

*avec AstraZeneca et Abbott
pour des formations académiques
liens d'intérêt*

Toxicité systémique des anesthésiques locaux

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JARP

Juin 2014

Toxicité systémique

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Anesthesiology

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Anesthesiology
51:285-287, 1979

Première description: Albright Editorial Views

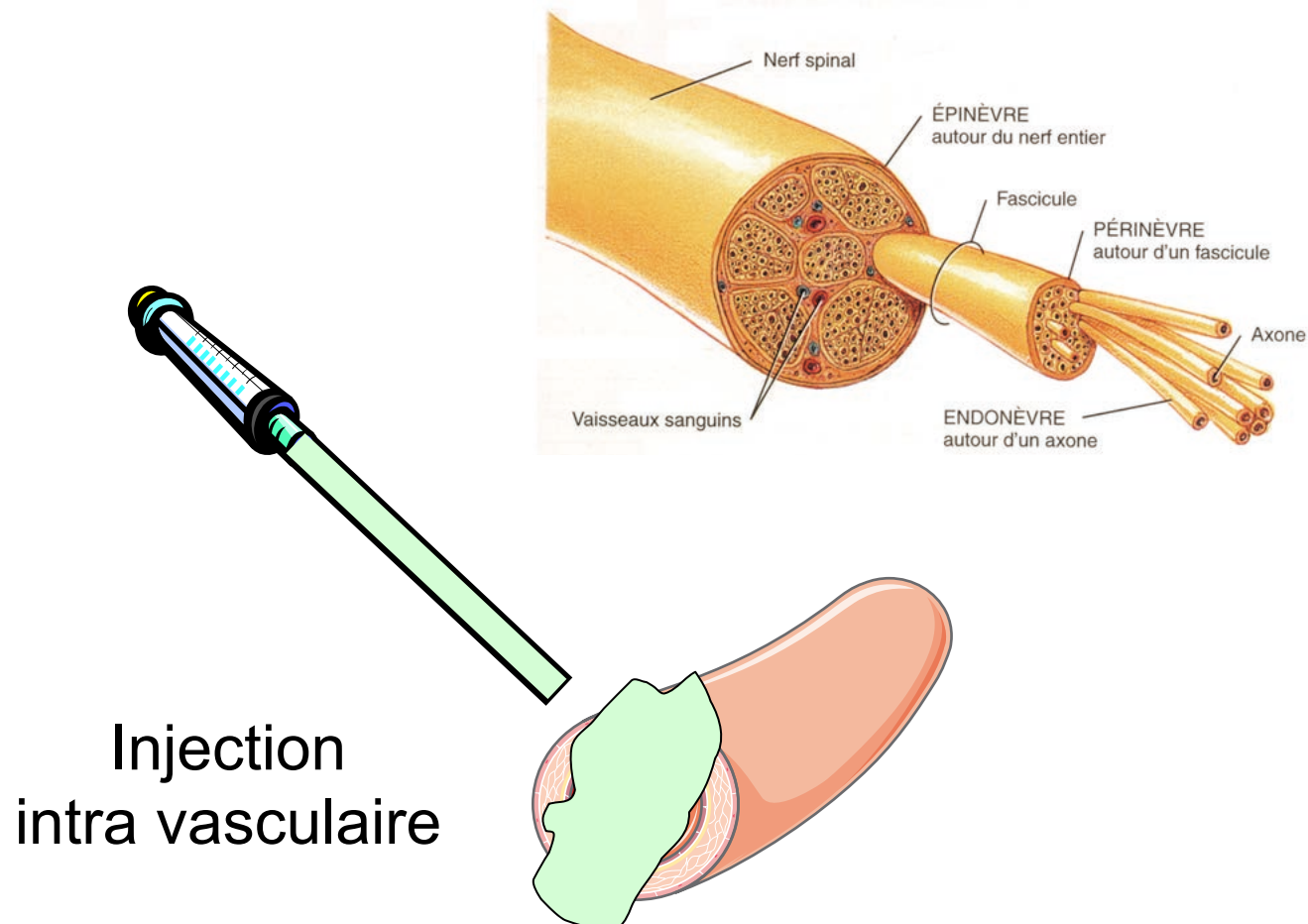
*Cardiac Arrest Following Regional Anesthesia
with Etidocaine or Bupivacaine*

Technique	Seizures	Cardiac Arrest
Peripheral nerve block	4.9/10,000	0,54/10,000
Epidural	1.3/10,000	0.57/10,000

Mitchell ME. Local anesthetic toxic effects.
In: Atlee JL (ed.). Complications in Anesthesia. 2008

Toxicité systémique

élévation rapide et importante de la concentration plasmatique de la fraction libre des AL



Injection intravasculaire



TABLE 5. Immediate and Delayed Complications According to Nerve Localization Technique

Complication	Nerve Localization Technique			Total (n = 8189)
	Nerve Stimulation (n = 2507)	Ultrasound (n = 5141)	Other (n = 541)	
Local anesthetic toxicity	1.2 (0.25–3.5)	0.8 (0.2–2.0)*	1.8 (0.05–10.3)	0.98 (0.42–1.9)
Unintentional vascular puncture†	13.9 (8.2–21.9)	5.1 (3.0–8.1)‡	2.3 (0.06–12.8)	7.2 (5.1–10.0)
Unintended paresthesia†	10.8 (5.9–18.1)	20.5 (15.9–25.9)*	2.3 (0.06–12.8)	16.8 (13.4–20.8)
Late neurologic deficit	0.8 (0.1–2.9)	0.2 (0.005–1.1)*	—	0.4 (0.08–1.1)
Long-term neurologic deficit	0.4 (0.01–2.2)	0.2 (0.05–1.1)*	—	0.2 (0.03–0.9)

Data are presented as n/1000 (95% CI) procedures.

Ultrasound includes ultrasound used as the sole technology and combined ultrasound and nerve stimulation. *Other* comprises techniques not using nerve stimulation or ultrasound technology.

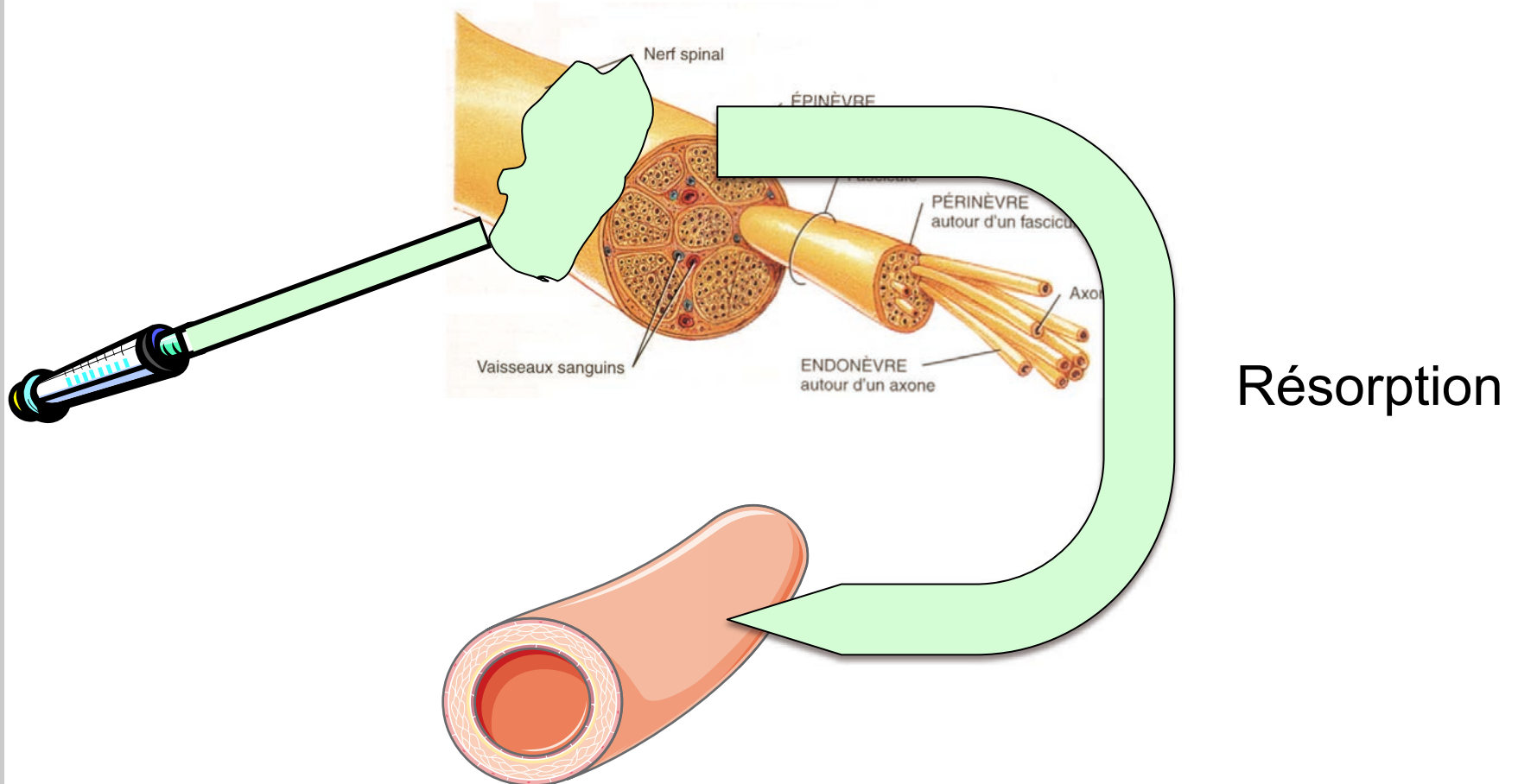
*Not statistically significant.

†Reduced total cohort (n = 4991), for nerve stimulation (n = 1297), ultrasound (n = 3260), and other (n = 434).

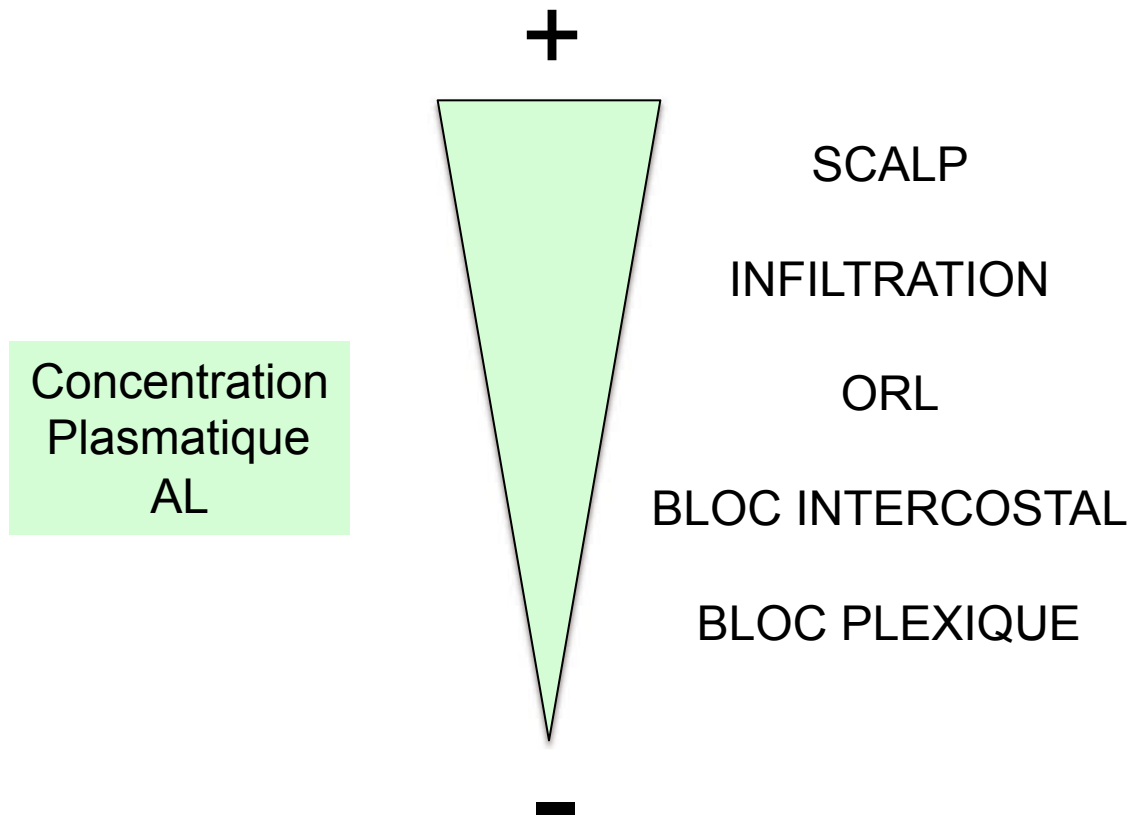
‡Indicates a statistically significant difference ($P = 0.001$; Poisson regression) between ultrasound and nerve stimulation and other techniques.

