Pharmacological basis in the development of agents against myocardial ischemia

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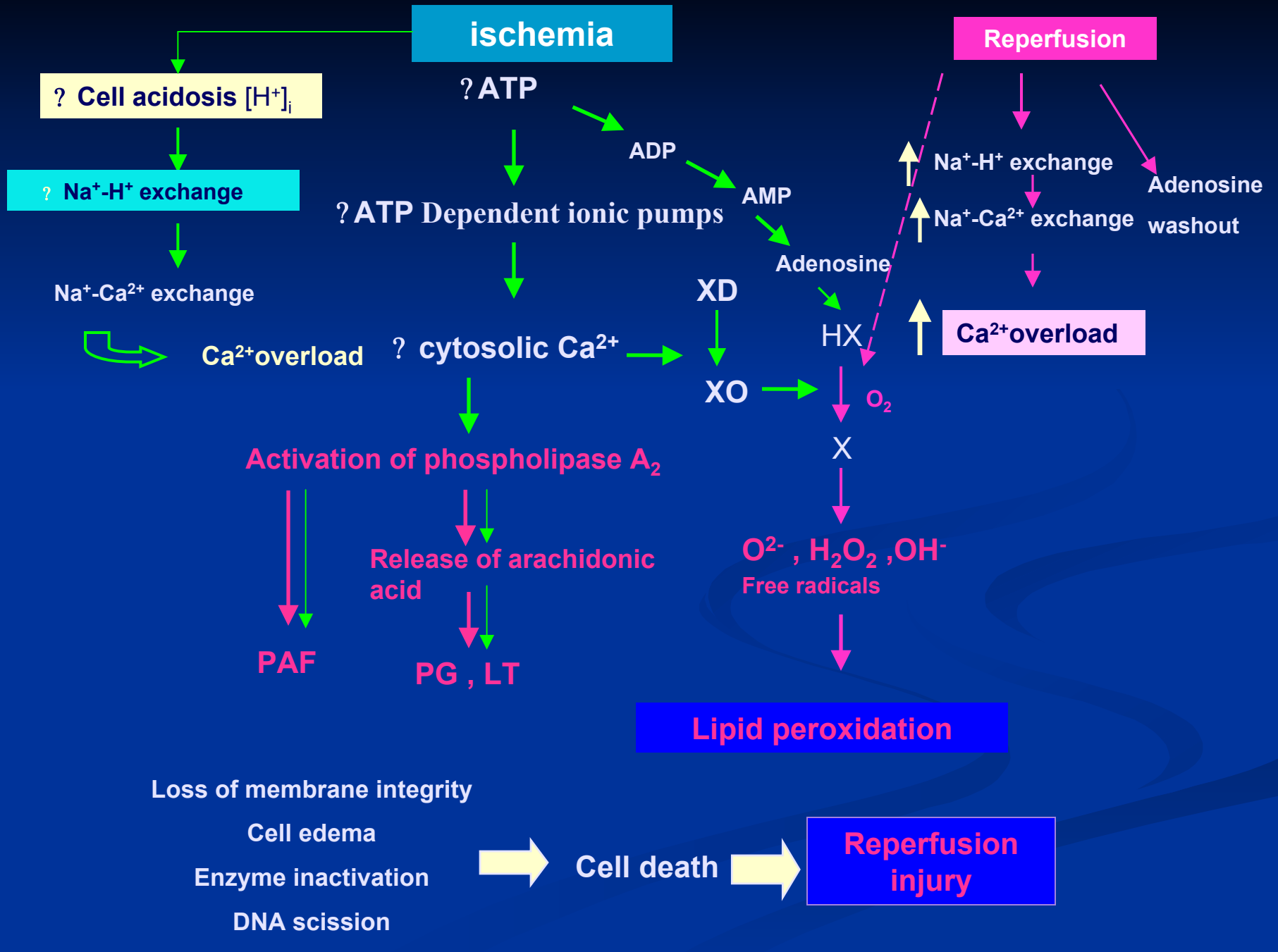
Pathological Consequence of Reperfusion of Ischemic Myocardium

1. Excessive generation of free radical
2. Secondary injury of myocardium and coronary vessel
3. Severe cardiac arrhythmia
4. Sudden death
5. Remodel of myocardium

