The International Journal of Biochemistry & Cell Biology 43 (2011) 14–19

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

Medicine in focus

From analgesia to myopathy: When local anesthetics impair the mitochondrion

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

[a] MRGM – Maladies Rares: Génétique et Métabolisme, Université Victor Segalen Bordeaux 2, F-33076 Bordeaux, France
[b] Pôle d'Anesthésie Réanimation, Hôpital Pellegrin, Centre Hospitalier Universitaire de Bordeaux, F-33076 Bordeaux, France
[c] Institut National de la Santé et de la Recherche Médicale (INSERM) ERI 25, F-34925 Montpellier, France
[d] Laboratoire de Physiologie, Université Montpellier1, F-34925 Montpellier, France
[e] DAR Hôpital Lapeyronie, Centre Hospitalier Universitaire de Montpellier, F-34925 Montpellier, France

ARTICLE INFO

Article history:
Received 31 August 2010
Received in revised form 11 October 2010
Accepted 12 October 2010
Available online 19 October 2010

Keywords:
Bupivacaine
Myotoxicity
Mitochondria
Regional analgesia

ABSTRACT

The expanding utilization of local anesthesia and analgesia revealed the occurrence of myopathies induced by local anesthetics. Such iatrogenic effect encouraged anesthesiologists to study the toxicity of local anesthetics and to reevaluate their protocols in order to reduce muscle pain and dysfunction. Studies performed in rats and human cells showed that bupivacaine induces muscle histological damages with sarcomers disruption along with structural alteration of mitochondria, the powerplant of the cell. Bupivacaine-induced myopathies (BIM) are underestimated as patients are not examined by the anesthesiologist after the surgery. Biochemical analyses indicate that BIM could be explained both by the alteration of mitochondrial energetics with consecutive oxidative stress and mitophagy, and the modification of sarcoplasmic reticulum activity with perturbations of calcium homeostasis. BIM is time-dependent, local anesthetic concentration-dependent, enhanced by preexisting metabolism alteration or young age, and could be prevented in part by antioxidant agents and rhEPO. These observations suggest that adapted changes in postoperative analgesia protocols, including the adjustment of LA concentration and volume, a more precise delivery of the drug and an adapted duration of analgesia, may prevent myopathies consecutive to local anesthesia.

1. Introduction

Mitochondrial toxicity of pharmacological compounds is an emerging cause of myopathies and cardiomyopathies (see review in Sardao et al. (2008)): AIDS treatment with antiretroviral medicine triggers mitochondrial DNA depletion with subsequent mitochondrial myopathy, statins block coenzyme Q biosynthesis, a respiratory chain major component, and also leads to such myopathies, and the anti-cancer agent doxorubicin interacts with mitochondrial respiratory chain, stimulates ROS production and triggers cardiomyophy. Such undesirable effects of so-called "mitotoxic" compounds were discovered for several drugs including anticonvulsants, psychotropics, cholesterol medications, analgesics and anti-inflammatory pain relievers. In the present article we discuss the impact of local anesthesia and analgesia on the mitochondrion and the consecutive occurrence of undesired myopathies.

2. Local anesthetics in clinical practice

2.1. Regional anesthesia and analgesia

Regional blocks performed with local anesthetics (LA) improve postoperative analgesia and postoperative rehabilitation in children and in adult patients. For what concerns knee surgery, patients with continuous femoral block (compared with the patient receiving controlled morphine administration) showed significantly (i) lower visual analog scale scores at rest and during continuous passive motion, and (ii) earlier postoperative knee mobilization closer to the target levels prescribed by the surgeon (Capdevila et al., 1999; Ilfeld et al., 2010). According to the type of surgery, different peripheral nerve blocks and wound infiltrations can be performed by the practitioner (Table 1), using single shot injections or continuous infusions of local anesthetics (LAs) (Marhofer et al., 2010b). The technique of continuous peripheral nerve blocks with local anesthetics injected via a catheter, are recognized as safe and effective techniques for postoperative pain relief and chronic pain therapy (Dadure et al., 2005; Capdevila et al., 1999). In clinical practice, the local-anesthetics doses of 2–3 mg/kg, with a 15–20 mM stock solution (0.5 mg/ml Bupivacaine, 7.5 mg/ml Ropivacaine are usely used). In muscle patients, intratissue local anesthetic concentration has not been measured. Nevertheless, muscle bupivacaine

* Corresponding author at: MRGM – Maladies Rares: Génétique et Métabolisme, Université Victor Segalen Bordeaux 2, F-33076 Bordeaux, France.
E-mail address: karine.nouette-gaulain@u-bordeaux2.fr (K. Nouette-Gaulain).

1357-2725/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biocel.2010.10.005

Table 1
Principal surgeries and corresponding peripheral nerve block.