Toxicité systémique

élévation rapide et importante de la concentration plasmatique de la fraction libre des AL



Résorption



Conférence d'experts 2002
Pratique des AL et ALR par des médecins non spécialisés en
anesthésie-réanimation

Prévention de la toxicité systémique

Agent	Bloc au membre supérieur	Bloc au membre inférieur
lidocaïne adrénalinée	500 mg	700 mg
Mépivacaïne	400 mg	400 mg
bupivacaïne adrénalinée	150 mg	180 mg
Ropivacaïne	225 mg	300 mg

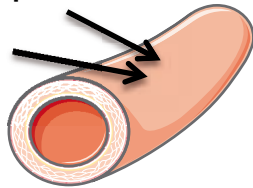
13.7.1 L'intervalle de temps entre deux injections successives ne doit pas être inférieur au tiers de la demi-vie de l'agent considéré, soit 30 minutes pour la lidocaïne, la prilocaïne et la mépivacaïne, et 45 minutes pour la bupivacaïne, l'étidocaïne et la ropivacaïne (consensus professionnel).

13.7.2 La dose utilisée pour la deuxième injection doit correspondre au plus, au tiers de la dose initiale maximale autorisée après le temps précité, ou à la moitié de cette dose après 60 et 90 minutes respectivement (consensus professionnel).