Mechanisms of Ischemia and ischemia-reperfusion injury

1. Disturbance of cellular ion homeostasis including H^+, Na^+, and Ca^{2+}
2. Reduced ATP level
3. Increased oxidative stress
4. Increased electrical disturbance
5. Gap junction uncoupling
6. Release of inflammatory cytokines (TNFα, IL-1β, IL-6) and other inflammatory mediators(PAF)


ischemia
Reperfusion
? Cell acidosis [H+]i
? ATP
ADP
AMP
Adenosine
? Na+-H+ exchange
? ATP Dependent ionic pumps
Na+-H+ exchange
Adenosine washout
Na+-Ca2+ exchange
Na+-Ca2+ exchange
Ca2+overload
? cytosolic Ca2+
XD
HX
Ca2+overload
XO
O2
X
Activation of phospholipase A2
Release of arachidonic acid
O2- , H2O2 ,OH-
Free radicals
PAF
PG , LT
Lipid peroxidation
Loss of membrane integrity
Cell edema
Enzyme inactivation
DNA scission
Cell death
Reperfusion injury

Object of Drug Treatment

1. Conversion of arrhythmia to normal rhythm
2. Prevention of reperfusion injury
3. Prevention of myocardial infarction
4. Prevention of progression of disease

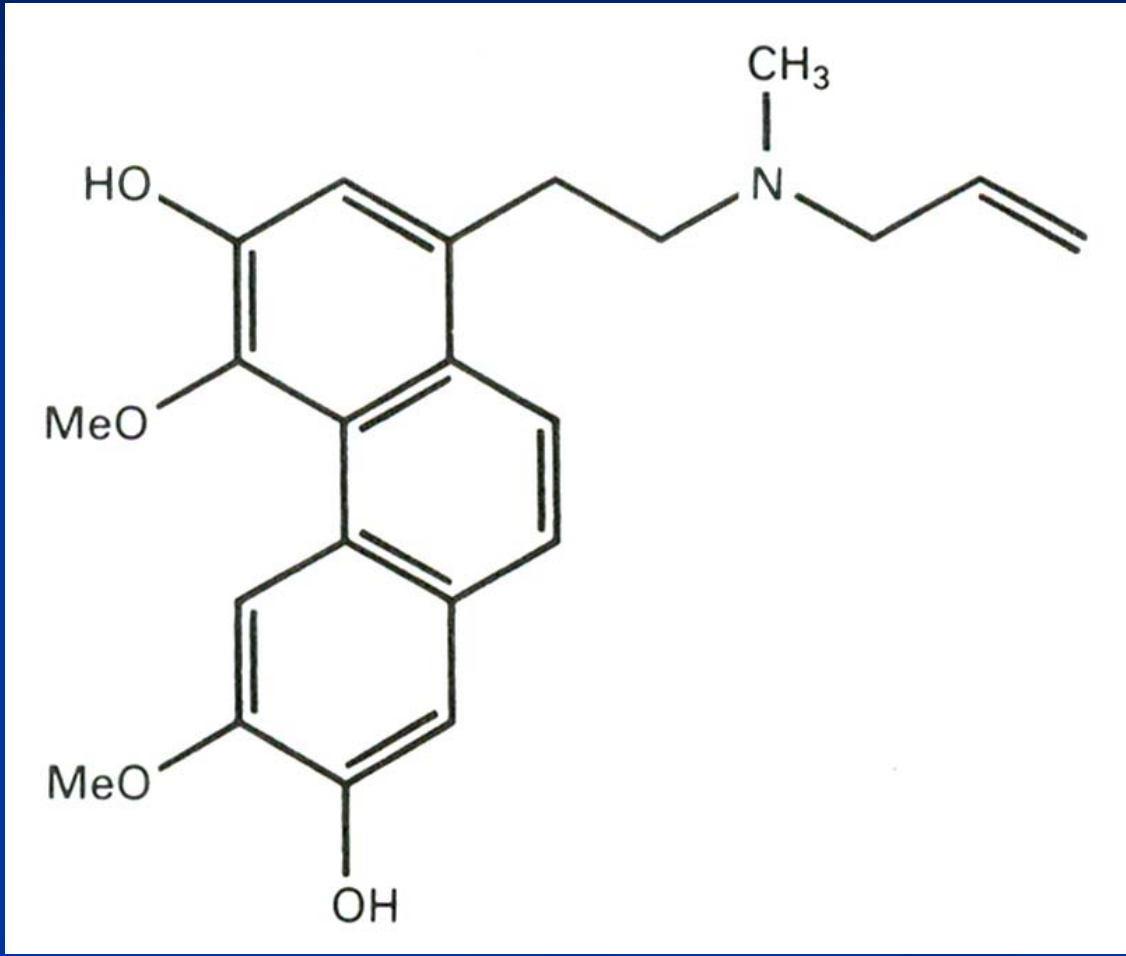
Ideal Therapeutic Agent

1. Exert antiarrhythmic activity dose-dependently
2. Inhibit myocardial infarction dose-dependently
3. Increase survival rate
4. Prevent progression of disease

