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TITLE: Effects of Halothane on Calcium and Potassium Currents in Isolated Smooth Muscle Cells of Dog Coronary Arteries

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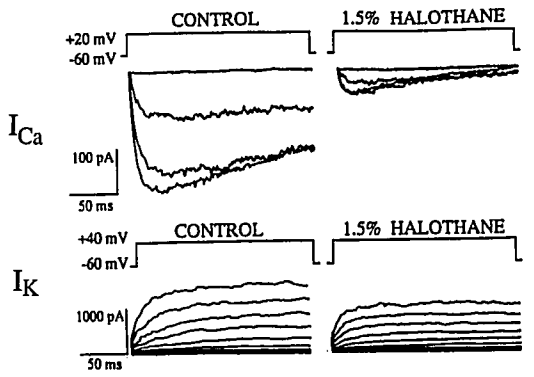
The purpose of this study was to examine the effect of halothane on the whole cell calcium inward current (I_{Ca}) and delayed rectifier potassium current (I_K) recorded from enzymatically isolated smooth muscle cells from the canine epicardial coronary arteries using a single-pipette voltage-clamp technique. These currents were chosen because: a) arterial smooth muscle tone is regulated by membrane potential primarily *via* the voltage dependence of Ca^{2+} channels;[1] and b) the majority of the sarcolemmal K^+ permeability is due to a high conductance Ca^{2+}-activated K^+ channels.[2]

The left circumflex coronary artery was carefully removed, cut into 2 mm rings, and placed into a small vial containing low Ca^{2+} enzyme solution of collagenase and papain at 37°C for 1-2 hours. Whole-cell membrane currents were recorded using a patch-clamp amplifier (List EPC 7) at room temperature as described previously.[3] Individual currents were isolated by using different external and pipette solutions. Halothane was equilibrated in the bath solution at a final bath concentration of 0.85 mM (1.5% effective partial pressure at room temperature) as verified by gas chromatography.

Typical record of the magnitude and time course of the whole-cell calcium current (I_{Ca}) recorded in 10 mM $[Ba^{2+}]_o$ is shown in the upper part of the figure. We could find only L-type I_{Ca} and failed to detect low threshold rapidly-inactivating T-type I_{Ca} as also shown by other investigators.[1] The superimposed current traces were elicited with 200 msec depolarizing voltage-clamp pulses from a holding potential of -60 mV to a test potential of -60, 0, +10 and +20 mV. The effects of halothane were very rapid, taking less than two minutes for maximal changes. The peak I_{Ca} decreased to 32% in the presence of 1.5% halothane (N=7). A large voltage-dependent outward current was elicited in response to voltage-steps spaced 10 mV apart from -60 up to +40 mV as shown in the lower part of the figure . In the presence of 1.5% halothane, I_K at all voltage steps decreased to 64% at peak current, and the decrease was less as compared to a depression of I_{Ca}.



This study is the first to examine the effects of halothane on the inward Ca^{2+} and delayed rectifier K^+ currents in freshly isolated single coronary smooth muscle cells. The main finding is that the same concentration of halothane depresses the I_{Ca} to a greater degree than the I_K. Very similar depressions were also observed in cardiac muscle cells.[3,4] In summary, the mechanism of a halothane-induced vasodilation of coronary vessels most likely involves a significant depression of I_{Ca}, although other effects of halothane can not be excluded.

References: 1) *J Physiol (Lond)* 427:657,1990; 2) *Circ Res* 65:1718,1989; 3) *Anesthesiology* 74:340,1991; 4) *Anesth Analg* 72:S286,1991.

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TITLE: PULSED IONTOPHORETIC DELIVERY OF AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

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Transdermal drug delivery through iontophoresis is a new form of drug therapy in which electrically charged molecules are induced to pass through the skin by an electrical field. Pulsed constant current iontophoretic delivery has been shown to enhance efficiency by a reduction of both skin impedance at high frequencies and polarization effects. We have developed a novel pulsed iontophoretic system. This paper reports its enhanced efficiency during antihypertensive therapy with an angiotensin-converting enzyme (ACE) inhibitor.

METHODS: Experiments were performed on eight adult New Zealand white rabbits (4.4 ± 0.7 kg). The animals were anesthetized using 1.75% halothane (inspired) in equal parts of oxygen and nitrous oxide. Blood pressure was recorded through central aortic catheterization. Hypertension was induced using a constant IV infusion of norepinephrine in saline at 0.02 mg/min (A on figure). The control group (n=4) was made hypertensive, but did not undergo iontophoresis. The treatment group (n=4) was made hypertensive; then pulsed iontophoretic ACE inhibitor therapy was employed using captopril in distilled water with a pulsed current density of 0.08 mA/cm^2 at 30% duty cycle (B on figure).

RESULTS: Baseline mean blood pressure (MBP) of 46 ± 4 mm Hg (n=8) was elevated by 38% to a hypertensive level of 63 ± 6 mm Hg (n=8). Following pulsed iontophoretic ACE inhibitor therapy, pressures were significantly reduced within 20 mins ($p<0.05$) by 30% to 44 ± 2 mm Hg. The change in MBP of the control group was found to be non-significant. Passive transdermal delivery of captopril produced no marked reduction in MBP. Results are shown in the figure.

CONCLUSION: The present investigation thus provides the first such successful pulsed iontophoresis of an ACE inhibitor. The system offers an effective means of enhanced transdermal drug delivery. The advantages of this drug deliver system include avoidance of GI tract absorption variability and hepatic first-pass metabolism. Lower doses of drugs are required for therapeutic effects thereby reducing the incidence of side effects.