Absence of Stereospecific Effects of Bupivacaine Isomers on Heart Mitochondrial Bioenergetics

François Sztark, M.D., Ph.D.,* Karine Nouette-Gaulain, M.D.,† Monique Malgat, Ph.D.,‡ Philippe Dabadie, M.D.,§ Jean-Pierre Mazat, Ph.D.¶

Background: Highly lipophilic local anesthetics interfere with mitochondrial energy metabolism. These metabolic effects could, in part, explain some toxic effects of local anesthetics, such as bupivacaine-induced myocardial depression. The purpose of this study was to compare the optically pure isomers of bupivacaine on heart mitochondrial bioenergetics.

Methods: Both bupivacaine enantiomers were tested on rat heart isolated mitochondria. Oxygen consumption, adenosine triphosphate synthesis, and enzymatic activities of the four complexes of the respiratory chain were measured.

Results: No significant differences were found between R(+) - and S(−)-bupivacaine on mitochondrial oxidative phosphorylation with a similar dose-dependent decrease in adenosine triphosphate synthesis. Complex I (nicotinamide adenine dinucleotide ubiquinone reductase) was the enzymatic complex of the respiratory chain most sensitive to the bupivacaine isomers. Half-inhibitory concentrations for R(+) - and S(−)-bupivacaine were not statistically different (3.3 ± 0.4 mM and 2.8 ± 0.6 mM, respectively).

Conclusions: No stereospecific effects of bupivacaine enantiomers were shown in the inhibition of complex I activity and uncoupling of oxidative phosphorylation. This can be correlated with the lack of stereospecific effects of bupivacaine on myocardial depression. The lipid solubility of local anesthetics appears to be the principal physicochemical factor affecting the potency of these tertiary amines on mitochondrial bioenergetics. (Key words: Local anesthetics, mitochondria, stereoisomers.)

BUPIVACAINE, like other highly lipophilic local anesthetics, impairs mitochondrial energy metabolism. Such effects could be associated with certain toxic effects of local anesthetics. Indeed, bupivacaine-induced myocardial depression may be, in part, the result of interference with mitochondrial energy transduction. Bupivacaine induces a decrease in adenosine triphosphate (ATP) synthesis in the cell by at least two major mechanisms: (1) an uncoupling effect between oxygen consumption and ATP synthesis by increasing mitochondrial membrane permeability to protons; and (2) a direct inhibition of complex I of the mitochondrial respiratory chain.

We have previously reported that ropivacaine disturbs mitochondrial energy metabolism less than bupivacaine. Unlike bupivacaine, which is prepared and used as a racemic solution, ropivacaine is prepared as a single enantiomer S(−). Moreover, the N-propyl radical of ropivacaine confers a lower lipid solubility than that of bupivacaine. Both chemical differences between bupivacaine and ropivacaine may explain the lower toxicity of the latter. Stereoselective effects of local anesthetics have been shown on neuronal or cardiac Na+ channels, and the two bupivacaine enantiomers may exert different blocking and toxic effects. Recently, Graf et al. demonstrated that bupivacaine had isomer-specific effects on cardiac electrophysiology and that the R(+) -isomer prolonged atrioventricular conduction the most. Finally, preclinical evaluation of l-bupivacaine has...
confirmed that the $S(-)$-isomer of bupivacaine induces less cardiotoxicity than the racemic bupivacaine.\textsuperscript{18}

Membrane-mediated effects of local anesthetics on mitochondrial metabolism, such as uncoupling of oxidative phosphorylation, seems mainly to depend on the lipid solubility of the molecule. However, local anesthetic isomers could have different direct effects on the enzymatic complexes of the respiratory chain. The current study was undertaken to determine whether optically pure isomers of bupivacaine exhibit stereospecific effects on energy metabolism in isolated rat heart mitochondria.