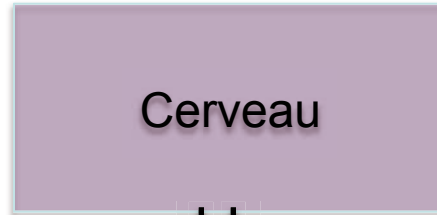
Pharmacocinétique

α 1-glycoprotéine acide

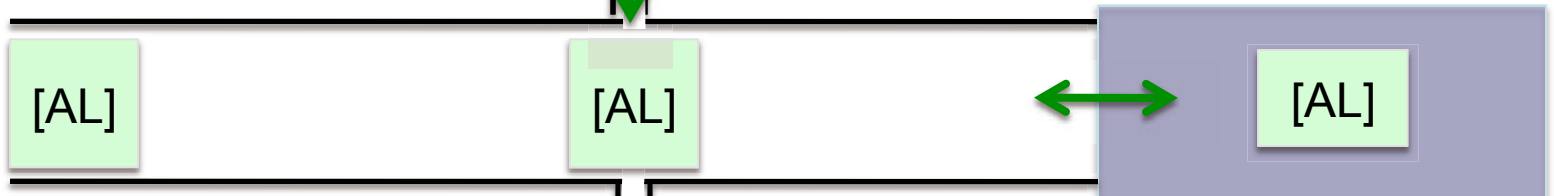
albumine



intravasculaire

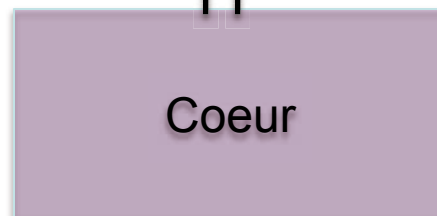


Organes faiblement perfusés

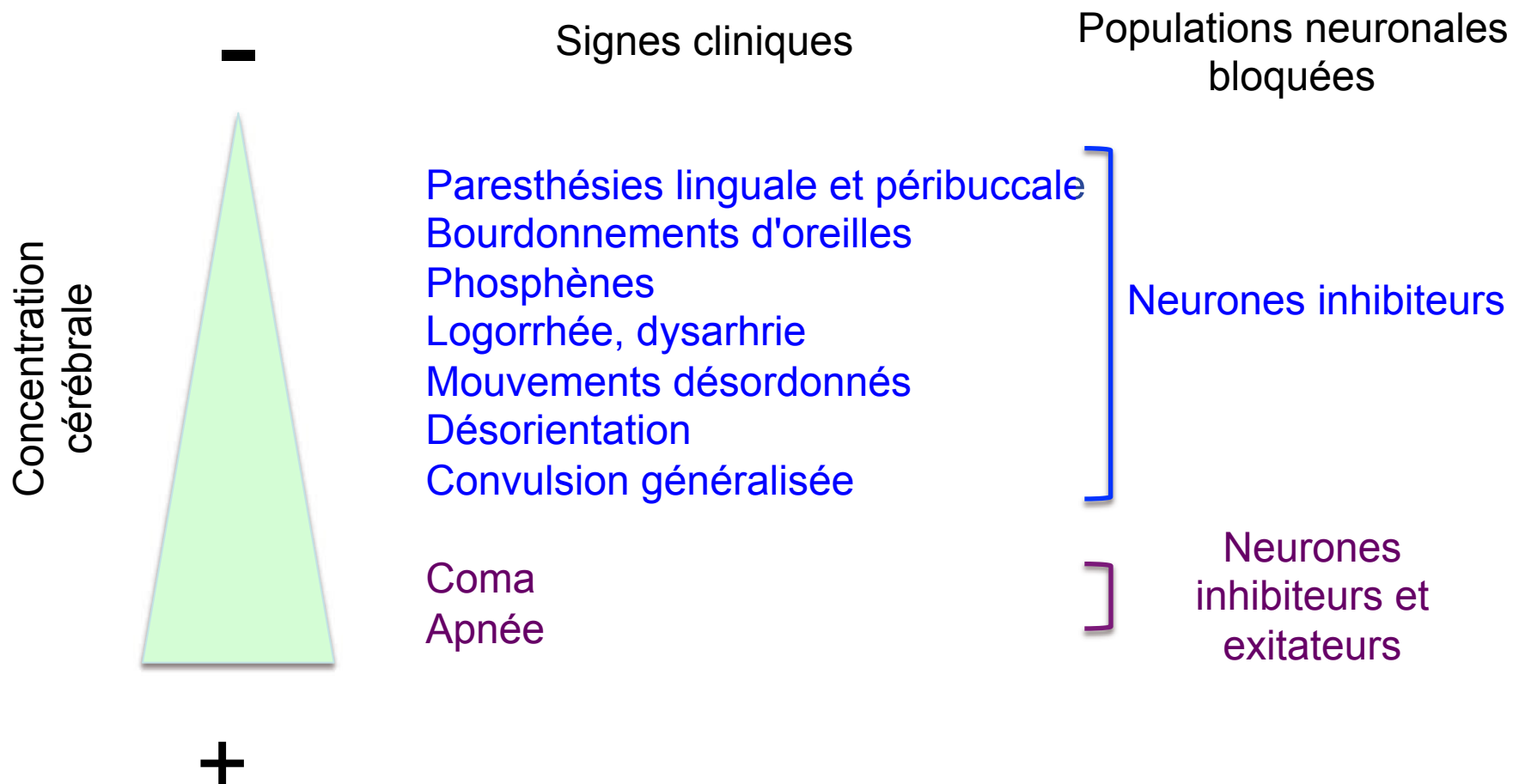


Compartiment central

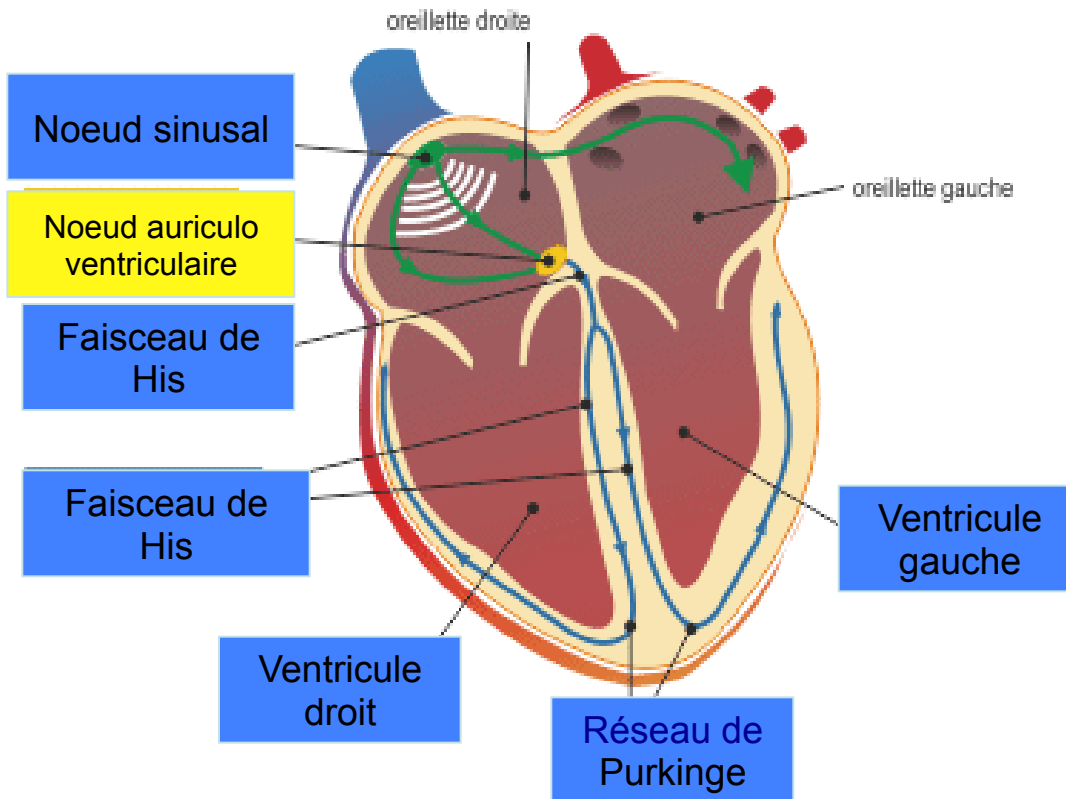
[AL] Fraction libre



Toxicité neurologique



Toxicité cardiaque

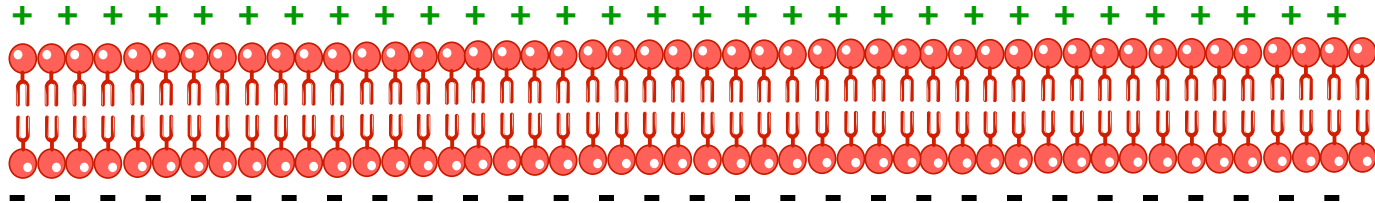


Conduction cardiaque

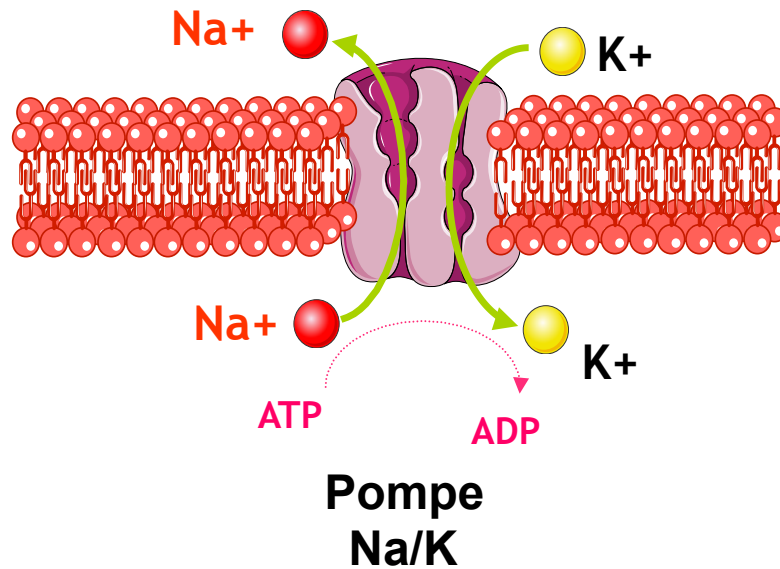
Canal sodique

Canal calcique

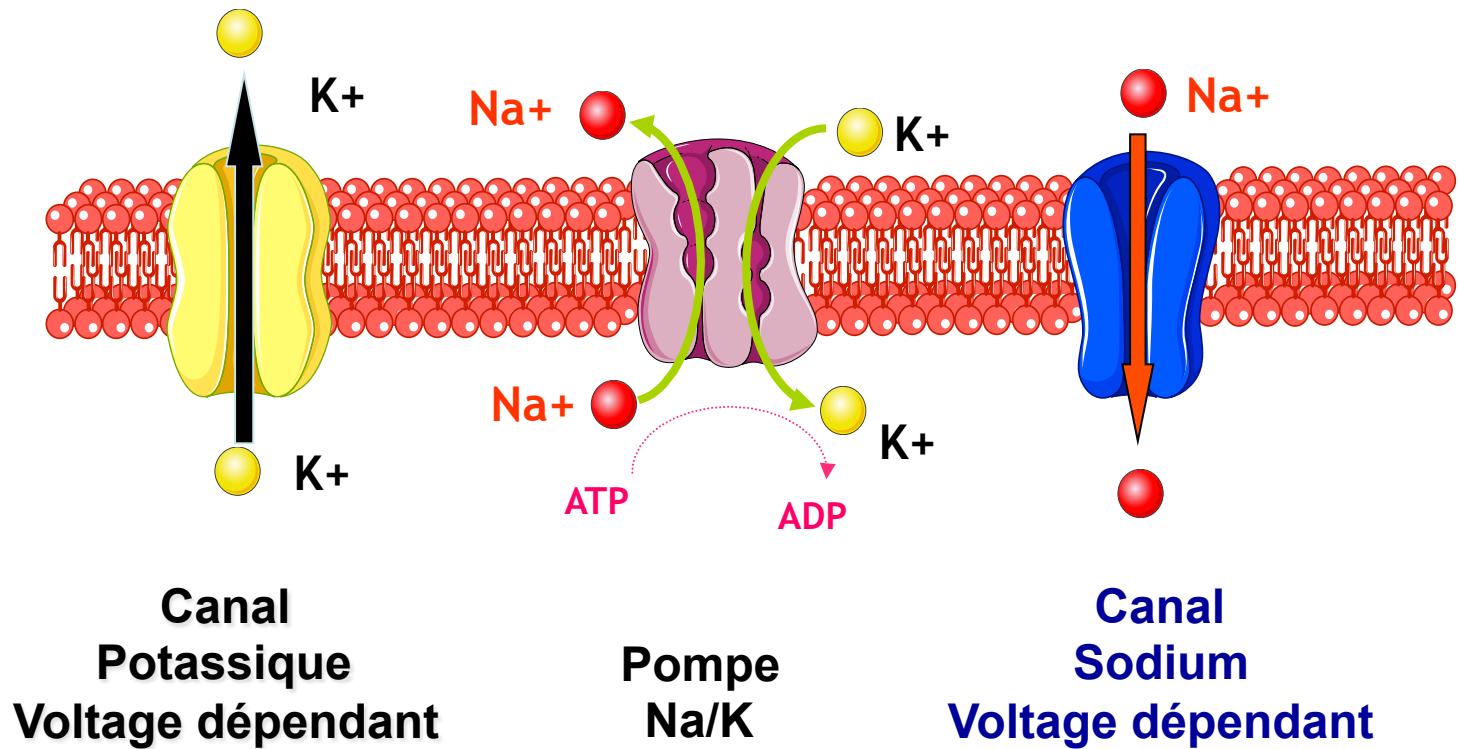
Potentiel de Repos



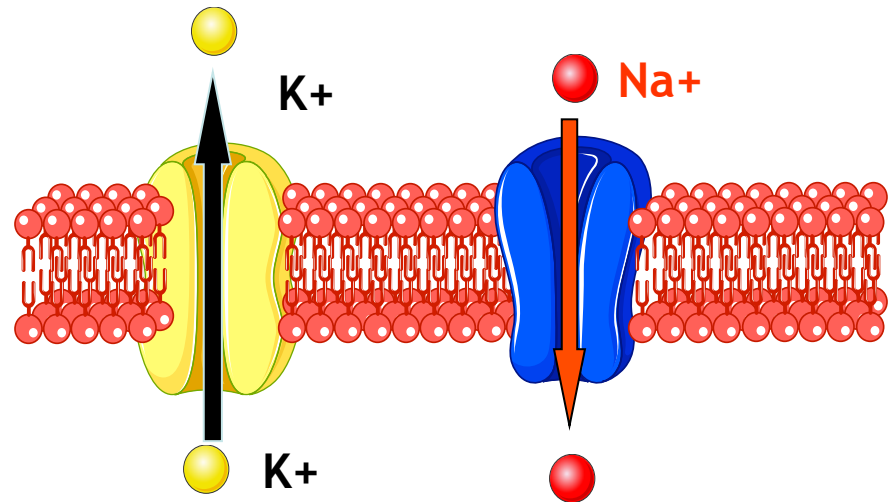
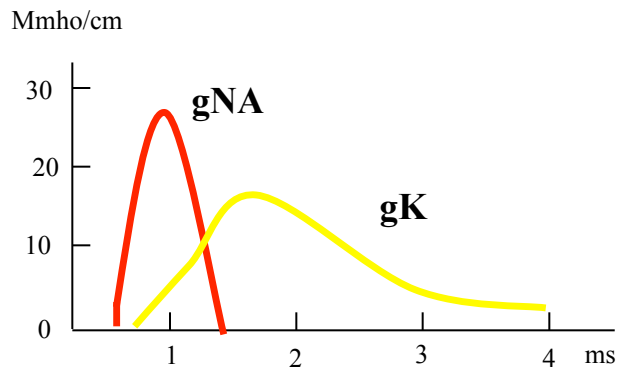
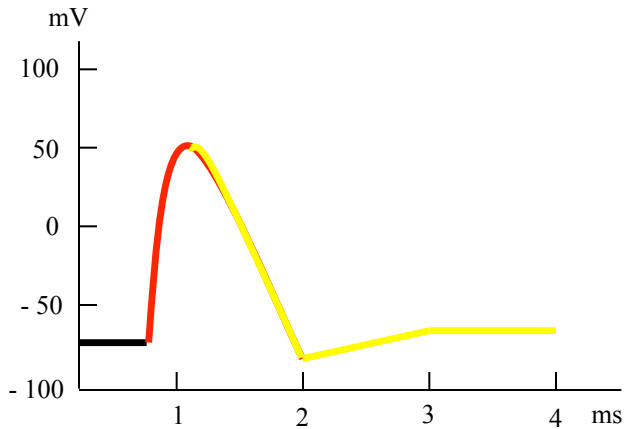
Potentiel de Repos



Potentiel d'action

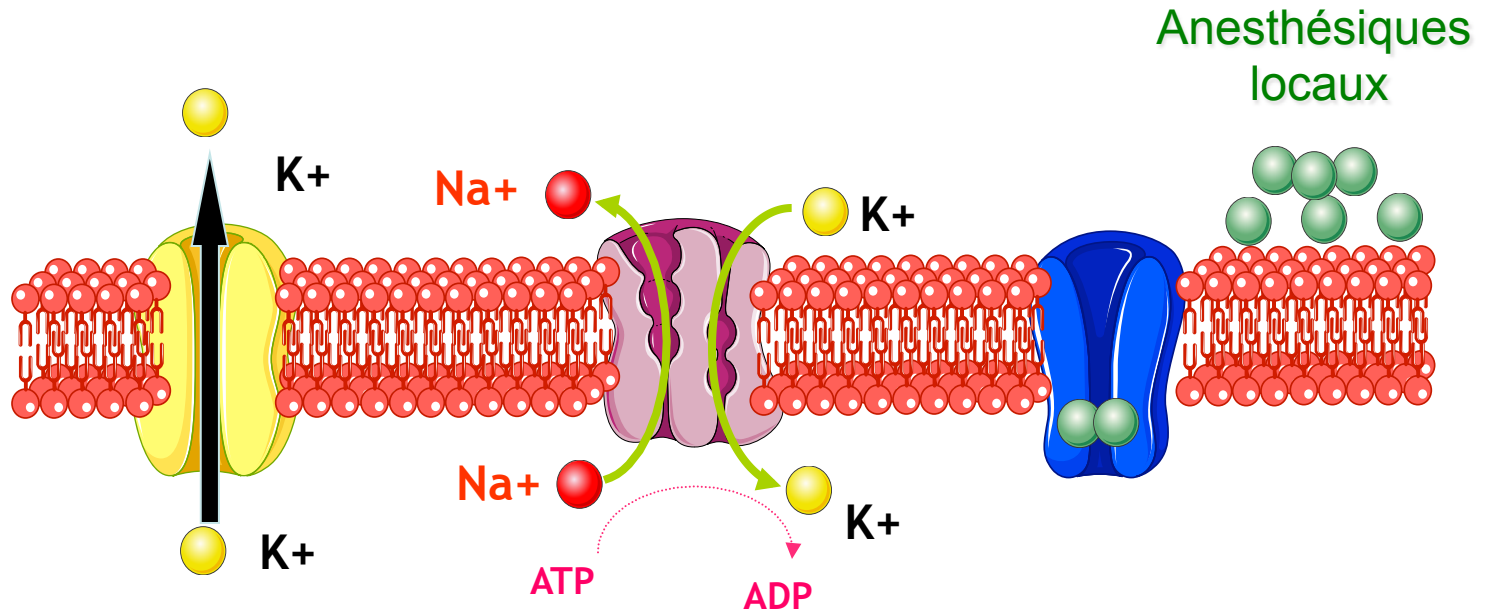


Potentiel d'action

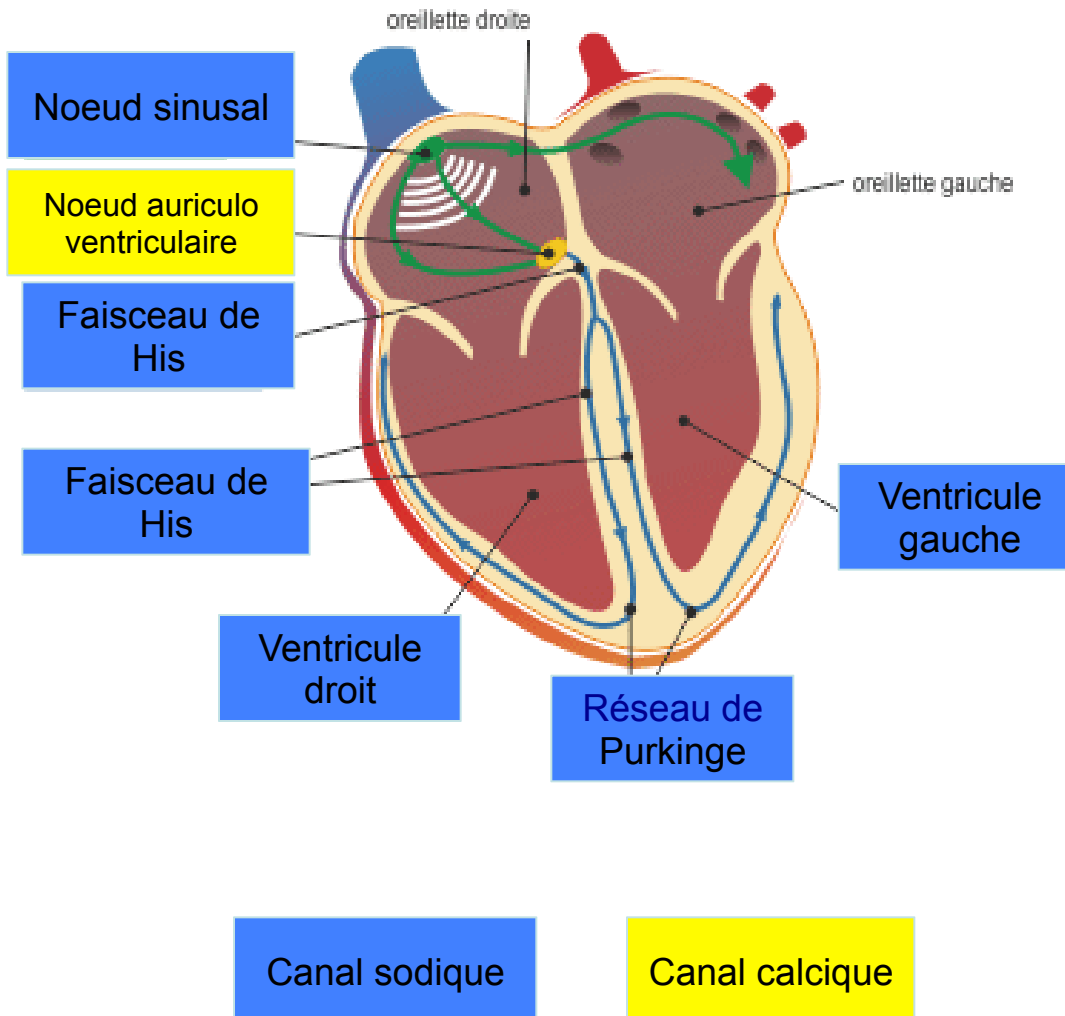


Hodgkin et Huxley
Prix Nobel 1963

Mécanisme d'action



Toxicité cardiaque



- Conduction

- Ralentissement des vitesses de conduction intraventriculaire

- Blocs fonctionnels de conduction, facilitent la survenue de tachycardies ventriculaires par réentrée

