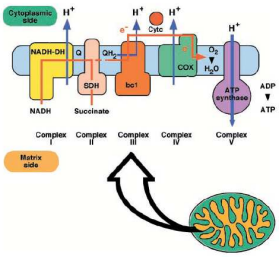
Découplage OXPHOS

Chute de la synthèse ATP et
Inhibition des complexes de la CR

Chute du potentiel de membrane et
Fragmentation du réseau mitochondrial

Probable mitophagie,
Mécanismes de dégradation?
Altération du métabolisme calcique
Apoptose

AL et OXPHOS

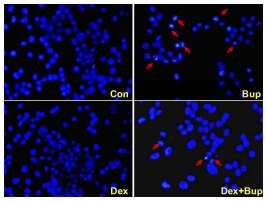


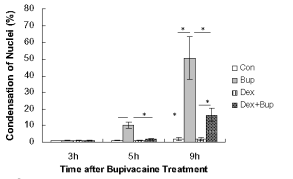
- In Vitro
  - Découplage des OXPHOS
  - Inhibition du Cx I
- In Vivo
  - Inhibition des Cx de la CR
  - Diminution de la synthèse d'ATP
- Facteurs modulateurs
  - Concentration
  - Temps
  - Potentialisation par hypoxie chronique
  - Protection par rhEPO

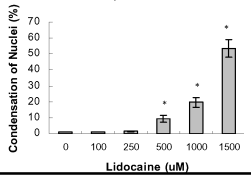
DEXAMETHASONE ATTENUATED BUPIVACAINE-INDUCED NEURON NJURY *IN VITRO* THROUGH A THREONINE–SERINE PROTEIN KINASE B-DEPENDENT MECHANISM

Ma et col. Neuroscience (2009), doi: 10.1016/j.neuroscience.2009.12.049

Bupivacaine 900 µM
Dexamethasone 10 µM 12h avant la bupivacaine







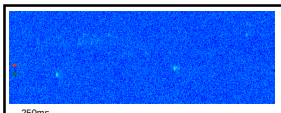
9H

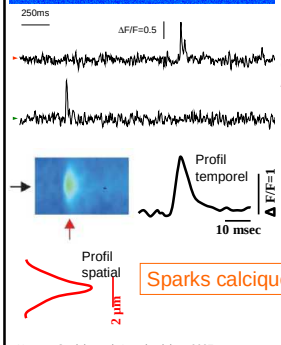
Productions de radicaux libres

Table I. Hydroxyl Radical Levels in Each Group (DHBA/Salicylate)

	BPVC-DMSO (−)	BPVC-DMSO (+)	saline-DMSO (−)	saline-DMSO (+)
2,5-DHBA				
2 hrs	1.566 ± 0.283##	0.710 ± 0.069***	1.230 ± 0.259	0.669 ± 0.093***
7 hrs	5.439 ± 1.218##	1.798 ± 0.222***	4.094 ± 0.869	1.842 ± 0.431***
2 days	4.319 ± 0.903###	3.320 ± 0.408**	2.666 ± 0.547	2.746 ± 0.425
4 days	4.308 ± 0.978#	4.817 ± 1.454	3.294 ± 0.790	3.932 ± 0.716
2,3-DHBA				
2 hrs	0.165 ± 0.064	0.043 ± 0.018***	0.142 ± 0.038	0.070 ± 0.037***
7 hrs	0.398 ± 0.064#	0.097 ± 0.022***	0.342 ± 0.043	0.080 ± 0.013***
2 days	0.293 ± 0.089#	0.153 ± 0.016***	0.233 ± 0.072	0.210 ± 0.092
4 days	0.292 ± 0.047	0.206 ± 0.025***	0.318 ± 0.132	0.219 ± 0.071

Homéostasie calcique





Sparks calciques

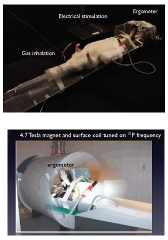
Lévobupivacaïne entraîne des modifications de l'homéostasie calcique *in vivo* :

Augmente la fréquence des sparks
Diminue la charge du RS en calcium
Augmente l'amplitude des sparks

Mécanismes impliqués après exposition aiguë à l'échelon cellulaire?

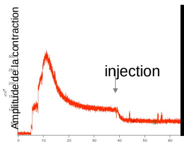
Nouette-Gaulain et al. Anesthesiology 2007

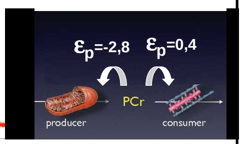
Exploration fonctionnelle in vivo



Effet direct d'une single shot

Effet chronique après 7 injections





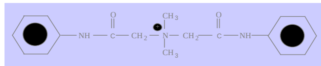
Effet direct sur l 'appareil contractile

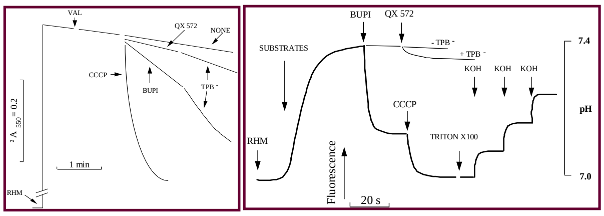
Pas de modification de l'énergétique pour une contraction musculaire modérée

Nouette-Gaulain SFAR 2008 R119

Effet protonophore de la bupivacaïne

Comparaison Bupivacaine / QX572

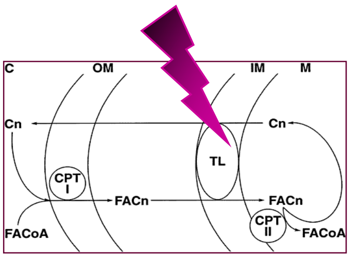




Schönfeld P. FEBS 1992,304 :273-276

Métabolisme des acides gras

Inhibition de la carnitine-acylcarnitine translocase



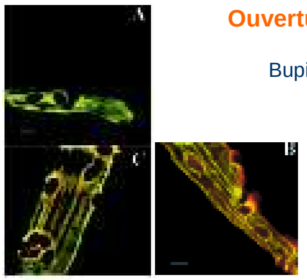
-Acides gras :
Substrat préférentiel énergétique du cœur

-Toxicité cardiaque décrite chez l'homme

IC 50 de la bupi : 0,26 mM

Weinberg G. Anesthesiology 1998, 92 :253-8

Apoptose et AL



CsA + Bupi   Bupi

Ouverture du PTP

Bupivacaïne 1mM

Redistribution du cytochrome c

Cyclosporine A

Effet préventif

Irwin W. JBC 2002, (277)14 : 12221-27