**Materials and Methods**

**Mitochondrial Isolation**

Care of the animals conformed to the recommendations of the Institutional Animal Care Committee and the French Ministry of Agriculture. Because all anesthetic agents used could potentially alter mitochondrial function after isolation, adult male Wistar rats (weight, 250–350 g) were killed by cervical dislocation. Rat heart mitochondria were isolated by differential centrifugation as previously described.\textsuperscript{7} The mitochondrial pellet was confirmed that the $S(-)$-isomer of bupivacaine induces less cardiotoxicity than the racemic bupivacaine.\textsuperscript{18}

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**Respiration Assay**

The oxygen consumption rate was measured polarographically at 30°C using a Clark-type electrode connected to a computer that gave an online display of rate values. Solubility of oxygen in the medium was considered to be equal to 450 nmol/ml. The incubation medium contained 25 mM sucrose, 75 mM mannitol, 100 mM KCl, 10 mM Tris-phosphate, 50 $\mu$M EDTA, 10 mM Tris-HCl, pH 7.2, with 10 mM pyruvate or 10 $\mu$M palmitoyl-carnitine, plus 10 mM malate, as substrates. Respiration rates were expressed in nanomoles of oxygen per minute and per milligram of mitochondrial protein. Bupivacaine enantiomers were added in the oxygraph chamber after equilibration of the mitochondrial suspension with the respiratory substrates. Achievement of the steady state action of local anesthetic was assumed when the oxygen consumption rate was constant.

**Measurement of Adenosine Triphosphate Synthesis**

During the same conditions as in the respiration assay, the ATP synthesis rate of isolated mitochondria was determined by bioluminescence measurement (luciferine–luciferase system) of the ATP produced after addition of 1 mM of adenosine diphosphate (ADP).\textsuperscript{19} At various time intervals after addition of ADP, 20-$\mu$l aliquots were withdrawn from the oxygraph chamber, quenched in 100 $\mu$l dimethyl sulfoxide (DMSO), and diluted in 5 ml ice-cold distilled water. Standardization was performed with known quantities of ATP measured during the same conditions.

**Enzymatic Determinations**

Enzymatic activities were measured using previously described spectrophotometric procedures and expressed in nanomoles of substrate transformed per minute and per milligram protein.\textsuperscript{20} Activities of the four respiratory chain complexes were measured on mitochondria broken down by freeze thawing three times.

**Complex I (Reduced Nicotinamide Adenine Dinucleotide Ubiquinone Reductase).** The oxidation of reduced nicotinamide adenine dinucleotide (NADH) by complex I was recorded using the ubiquinone analog decylubiquinone as electron acceptor. The decrease in absorption caused by NADH oxidation was measured at 30°C and at 340-nm wavelength. Complex I activity was calculated from the difference in rate before and after the addition of rotenone (2 $\mu$m), a specific inhibitor of complex I.

**Complex II (Succinate Dehydrogenase).** Complex II-specific activity was measured by monitoring the reduction of 2,6-dichlorophenol indophenol at 600 nm and 30°C, in the presence of phenazine methosulphate.

**Complex III (Ubiquinol Cytochrome c Reductase).** The oxidation of the ubiquinol analog decylubiquinol by complex III was determined using cytochrome c(III) as electron acceptor. The reduction of cytochrome c(III) was recorded at 30°C and at 550 nm.

**Complex IV (Cytochrome c Oxidase).** Complex IV activity was measured using cytochrome c(II) as substrate. The oxidation of cytochrome c was monitored at 550 nm at 30°C.

**Chemicals**

The $R(+) \text{ and } S(-)$-enantiomers of bupivacaine were a gift from Astra Pain Control (Södertälje, Sweden). Local anesthetics (base form) were dissolved in DMSO at 250 mM concentration and were tested in a 0–5-mM concentration range. Control values were obtained in the same conditions in the presence of DMSO. Measurement of ATP synthesis was performed with the ATP Bioluminescence Assay Kit HS II (Boehringer Mannheim, Munich, Germany).

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Germany). All the other chemicals were obtained from Sigma Chemical Company (St. Louis, MO).

Data Analysis

Results are expressed as mean ± SD (n = 5). Data were plotted and analyzed using SigmaPlot 5.0 and SigmaStat 2.0 (SPSS Inc., Chicago, IL). Concentration-response curves of inhibition of ATP synthesis rate or complex I activity were fitted to a Hill equation of the form $y = \frac{100}{1 + (C/IC_{50})^n}$, where C is the enantiomer concentration, IC50 is the half-inhibitory concentration, and n is the Hill coefficient. The closeness of curve fitting was indicated by $r^2$. Statistical analysis was performed using analysis of variance and the Student unpaired $t$ test when appropriate. Probability values less than 0.05 were considered significant.