- Contractilité

Recommandations professionnelles



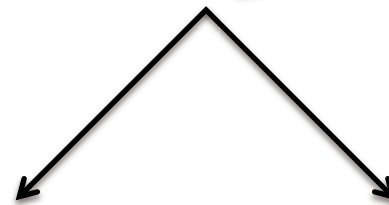
Françaises

2010

Internationales

ASRA Practice Advisory on Local
Anesthetic Systemic Toxicity

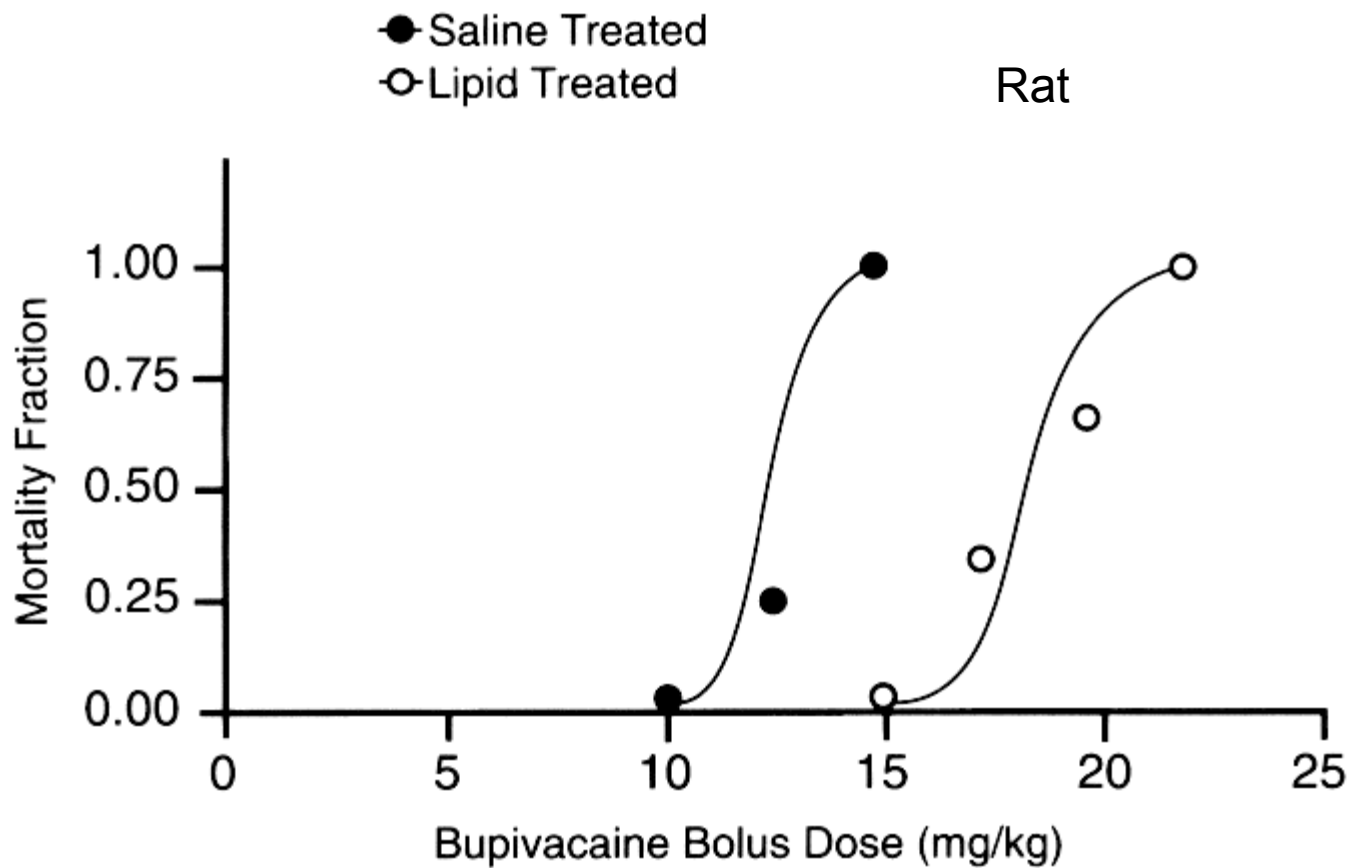
RAPM 2010, 2012



Intralipides

Adrénaline
(faibles posologies)

Intralipides



Wenbeirg *et al.* Anesthesiology 1998

Intralipides

REVIEW

Lipid emulsions in the treatment of acute poisoning:
a systematic review of human and animal studies

Modèles murins +
Chiens +
Cochon -

Jamaty *et al.*,
Clinical Toxicology 2010

Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient
after a Presumed Bupivacaine-related Cardiac Arrest

Meg A. Rosenblatt, M.D.,* Mark Abel, M.D.,† Gregory W. Fischer, M.D.,† Chad J. Itzkovich, M.D.,‡ James B. Eisenkraft, M.D.§

Anesthesiology 2006

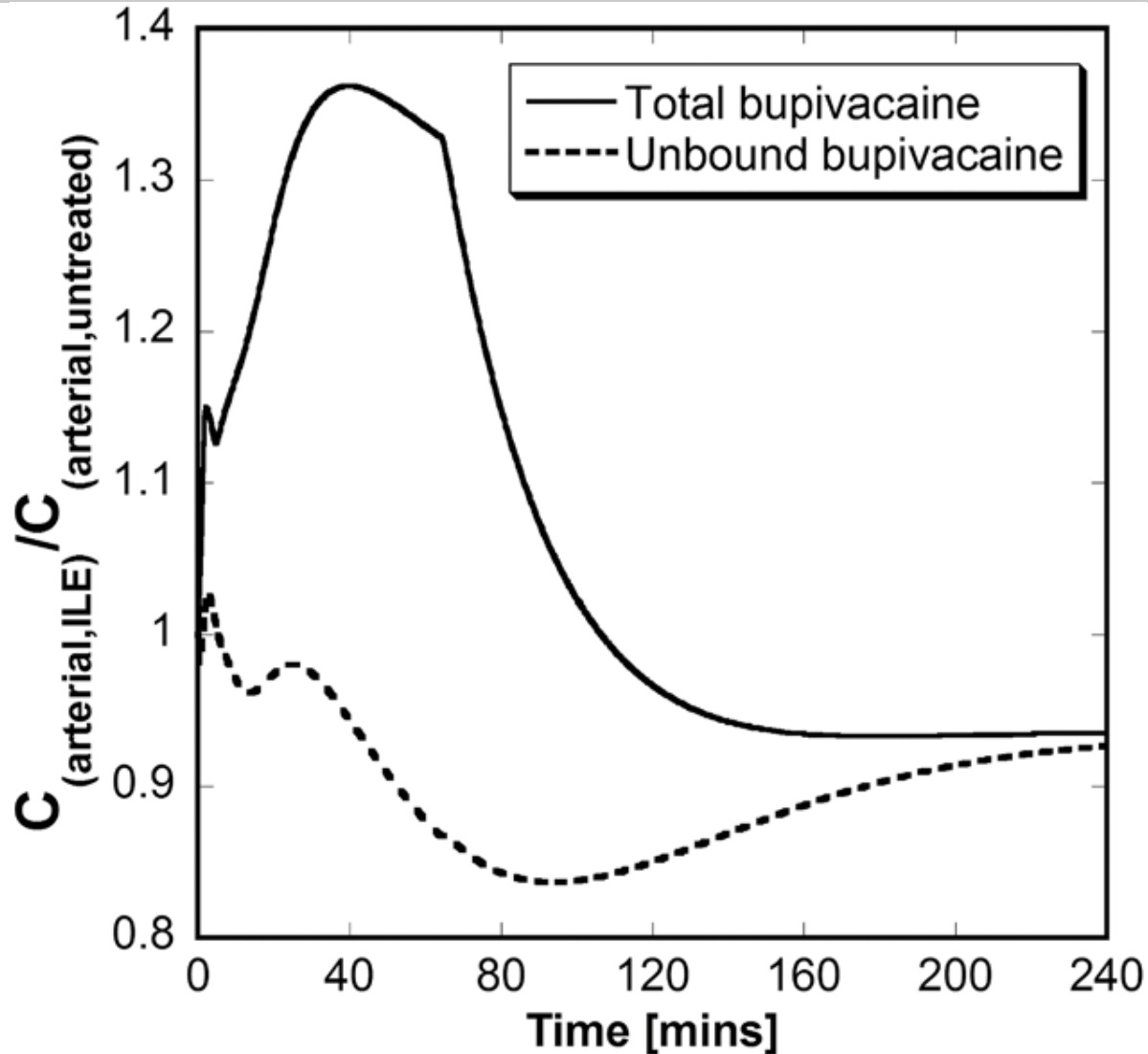
Plus d'une quarantaine de cas cliniques décrivant l'efficacité des Intralipides

Piège lipidique

Compartment	AUC _{tissue} (µM·min)		AUC Reduction due to Therapy	Acute Reduction in Tissue Concentration of Bupivacaine (Time following Initiation of Therapy)
	Untreated	Intralipid Therapy		
Blood (arterial)	559	608	—	—
Lungs	559	609	4%	4% (14 min)
Gut	1,074	998	7%	16% (10 min)
Pancreas	1,111	1,027	8%	17% (11 min)
Spleen	430	413	4%	7% (2 min)
Heart	546	518	5%	11% (3 min)
Muscle	313	277	11%	—
Adipose	1,438	1,392	3%	—
Kidney	695	670	4%	4% (13 min)
Skin	1,181	1,044	12%	—
Brain	969	892	8%	18% (15 min)
Bones	358	316	12%	—
Liver	275	275	0%	—