Methods for evaluation of drug effects on cardiac tissues

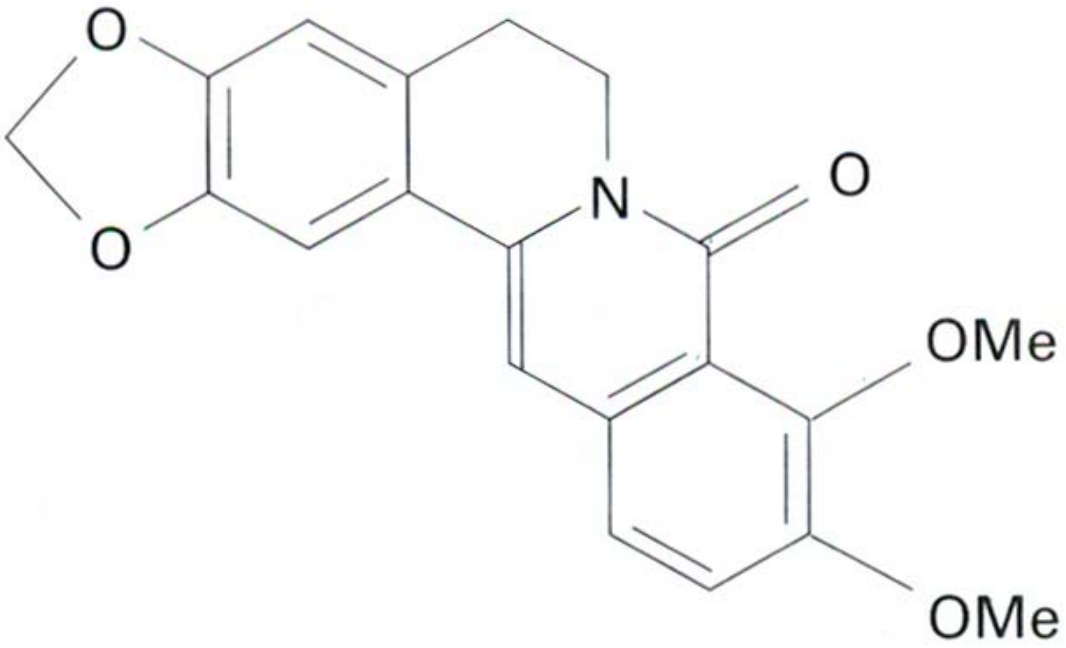
1. Effect on ionic currents of cardiac cells
2. Electrophysiological effect on Langendorf-perfused heart
3. Effect on chemical-induced arrhythmia
4. Effect on ischemia-induced arrhythmia
5. Effect on reperfusion-induced arrhythmia
6. Measurement of infarct zone
7. Measurement of cardiac function

The electrophysiological effects of antiarrhythmic potential of a secoaporphine, N-allylsecoboldine



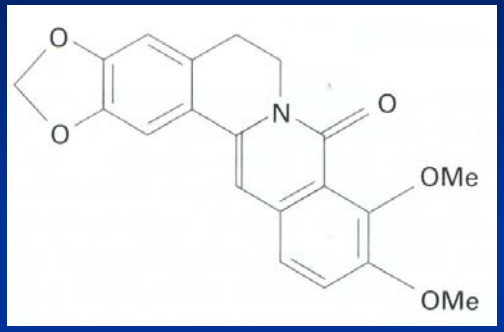
Br. J. Pharmacol. (1994), **113**, 221-227