Results

Effects of Bupivacaine Isomers on Mitochondrial Oxidative Phosphorylation

Concentration-dependent effects of bupivacaine isomers were measured for mitochondrial respiration supported by pyruvate (10 mM) or palmitoylcarnitine (10 μM) in the presence of malate (10 mM). As previously reported with the racemic mixture, bupivacaine enantiomers in the concentration range (0–5 mM) strongly stimulated basal mitochondrial respiration supported by the nonlipid substrate pyruvate (fig. 1). No significant differences were found between $R$- and $S$-bupivacaine. This stimulation of oxygen consumption corresponds to the classic uncoupling effect of lipophilic local anesthetics. Consequently, phosphorylation of ADP by the ATP synthase was inhibited. Both isomers decreased ATP synthesis equally and dose-dependently (fig. 2). From curve fitting, the IC50 for $R$-bupivacaine (2.2 ± 0.4 mM) was not significantly different from that of $S$-bupivacaine (2.5 ± 0.2 mM). At 5 mM, both enantiomers reduced the ATP-to-oxygen ratio similarly; therefore, both molecules had the same effects on oxidative phosphorylation (table 1).

Fig. 2. Effects of bupivacaine enantiomers on mitochondrial adenosine triphosphate (ATP) synthesis during adenosine diphosphate (ADP)-stimulated respiration with pyruvate as substrate. ATP produced was measured by bioluminescence after addition of 1 mM ADP in the oxygraph cuvette. ATP synthesis rate in the presence of local anesthetics is given as the percent of the ATP production in the absence of local anesthetics. Data are presented as mean ± SD (n = 5). From curve fitting: for $R$-bupivacaine, IC50 = 2.2 ± 0.4 mM, n = 1.7 ($r^2 = 0.9884$); for $S$-bupivacaine, IC50 = 2.5 ± 0.2 mM, n = 2.1 ($r^2 = 0.9976$).


MITOCHONDRIAL EFFECTS OF BUPIVACAINE ISOMERS

Table 1. Effects of Bupivacaine Isomers on Oxidative Phosphorylation in Rat Heart Mitochondria

<table>
<thead>
<tr>
<th>Oxygen consumption</th>
<th>−ADP</th>
<th>+ADP</th>
<th>ATP Synthesis</th>
<th>ATP/O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>41 ± 4</td>
<td>298 ± 28</td>
<td>771 ± 42</td>
<td>2.6 ± 0.2</td>
</tr>
<tr>
<td>R(+)-bupivacaine 5 mM</td>
<td>289 ± 27*</td>
<td>308 ± 18</td>
<td>165 ± 29*</td>
<td>0.5 ± 0.1*</td>
</tr>
<tr>
<td>S(−)-bupivacaine 5 mM</td>
<td>300 ± 24*</td>
<td>325 ± 23</td>
<td>147 ± 32*</td>
<td>0.4 ± 0.1*</td>
</tr>
</tbody>
</table>

Experimental conditions are described in Materials and Methods. Basal, without ADP, and ADP-stimulated oxygen consumption rates supported by pyruvate are expressed in nmol oxygen·min⁻¹·mg protein⁻¹. Adenosine triphosphate (ATP) synthesis rate is expressed in nmol ATP·min⁻¹·mg protein⁻¹. ATP-to-oxygen ratio is calculated as the ratio of the rate of ATP synthesis to the rate of the concomitant respiration in the presence of ADP. Values are mean ± SD (n = 5).

* P < 0.05 versus control.

ADP = adenosine diphosphate; ATP = adenosine triphosphate; ATP/O = adenosine triphosphate to oxygen ratio.