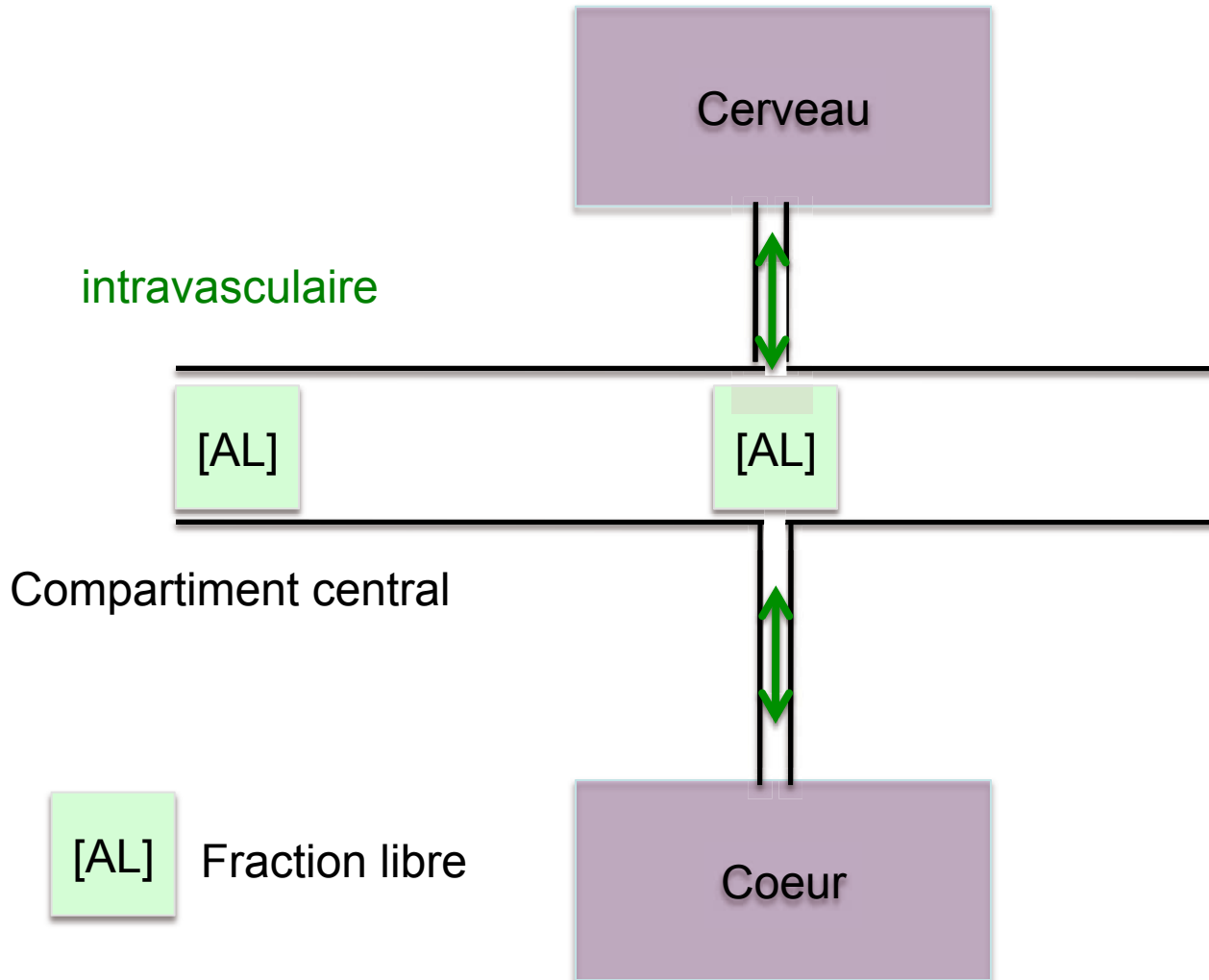
Modélisation

Piège lipidique

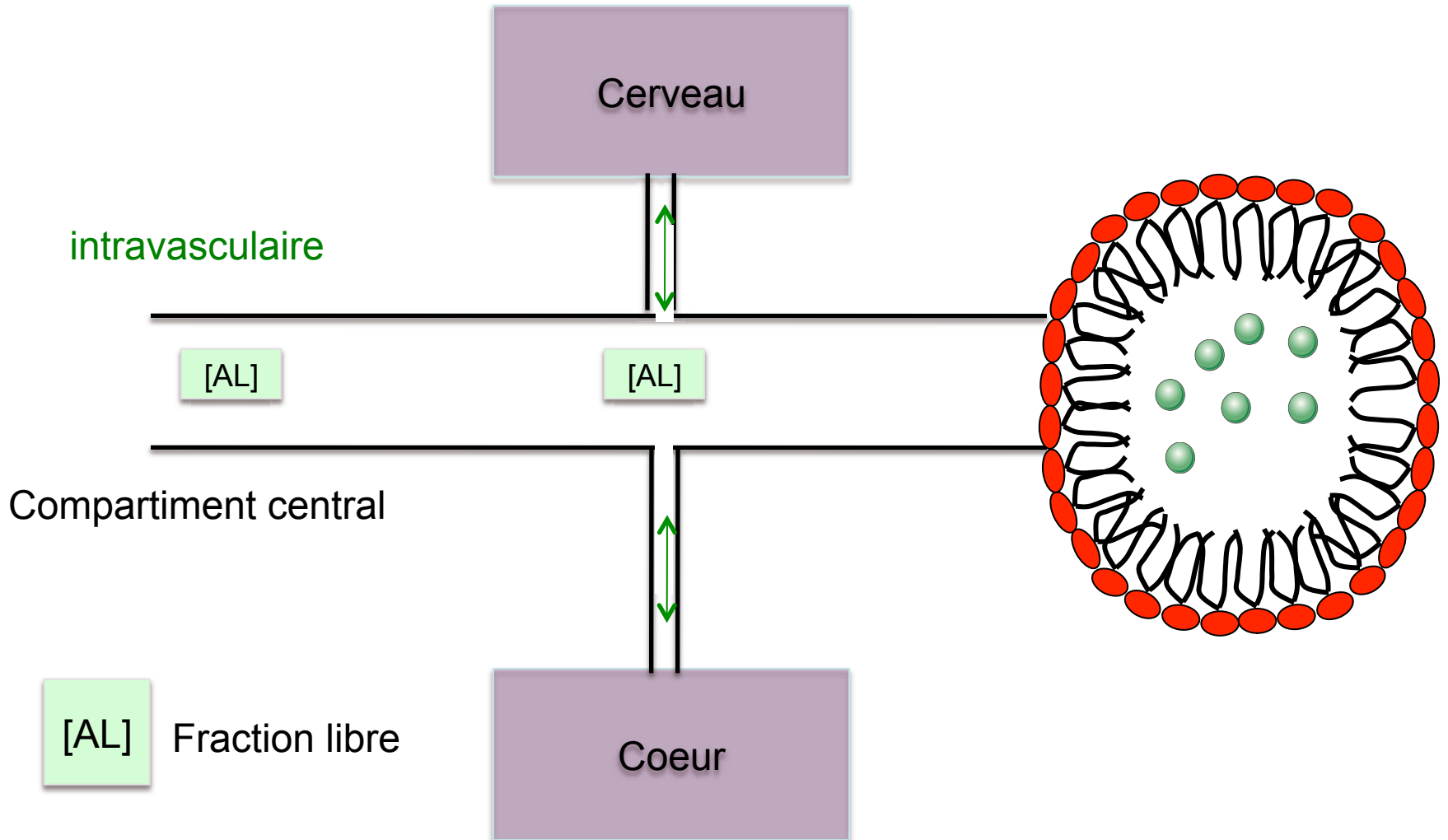


Modélisation

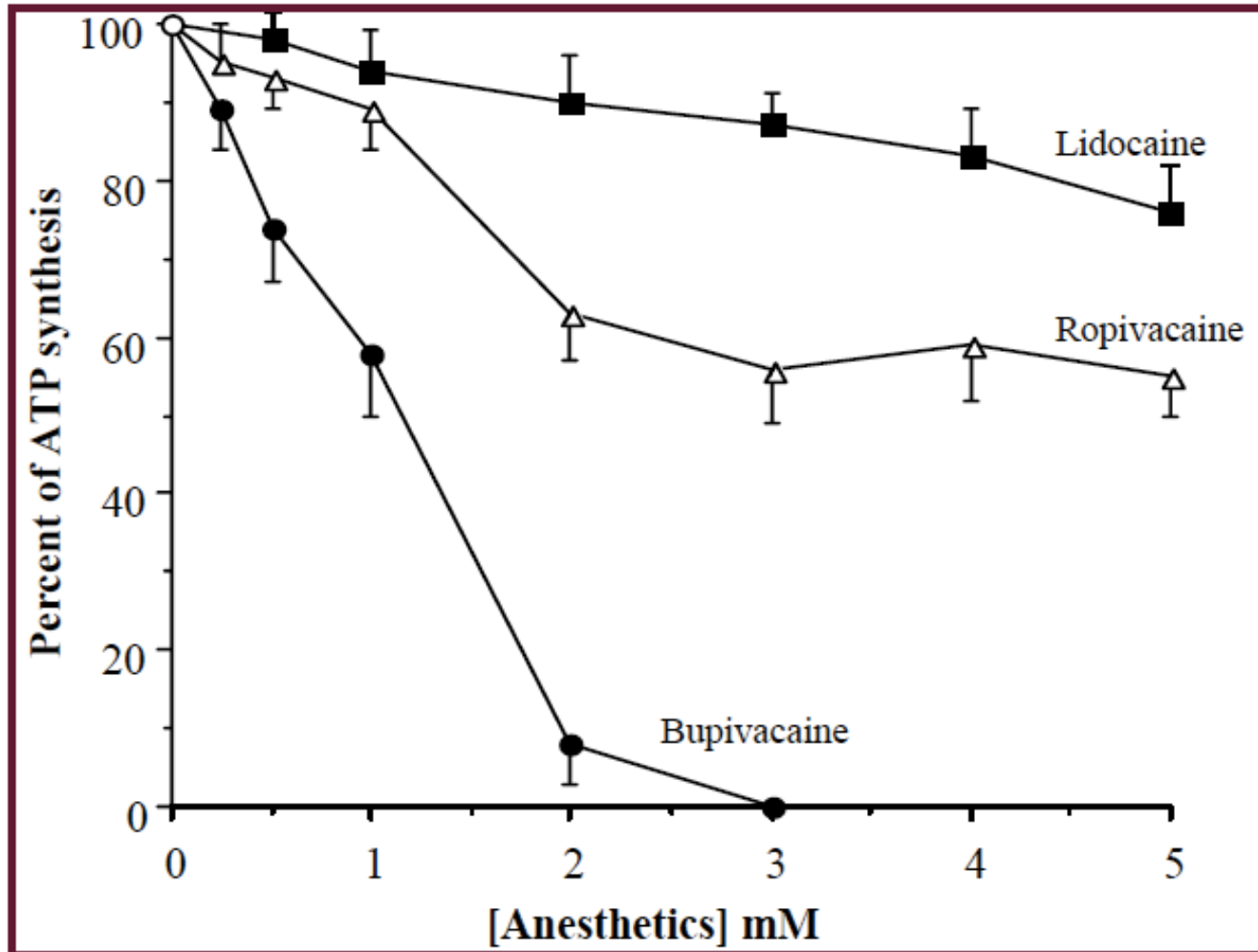
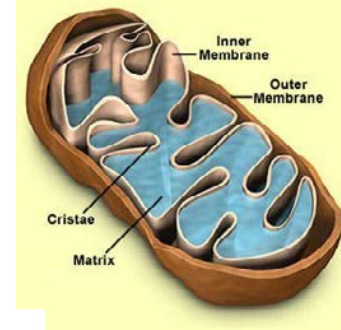
Piège lipidique



Piège lipidique



Toxicité mitochondriale

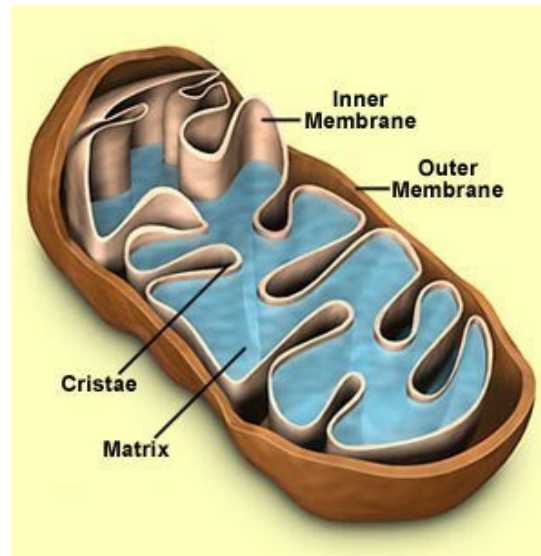
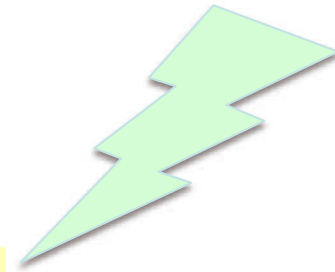
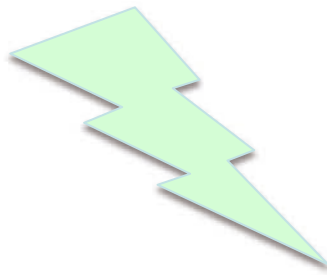


Mécanismes toxicité mitochondriale

Découplant de membrane

AL

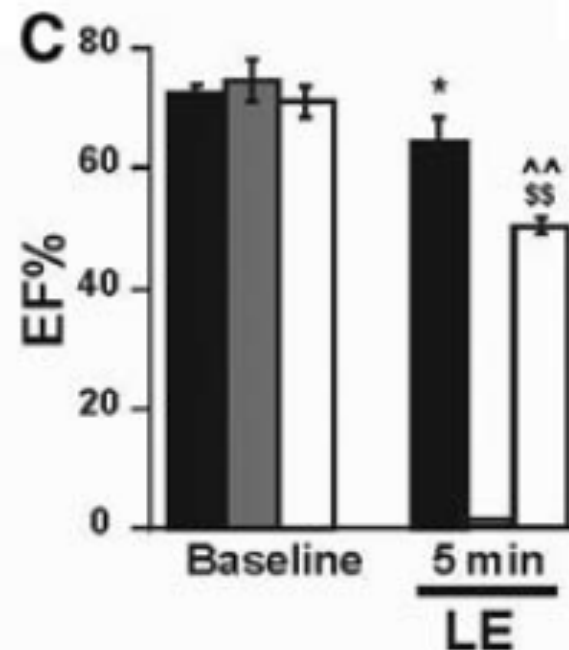
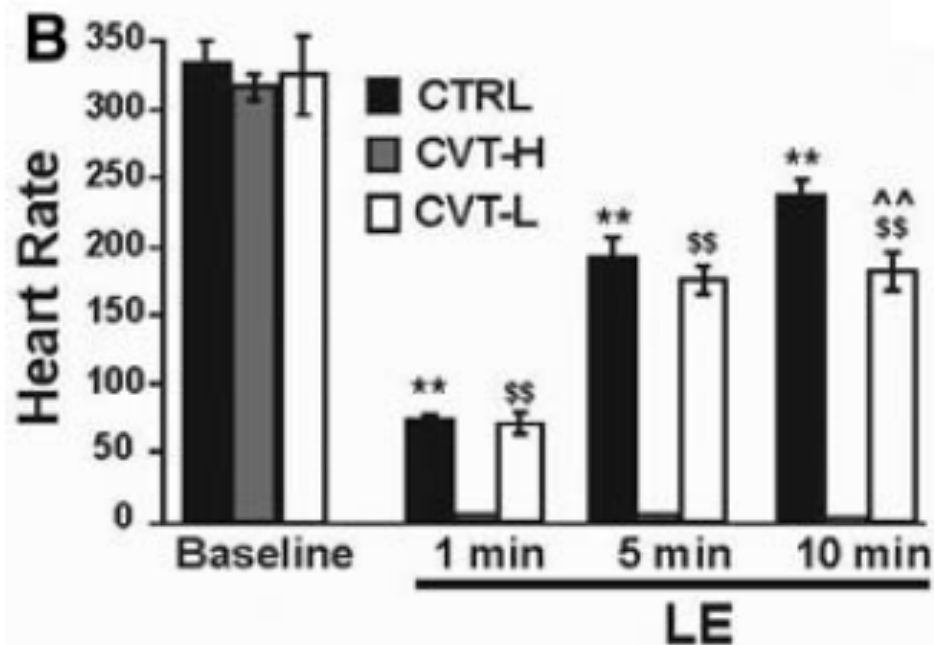
Inhibe transport des acides gras



Métabolisme cellulaire

Modèle murin d'arrêt cardiaque induit par administration de bupivacaïne
CVT: inhibiteur de l'oxydation mitochondriale des acides gras

LE: intralipides 20%

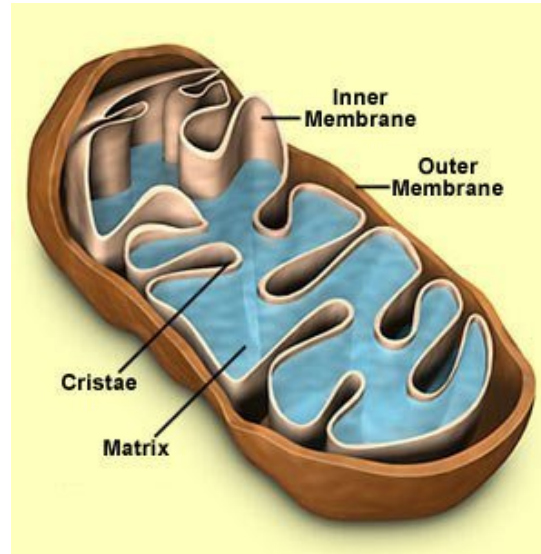
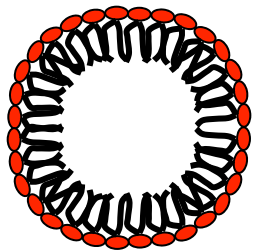