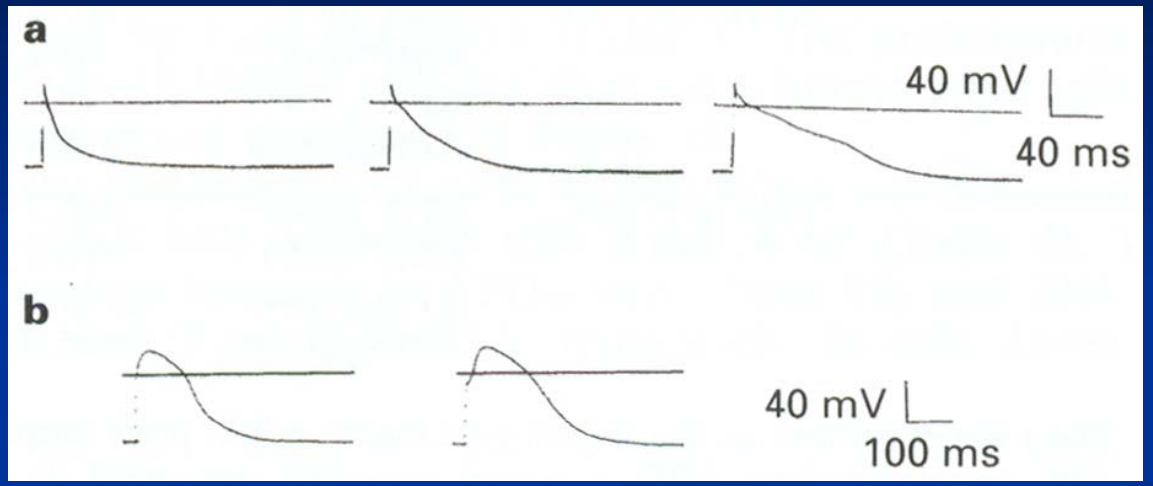
Mechanical and electrophysiological effects of 8-oxoberberine(JKL1073A) on atrial tissue

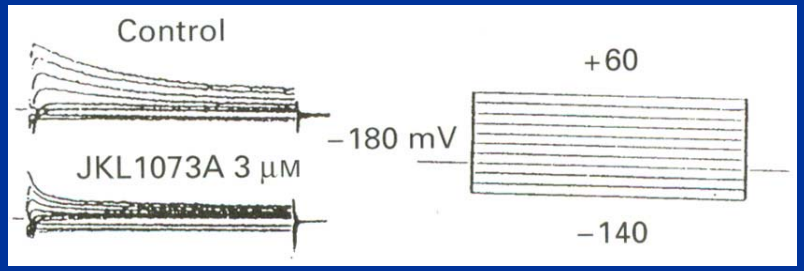


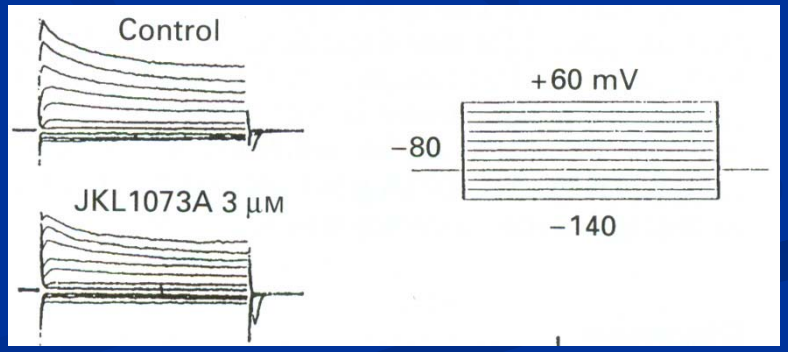
British Journal of Pharmacology(1996) **118**,503-512

8-Oxoberberine prolong APD of Atrial cells by Inhibition of 4-AP Sensitive Potassium Outward Current