Peripheral nerve block	Surgery	Benefits
Interscalene block	Shoulder	Reduction of postoperative pain and opioid consumption
Infraclavicular nerve block Supraclavicular nerve block	Hand and forearm	Reduction of postoperative pain and opioid consumption.
Axillary nerve block		Increase of the skin temperature, for 24 h after microvascular surgery of the crushed finger
Femoral nerve block	Knee surgery: arthroplasty, total knee replacement.	Lower opioid consumption and a better recovery at 6 weeks
Sciatic nerve blocks	Knee surgery, vascular surgery, and leg amputations; Distal approaches to the sciatic nerve: surgical procedures on the ankle and foot	Lower pain levels, analgesic requirements, and higher patient satisfaction
Ilioinguinal/iliohypogastric blocks TAP block	Provision of pain relief after abdominal surgery	Optimization of local anesthetic injections in appropriate space
Peribulbar anesthesia	Eyes: cataract	Motor and sensory block during surgery

concentration has been measured 1 h after the last injection of a clinically relevant protocol performed in rats. This concentration was approximately 30 nmol/mg of tissue or 30 μM. This concentration is underestimated because the authors could not measure precisely the local concentration of bupivacaine in the strict diffusion space within the muscle due to the limited sensitivity of the high-performance liquid chromatography system that would have required a larger biopsy. Thus, 1 mM bupivacaine is probably in the range of the actual concentrations delivered in the vicinity of the nerve catheter.

2.2. Bupivacaine-induced myopathies (BIM)

Just after the injection of the local anesthetics at the site of action (nerve extremity), the drug generally spreads into contact with neighboring muscles, as observed by ultrasound imaging during LA injection (Fig. 1). As a consequence, postoperative iatrogenic muscle pain can be observed, as reported in adults patients, scheduled to undergo cataract surgery with retrobulbar anesthesia using bupivacaine (Gomez-Arnau et al., 2003). Likewise, pain in the neck was described after bupivacaine injections (1.14 g of bupivacaine during 34-h period) by an interscalene catheter after surgery for capsular release of left shoulder (Hogan et al., 1994). In this patient, the muscle biopsy revealed the coexistence of degenerating and regenerating muscle fibers with structural evidences of myophagy (Hogan et al., 1994). While bupivacaine-induced myotoxicity is an accepted cause of myoptahies, this phenomenon remains underestimated. Indeed, after the surgery, muscle pain and dysfunction is not associated to regional analgesia since (i) the surgery induces a temporary decrease in movement amplitude and in patient mobilization, (ii) patients are systematically examined by surgeon few days later but not by the anesthesiologist, and (iii) the muscle force and/or metabolism are not investigated after regional anesthesia. Hence, a more thorough evaluation BIM post-surgery could allow determining the occurrence of the iatrogenic disorder.

3. Pathogenesis

3.1. Alteration of muscle and mitochondrial structure

The pathogenesis of BIM includes histopathologic damages and subcellular dysregulations which were described in our animal model of this disorder (Nouette-Gaulain et al., 2009b). In particular, biochemical and cell biology analyses of bupivacaine toxicity revealed a key role of mitochondria with a series of bioenergetic and structural alterations. Those were described on different experimental models ranging from isolated rat mitochondria to human myocytes in culture (Nouette-Gaulain et al., 2009a; Nouette-Gaulain et al., 2002; Irwin et al., 2002). Below we highlight the mechanisms involved in bupivacaine-induced myotoxicity, analyze the risk factors and describe the protective drugs and clinical "precaution", decreasing this iatrogenic effect.

Microscopic analyses of muscle integrity indicated that injections of high concentration of bupivacaine (16 mg/kg) in rat muscle induced disjointed fibers, interstitial edema and infiltrating cells (Duguez et al., 2002). Lower concentrations of LA (initial bolus of 3–5 mg/kg followed by a continuous infusion of 0.6–1 ml/kg during 6 h) cause a widespread interstitial and myoseptal edema, followed few hours later by disruption and condensation of myofilament, lytic degeneration of the sarcoplasmic reticulum and mitochondria, and pycnotic changes of the nuclei (Zink et al., 2003). Using a protocol of analgesia similar to what is performed on human, we showed that rats treated with 2.5 mg/kg bupivacaine, injected by a femoral nerve catheter, presented with a wide spectrum of morphological fiber abnormalities, ranging from absent, to focal, moderate and extreme (Nouette-Gaulain et al., 2009b). Moreover, most of these fibers exhibited myofibrillar disruption, with Z-line streaming or M-band disruption as well as disruption of the myofilament structure within sarcomeres. Furthermore, extreme muscle damage (area of disruption covering more than 10 adjacent myofibrils and/or continuous sarcomeres) was observed only after injections of LA, in comparison with saline. In this study, mitochondrial morphology was altered in muscle samples taken underneath the extremity of the catheter (Nouette-Gaulain et al., 2009a). In addition, we showed that bupivacaine induced subsarcolemmal aggregates of swollen mitochondria and partial loss of interfibrillar mitochondria. Alternatively, membranes thought to be autophagosomes surrounded either intact or degraded mitochondria which suggested the induction of mitophagy by bupivacaine (Meijer and Codogno, 2006). The internal organization of mitochondria was also severely affected in the bupivacaine-treated muscle, forming an onion-like structure that included rearrangements of matricial space and cristolysis. Such onion-like structure of mitochondria were previously associated with abnormal F_1F_0 ATP synthase oligomerization in yeast, which might suggest an interaction between bupivacaine and the mitochondrial ATP-synthase enzyme complex (Paumard et al., 2002). Although, the putative observation of autophagosomes surrounding mitochondria could be consistent with the activation of mitophagy in muscle treated with bupivacaine, molecular studies are needed to clarify this point. Abnormal mitochondrial autophagy was recently described in various pathological conditions, but this phenomenon remains poorly understood (Martinet et al., 2007).

3.2. Inhibition of mitochondrial energy production

Rats receiving bupivacaine according to a genuine clinical protocol (7 repeated injections of 0.25% bupivacaine 1 ml/kg via femoral