Title: DIFFERENTIAL ELECTROPHYSIOLOGIC EFFECTS OF HALOTHANE AND VERAPAMIL IN CANINE CARDIAC PURKINJE CELLS

Authors: M.R. Lauer, M.S., B.F. Rusy, M.D.

Affiliation: Departments of Anesthesiology and Physiology, University of Wisconsin Medical School, Madison, Wisconsin, 53792

Introduction. It has been reported that halothane (H), as with verapamil (V), may inhibit the Na/Ca-dependent slow inward current in cardiac muscle cells[1]. V has been shown to cause an increase in the slope of the plateau phase of the cardiac Purkinje cell fast response action potential (FRAP) and a decrease in the upstroke velocity of the Purkinje cell slow response action potential (SRAP), both results thought due to an inhibition of the slow inward current. While the electrophysiologic effects of V are largely reversed by increasing the extracellular Ca concentration, we have observed in the present study that this is not the case for H. We have examined and compared the effects of H and V on various parameters of the normal canine cardiac Purkinje cell FRAP in the presence of normal (2.7 mM) and 2X (5.4 mM) and 4X (10.8 mM) normal extracellular Ca concentrations.

Methods. Standard microelectrode techniques were used to record action potentials from canine cardiac Purkinje cells in false tendons. The tissue preparations were superfused in a tissue bath with oxygenated Tyrode solution (pH 7.3) at 37 °C and electrically stimulated at 90/min. H-containing Tyrode solutions are produced using a calibrated Draeger vaporizer. Concentrations of H are expressed as vaporizer setting. In some Purkinje cells, SRAPs were produced according to the method of Davis et al.[2] by reducing the pH of the Tyrode solution to 6.0. Continuous impalement of the same cell was maintained during each experiment.

Results. Data summarized in Table 1 indicate that the electrophysiologic effects of V are largely reversed by increasing the extracellular Ca concentration. Data summarized in Table 2 suggest that the electrophysiologic effects of 1% or 2% H are exacerbated by increasing the extracellular Ca concentration. In particular, unlike the situation with V, increasing the Ca concentration enhances the H-induced increase in slope phase 2, decrease in slope phase 3, and decrease in time to repolarize to -60 mV. That increasing the extracellular Ca concentration does indeed increase the slow inward current in H-treated cells is suggested by the results shown in Figure 1. The H-induced decrease in the SRAP upstroke velocity is reversed by increasing the extracellular Ca concentration.

Discussion. The results suggest that in canine Purkinje cells H does not simply mimic the electrophysiologic effects of V. Although the apparent H-induced inhibition of the slow inward current is reversed by increasing the extracellular Ca concentration, the data suggest that Ca may potentiate an effect of H to increase the magnitude of an outward current during the action potential plateau.

References.

1. Lynch C, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. Anesthesiology 55:360-368, 1981

2. Davis LD, Helmer PR, Ballantyne F: Production of slow responses in canine cardiac Purkinje fibers exposed to reduced pH. J Molec Cell Cardiol 8:61-76, 1976

TABLE 1

Parameter	Control 2.7 mM Ca	Verapamil (0.5ug/ml) 2.7 mM Ca	5.4 mM Ca	10.8 mM Ca
MDP	-92.7 (2.7)	-91.2 (2.4)	-91.8 (2.1)	-90.5 (2.6)
SLP2	150.8 (18.9)	246.0 (28.0)*	188.7 (16.2)+	173.8 (15.2)
SLP3	909.7 (47.0)	398.3 (81.2)*	573.5 (72.4)+	716.2 (70.5)
TT60	256.3 (32.4)	187.7 (14.5)*	196.7 (15.3)	203.2 (15.0)
APD	321.2 (16.0)	414.2 (18.9)*	358.8 (15.1)+	354.3 (16.6)

MDP = maximum diastolic potential (mV); SLP2 = slope of phase 2 of action potential (mV/sec); SLP3 = slope of phase 3 (mV/sec); TT60 = time to repolarize to -60 mV (msec); APD = action potential duration (msec)

Mean (+/- SD); N=6
* P<0.05 compared to control;
+ P<0.05 compared to verapamil plus 2.7 mM Ca
# P<0.05 compared to verapamil plus 5.4 mM Ca

TABLE 2

Parameter	Control 2.7 mM Ca	1% Halothane 2.7 mM Ca	5.4 mM Ca	10.8 mM Ca
MDP	-89.0 (4.4)	-84.0 (4.6)*	-81.5 (3.5)	-82.0 (3.7)
SLP2	142.7 (13.5)	175.2 (15.8)*	218.7 (23.1)+	260.8 (15.7)#
SLP3	898.2 (38.4)	665.0 (23.2)*	543.0 (32.8)+	445.2 (31.1)#
TT60	251.0 (17.6)	248.2 (20.1)	223.8 (17.1)+	199.2 (8.5)#
APD	314.8 (10.1)	334.8 (9.6)*	337.2 (6.5)	339.5 (9.3)
		2% Halothane		
MDP	-94.5 (4.2)	-87.8 (3.3)*	-87.3 (3.7)	-88.2 (3.1)
SLP2	142.7 (18.1)	249.8 (14.7)*	272.7 (15.8)+	294.7 (22.8)#
SLP3	906.3 (38.7)	488.7 (35.2)*	435.8 (27.5)+	362.5 (31.8)#
TT60	253.3 (15.2)	233.2 (19.2)*	212.2 (16.4)+	198.2 (12.9)#
APD	320.0 (8.3)	346.7 (14.5)*	350.8 (18.1)	355.0 (10.3)

Mean (+/- SD); N=6
* P<0.05 compared to control
+ P<0.05 compared to halothane plus 2.7 mM Ca
# P<0.05 compared to halothane plus 5.4 mM Ca

FIGURE 1