Intralipides et mitochondrie

Inhibe transport des acides gras

Découplant de membrane

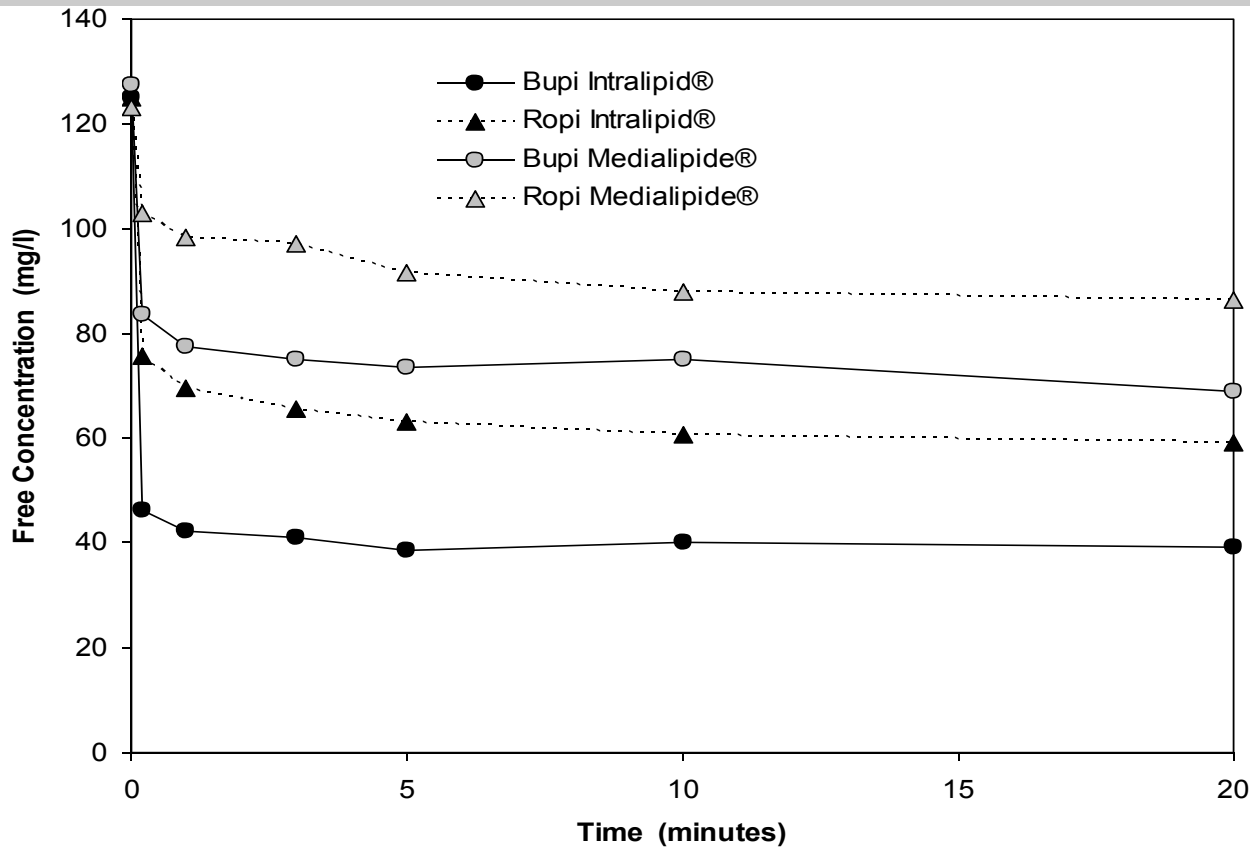
métabolisme acides gras



Sther *et al.*, Anest Analg 2002

Partownavid *et al.* Critical Care Med 2012

Type Intralipides



Rat

Mazoit *et al.*,
Anesthesiology 2009

	Intralipid® 2%	Lipofundine® 2%
Mepivacaïne	4,7 %	7,3 %
Ropivacaïne	16,5 %	25,8%
Bupivacaïne	22,3%	34,7%

In Vitro Plasma humain

Ruan *et al.*,
Anesthesiology 2012

Dose Intralipides

Rat IL 20%

TABLE 1. Triglycerides and Lipid Dose

	20 mg/kg	40 mg/kg	60 mg/kg	80 mg/kg	60 mg/kg	80 mg/kg	60 mg/kg	40 mg/kg	60 mg/kg
Baseline	67	65	142	53	81	86	162	62	106
30 min	2395	5920	9150	9760	8525	6845	7445	8180	6310
48 hr	66	64	68	Died	60	Died	Died	60	68

Hiller *et al.*, RAPM 2010

Lipid Emulsion Infusion

Resuscitation for Local Anesthetic and Other Drug Overdose

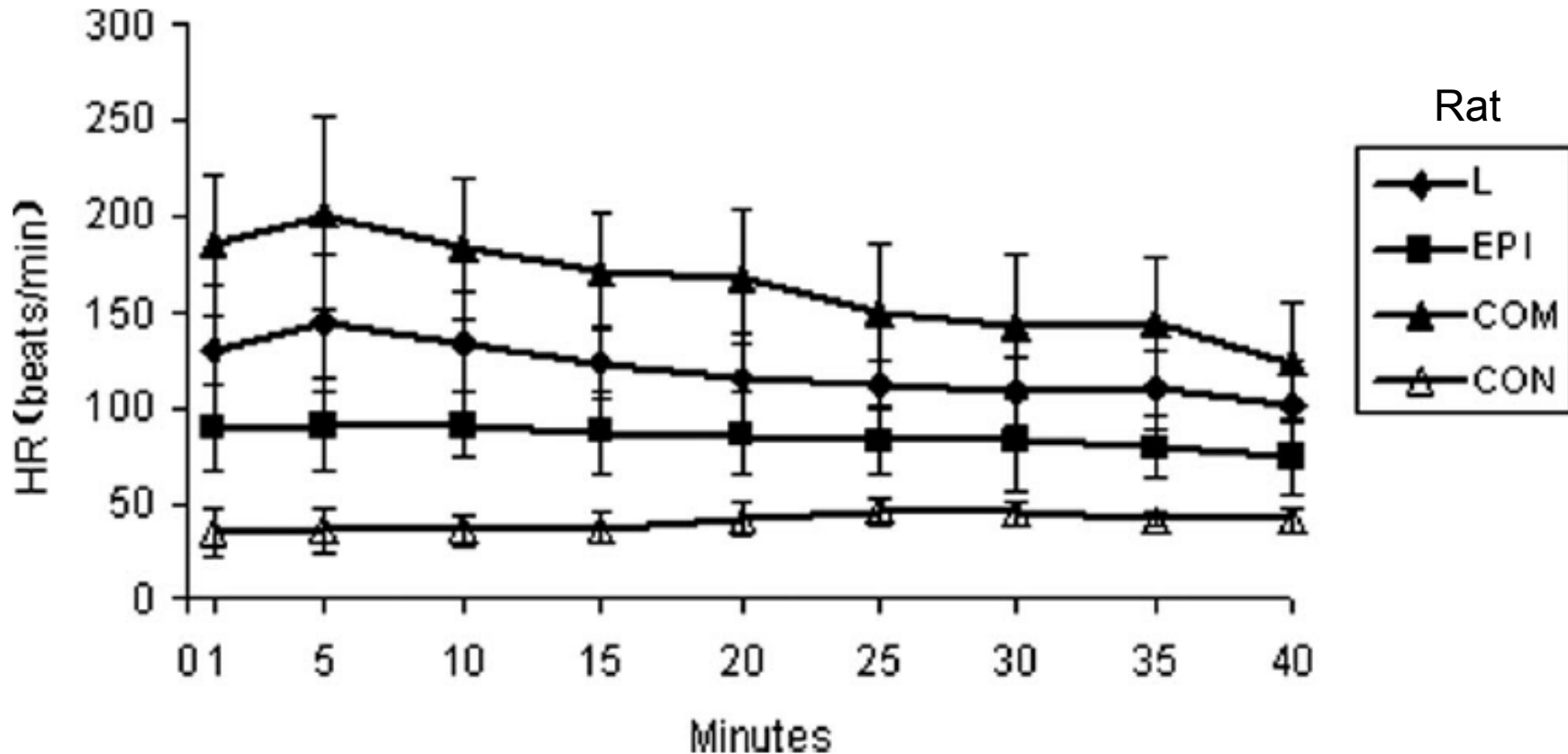
Weinberg *et al.*, Anesthesiology 2012

2 Cas cliniques

Hypertriglycémie et augmentation amylasémie sans pancréatite

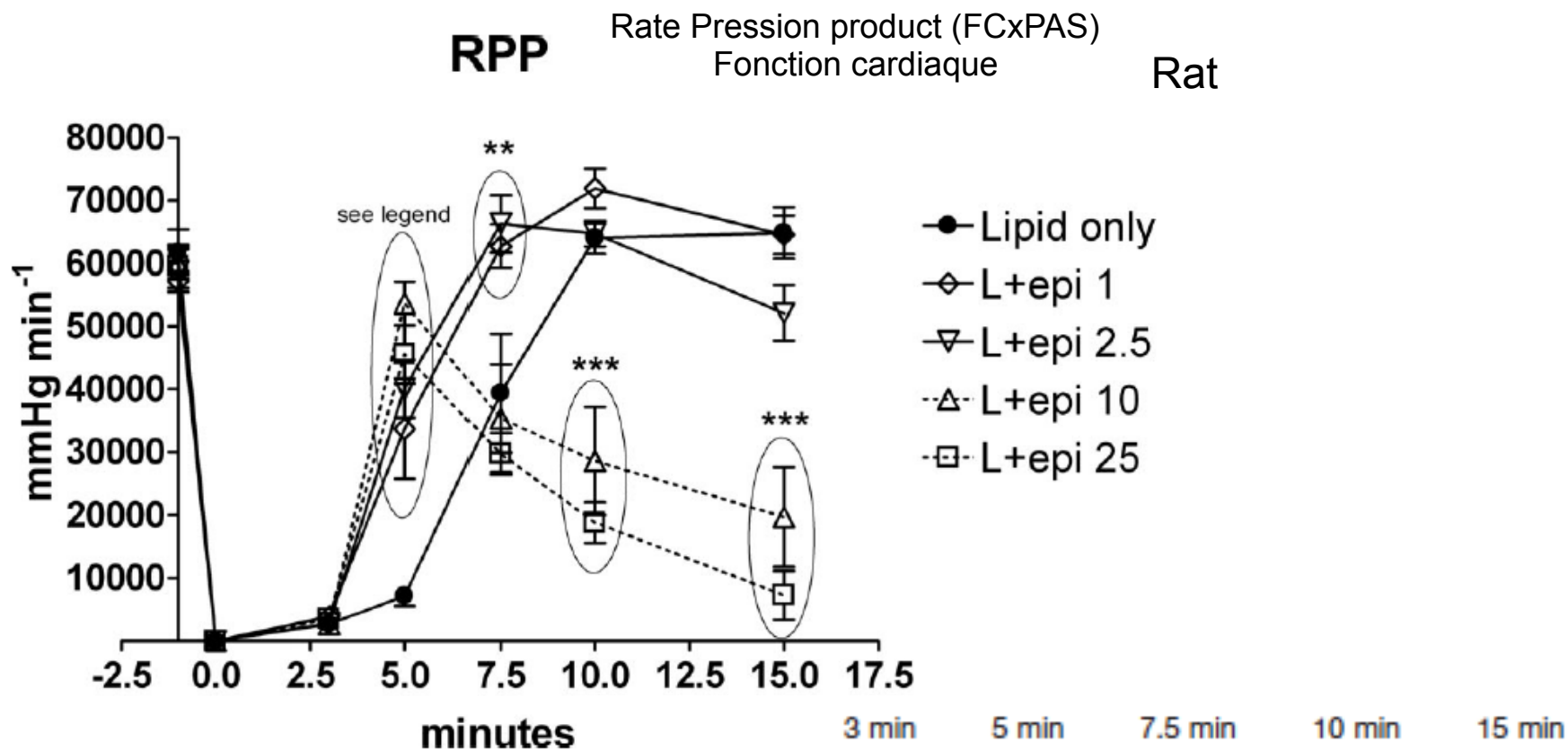
Dose maximale 10 ml/kg dans la première ½ heure