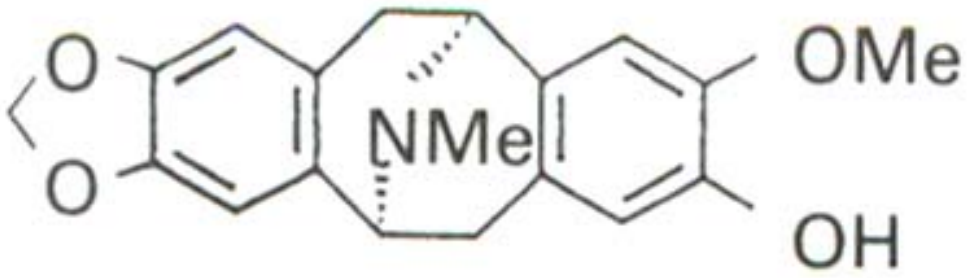




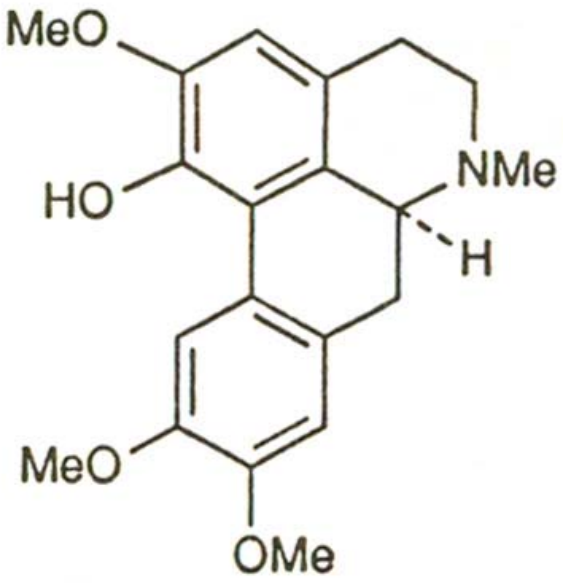


Electrophysiological basis for antiarrhythmic efficacy, positive inotropy and low proarrhythmic potential of (-)-caryachine