Effects of Bupivacaine Isomers on Enzymatic Complexes of the Respiratory Chain

The effects of R(+)- and S(−)-bupivacaine on the respiratory chain were also studied on the four separate enzymatic complexes of the inner mitochondrial membrane. Table 2 shows the effects of a 5-mM concentration of both enantiomers on these complexes. Complex I (NADH ubiquinone reductase) was inhibited by both molecules (P < 0.05). Complexes II, III, and IV were not affected. The inhibitory effect of bupivacaine enantiomers on complex I was concentration-dependent (fig. 4). Data were fitted to a Hill equation. From five determinations, we obtained IC₅₀ = 3.3 ± 0.4 mM and n (Hill coefficient) = 0.9 for R(+)-bupivacaine and IC₅₀ = 2.8 ± 0.6 mM and n = 1.0 for S(−)-bupivacaine. The difference between IC₅₀ was not statistically different.

Discussion

Equimolar concentrations of R(+) and S(−)-bupivacaine produced the same changes in mitochondrial energy metabolism with a significant decrease in ATP synthesis and in complex I activity. No evidence for stereospecific effects of the local anesthetic was found in oxidative phosphorylation supported by lipid or non-lipid substrates.

Steroselectivity corresponds to a difference of affinity or potency between the isomers for a specific target (a receptor, in general). Local anesthetics exhibit stereospecific effects on Na⁺ channels. In 1969, Akerman et al.13 showed that isomers of local anesthetics block nerve conduction differently. On cardiac muscle, stereoselective effects of bupivacaine enantiomers have also been demonstrated on electrophysiologic parameters.21 R(+)-bupivacaine has a higher potency than S(−)-bupivacaine to block the inactivated state of the cardiac Na⁺ channel.15

Two different effects of local anesthetics have been found in mitochondria: the uncoupling of oxidative phosphorylation and the inhibition of enzymatic complexes. The uncoupling effect of local anesthetics corresponds to the dissipation of the transmembrane proton gradient that reduces the efficiency of ATP synthesis, with a large decrease in the ATP-to-oxygen ratio. The mechanism of bupivacaine uncoupling has been extensively investigated.2,5,7,8,19,22 Tertiary-amine local anesthetics, such as bupivacaine, act mainly by cycling protons through the membrane. This effect depends on the lipid solubility of these molecules: lidocaine alone does not change mitochondrial respiration, and ropivacaine, which has an intermediate partition coefficient, disturbs mitochondrial function less than bupivacaine.10 Therefore, lack of stereoselectivity in the uncoupling effect is not unexpected. In neuronal tissue, it has been shown that uptake of local anesthetics or membrane partitioning are not dependent on optical isomers.23 Further-
more, in perfused isolated heart, Mazoit et al.\textsuperscript{24} showed that the two enantiomers of bupivacaine had similar myocardial pharmacokinetics, and that the tissue to perfusate concentration ratio was similar for both isomers. These results have recently been confirmed by a systemic and regional pharmacokinetic study in sheep.\textsuperscript{25}

On the contrary, a stereoselective inhibition of complex I by bupivacaine enantiomers could have been expected. The mitochondrial NADH dehydrogenase (NADH ubiquinone reductase) is the first enzyme complex of the respiratory chain. It oxidizes NADH (produced in the Krebs cycle or during fatty acid oxidation) and transfers electrons to the downstream elements of the respiratory chain. It is involved in ATP synthesis not only by generating the protonmotive force but also in the control of free radical production. In eukaryotic cells, complex I is a large multisubunit enzyme.\textsuperscript{26} Intriguingly, complex I appears to be a target for several anesthetic molecules. Cohen and Nahrwold\textsuperscript{27,28} reported that volatile anesthetics, such as halothane or isoflurane, decrease mitochondrial respiration. In their studies, complex I was the most sensitive to these anesthetics. More recently, propofol has been shown to inhibit electron transfer at the complex I level.\textsuperscript{29} Finally, the work of Kayser et al.\textsuperscript{30} clearly demonstrated that a change in a subunit of complex I (mutation in the gas-1 gene) increases sensitivity of Caenorhabditis elegans to volatile anesthetics. Therefore, mitochondrial functions seem to be directly involved in some anesthesia processes. Local anesthetics also decrease complex I activity. This enzymatic inhibition appears to be the main effect of local anesthetics on mitochondrial metabolism in living cells.\textsuperscript{6,10} Therefore, NADH ubiquinone reductase shows a high sensitivity to structurally different molecules. In the present study, the higher IC\textsubscript{50} values for bupivacaine isomers than that previously reported for racemic bupivacaine\textsuperscript{10} could be explained by a modification of the experimental procedure, with the use of free-base local anesthetics dissolved in DMSO instead of HCl salts. The lack of differences between both bupivacaine isomers for the inhibition of complex I activity indicates that the site of action of these agents is not a protein receptor but rather that local anesthetics inhibit complex I by a nonspecific effect, e.g., by modifying the lipid environment of the enzyme subunits. More generally, a high sensitivity of complex I to its lipid surrounding could explain why chemically different molecules inhibit its activity.