Adrénaline et intralipides



Chronotropisme
Inotropisme

Dose Adrénaline

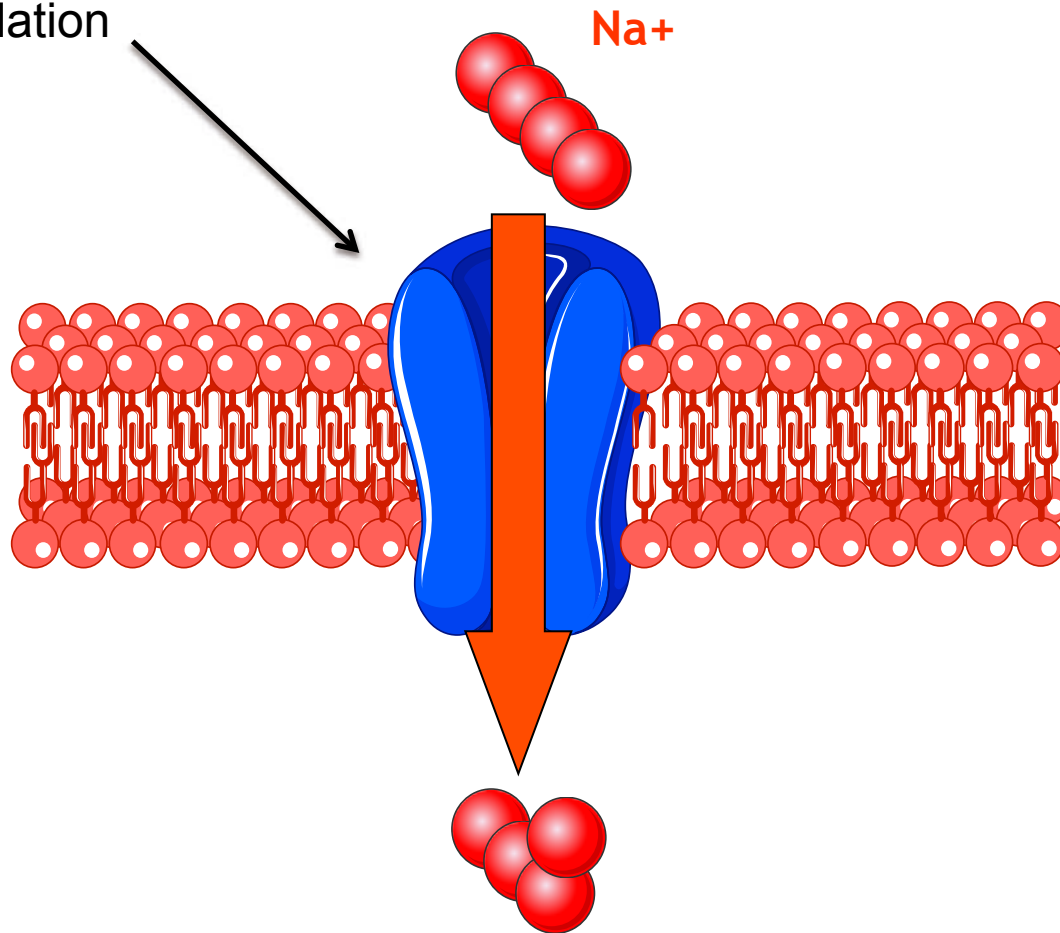


Hiller *et al.*,
Anesthesiology 2009

Saline	0	0	0	0	1
Lipid control	0	0	4	5	5
1 mcg/kg	0	4	5	5	5
2.5 mcg/kg	0	5	5	5	5
10 mcg/kg	0	5	4	3	3
25 mcg/kg	0	5	5	3	1