Taking together our present and previously reported results,\textsuperscript{10} we hypothesize that the mitochondrial effects of local anesthetics are principally dependent on the partition coefficient of these molecules, although the membrane permeability of drugs is not proportional to their hydrophobicity in all circumstances.\textsuperscript{31} In this respect, the less potent action of ropivacaine than bupivacaine on mitochondrial bioenergetics appears to be the result of the difference in lipid solubility rather than their preparation as a single enantiomer. However, other mitochondrial functions could be affected by local anesthetics. Recently, Weinberg et al.\textsuperscript{32} demonstrated that bupivacaine decreases fatty acids transport into mito-

### Table 2. Effects of Bupivacaine Isomers on the Enzymatic Complexes of the Respiratory Chain

<table>
<thead>
<tr>
<th>Complex</th>
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<th>R(+) bupivacaine 5 mM</th>
<th>S(-) bupivacaine 5 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex I</td>
<td>869 ± 41</td>
<td>329 ± 19*</td>
<td>305 ± 16*</td>
</tr>
<tr>
<td>Complex II</td>
<td>473 ± 54</td>
<td>456 ± 51</td>
<td>464 ± 38</td>
</tr>
<tr>
<td>Complex III</td>
<td>1,456 ± 110</td>
<td>1,652 ± 158</td>
<td>1,431 ± 149</td>
</tr>
<tr>
<td>Complex IV</td>
<td>2,788 ± 93</td>
<td>2,648 ± 101</td>
<td>2,683 ± 79</td>
</tr>
</tbody>
</table>

Values are mean ± SD (n = 5). The activities of complexes are measured as described in Materials and Methods and are expressed as nmol substrate transformed · min\textsuperscript{-1} · mg mitochondrial protein\textsuperscript{-1}.

\* P < 0.05 versus control.

Fig. 4. Dose dependence inhibition of the complex I of the respiratory chain by bupivacaine isomers. Data are presented as mean ± SD (n = 5). From curve fitting: for R(+) bupivacaine, IC\textsubscript{50} = 3.3 ± 0.4 mM, n = 0.9 (r\textsuperscript{2} = 0.9935); for S(-) bupivacaine, IC\textsubscript{50} = 2.8 ± 0.6 mM, n = 1.0 (r\textsuperscript{2} = 0.9847).
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chondria by inhibiting the carnitine-acylcarnitine translocase. Such effect could contribute to bupivacaine cardiotoxicity, and a difference between the enantiomers of bupivacaine is possible at this level.

The lack of stereospecificity in the effects of bupivacaine isomers on mitochondrial energy metabolism is consistent with previous results of toxicologic studies in isolated heart or in animals. Graf et al.17 demonstrated in the perfused guinea pig heart that bupivacaine isomers equally and dose-dependently decreased cardiac function. Only atrioventricular conduction was significantly more delayed by $R(\pm)$-bupivacaine. In the sheep, although $S(-)$-isomer of bupivacaine was less likely to produce lethal arrhythmia than racemic bupivacaine, both local anesthetic solutions had comparable negative inotropic effects.18 Hence, bupivacaine-induced myocardial depression, which could be explained, in part, by an energy failure of the cell, does not show any stereoselective properties.

In conclusion, we did not find any difference in the effects of bupivacaine isomers on mitochondrial energy metabolism. This can be correlated with the lack of stereospecific effects of bupivacaine on myocardial depression. These results also indicate that the action of local anesthetics on oxidative phosphorylation mainly depend on the lipid solubility of these tertiary amines. In this respect, the lower lipid solubility of ropivacaine as compared with bupivacaine could explain the less potent effects of this molecule on mitochondrial bioenergetics.

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References

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