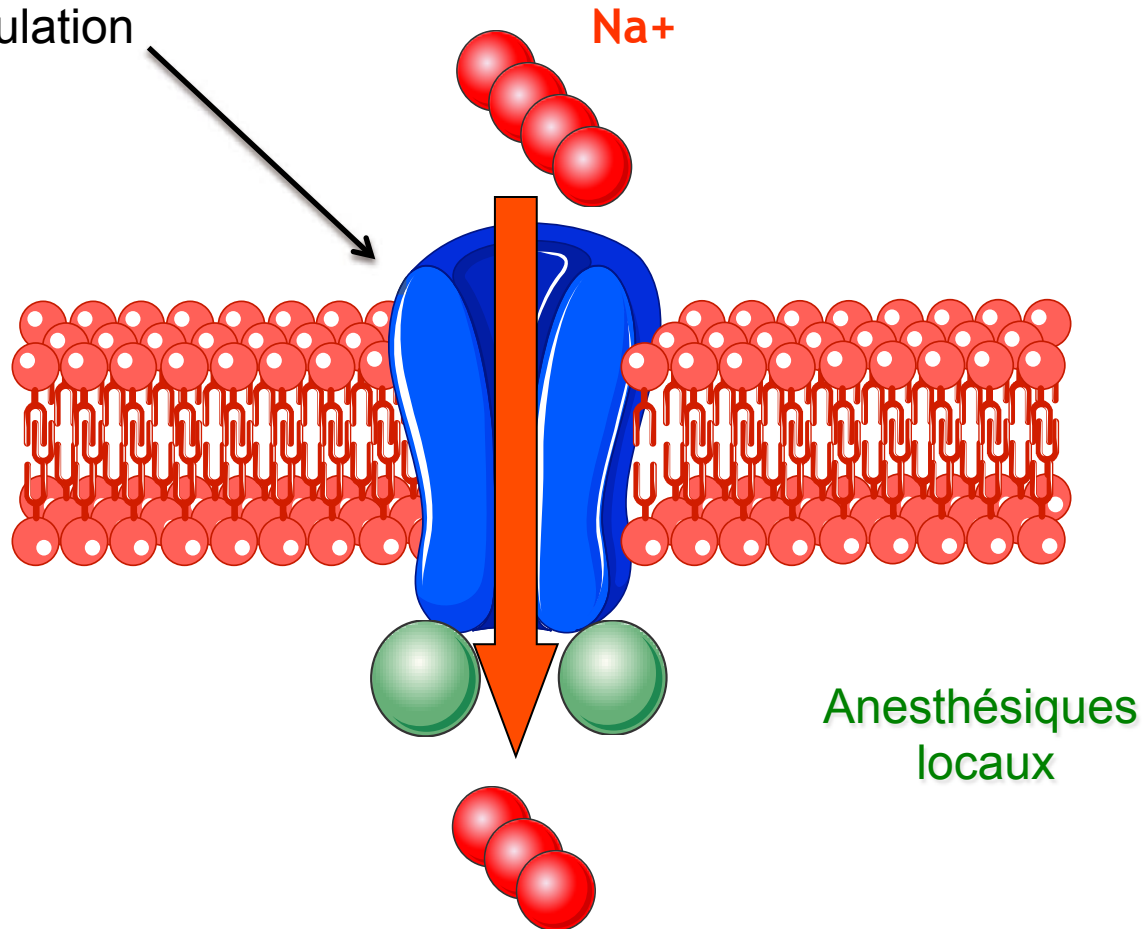
Use dependance ou bloc phasique

Stimulation



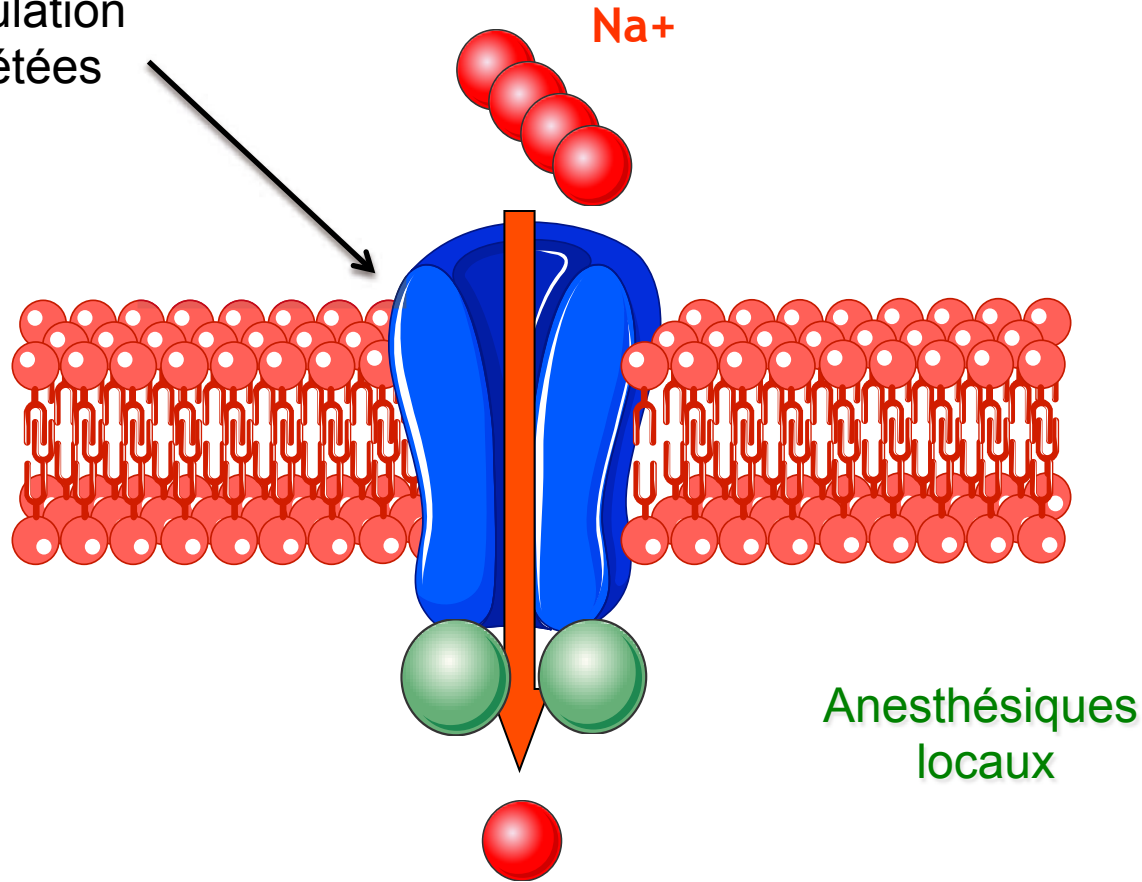
Use dependance ou bloc phasique

1 stimulation



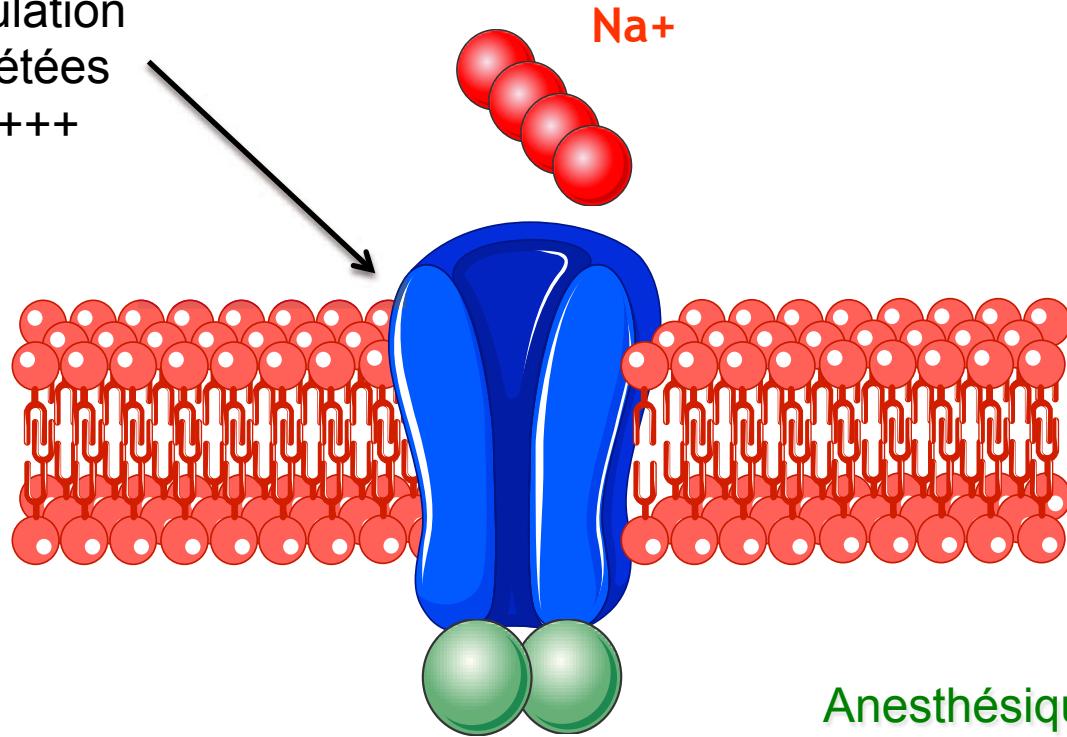
Use dependance ou bloc phasique

Stimulation
répétées



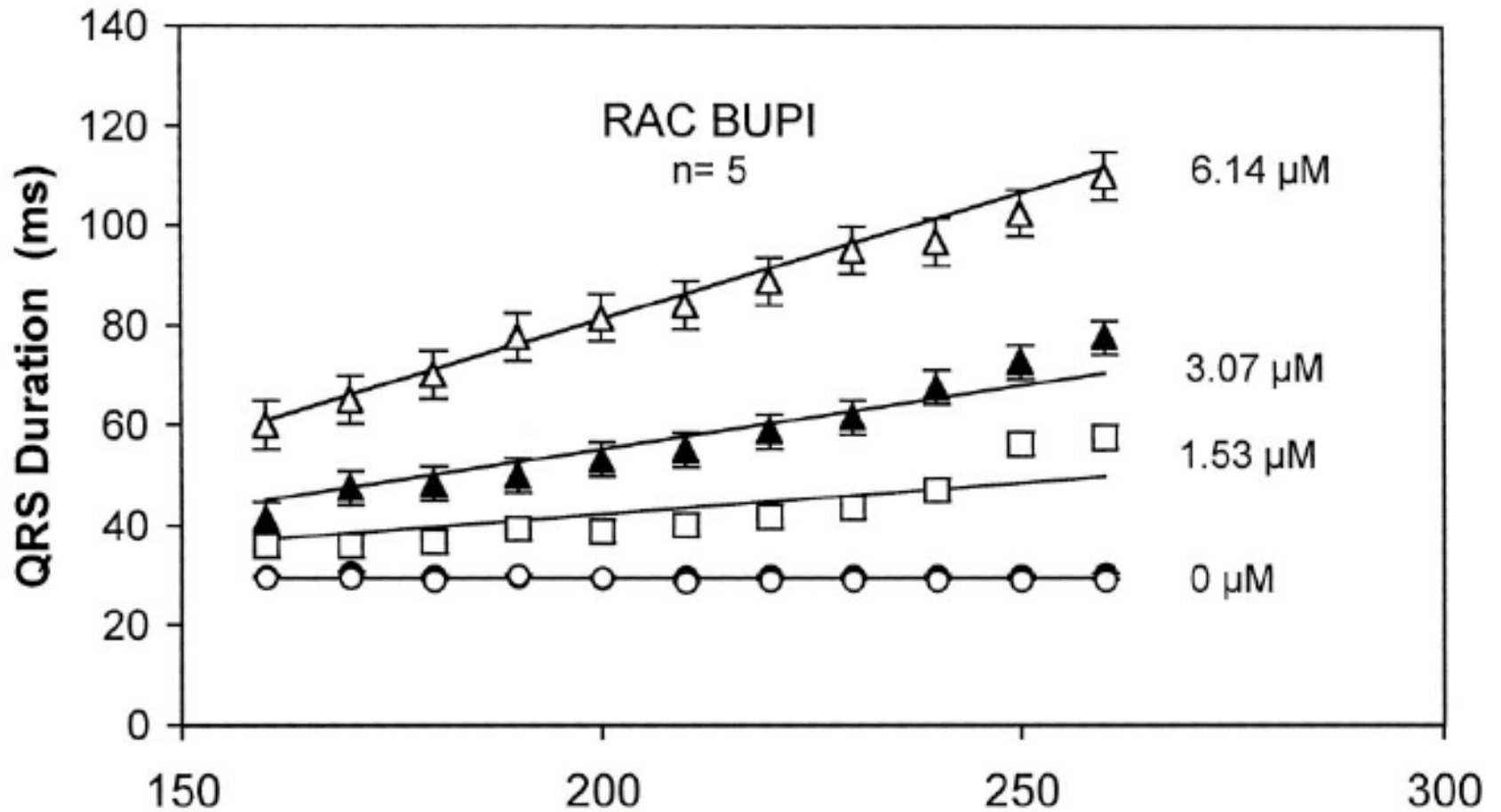
Use dependance ou bloc phasique

Stimulation
Répétées
+++++

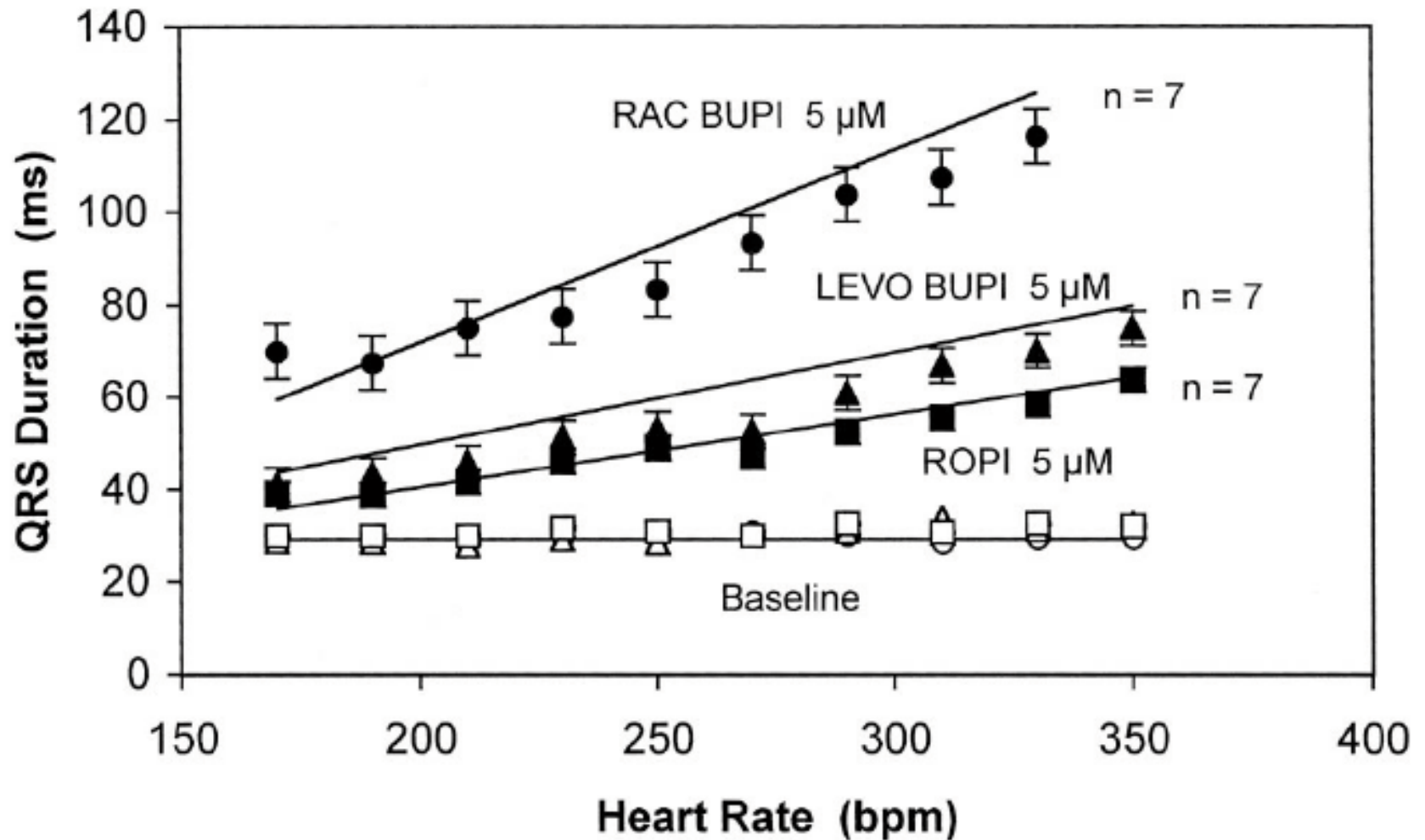


Anesthésiques
locaux

Bloc phasique



Bloc phasique



Check list ASRA

- Get Help**
- Initial Focus**
 - Airway management:** ventilate with 100% oxygen
 - Seizure suppression:** benzodiazepines are preferred; **AVOID propofol** in patients having signs of cardiovascular instability
 - Alert** the nearest facility having **cardiopulmonary bypass** capability
- Management of Cardiac Arrhythmias**
 - Basic and Advanced Cardiac Life Support (ACLS)** will require adjustment of medications and perhaps prolonged effort
 - AVOID vasopressin, calcium channel blockers, beta blockers, or local anesthetic**
 - REDUCE individual epinephrine doses to <1 mcg/kg**
- Lipid Emulsion (20%) Therapy** (values in parenthesis are for 70kg patient)
 - Bolus 1.5 mL/kg** (lean body mass) intravenously over 1 minute (~100mL)
 - Continuous infusion 0.25 mL/kg/min** (~18 mL/min; adjust by roller clamp)
 - Repeat bolus once or twice for persistent cardiovascular collapse
 - Double the infusion rate to 0.5 mL/kg/min if blood pressure remains low
 - Continue infusion** for at least 10 minutes after attaining circulatory stability
 - Recommended upper limit: Approximately 10 mL/kg lipid emulsion over the first 30 minutes
- Post LAST events at www.lipidrescue.org and report use of lipid to www.lipidregistry.org**

Check list ASRA

- Get Help**
- Initial Focus**
 - Airway management:** ventilate with 100% oxygen
 - Seizure suppression:** benzodiazepines are preferred; **AVOID propofol** in patients having signs of cardiovascular instability
 - Alert** the nearest facility having **cardiopulmonary bypass** capability
- Management of Cardiac Arrhythmias**
 - Basic and Advanced Cardiac Life Support** (ACLS) algorithms, including adjustment of medications and perhaps electrical cardioversion
 - AVOID** vasopressin, calcium channel blockers, beta blockers, or local anesthetic
 - REDUCE** individual epinephrine bolus to 1 mcg/kg
- Lipid Emulsion (20%) Therapy** (Doses and synthesis are for 70kg patient)
 - Bolus 1.5 mL/kg** (100 mg) intravenously over 1 minute (~100mL)
 - Continue infusion** at 0.5 mL/kg/min (~18 mL/min; adjust by roller clamp)
 - Repeat bolus for twice for persistent cardiovascular collapse
 - Double infusion rate to 0.5 mL/kg/min if blood pressure remains low
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Surveillance 12 h

Conclusion

Pourquoi continuer à parler de la toxicité systémique des AL en 2014 ?



Sujet toujours d'actualité

Prévention

Suivi des référentiels

DIU
Techniques UltraSoniques
en Anesthésie-Réanimation
TUSAR
Option ALR

vincent.compere@chu-rouen.fr

Toxicité systémique des AL

Pourquoi en parler en 2014 ?

Sujet ancien

En voie de
disparition

Pharmacologie des
AL connue de tous

Référentiels

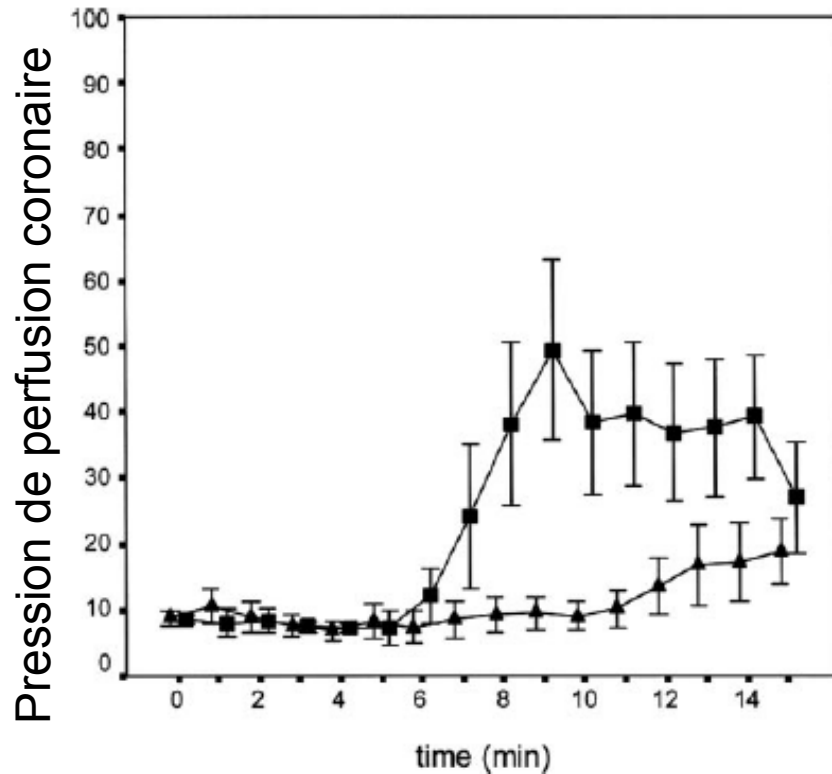
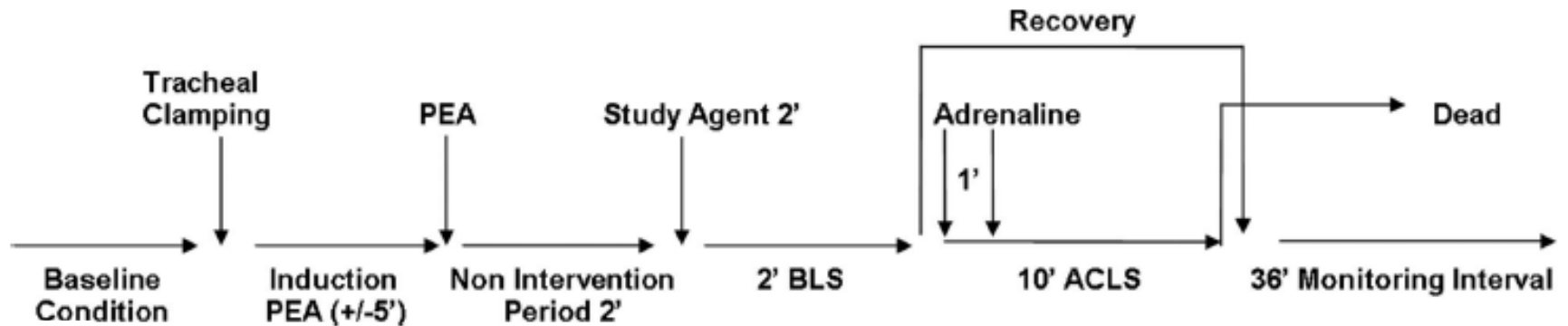
Mais

VRAIMENT ?

VRAIMENT ?

EN PRATIQUE ?

Rôle de l'hypoxie



Retour à un rythme cardiaque spontané

NaCl 7/11

Intralipide 1/12