a

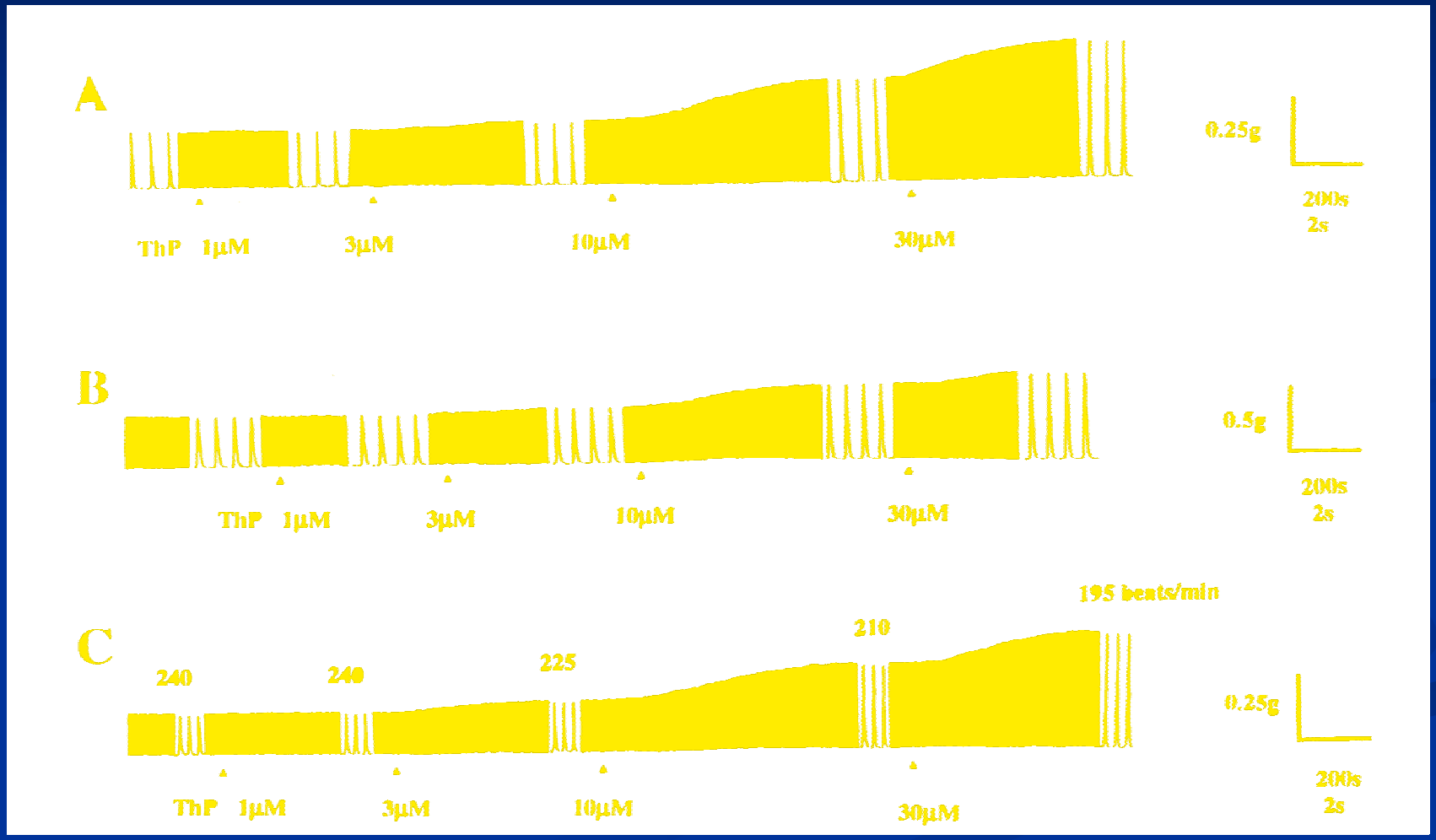


*British Journal of Pharmacology(***1995**) **116**,3211-3218

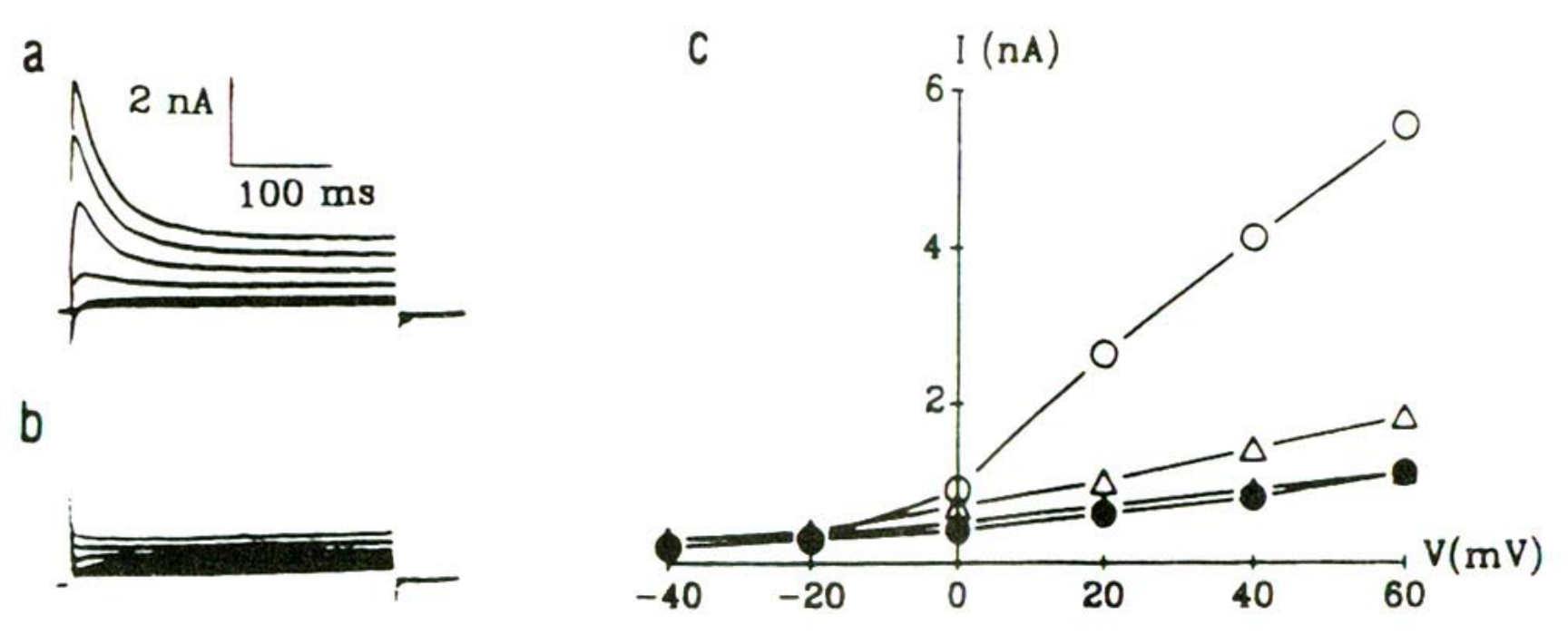


Thaliporphine

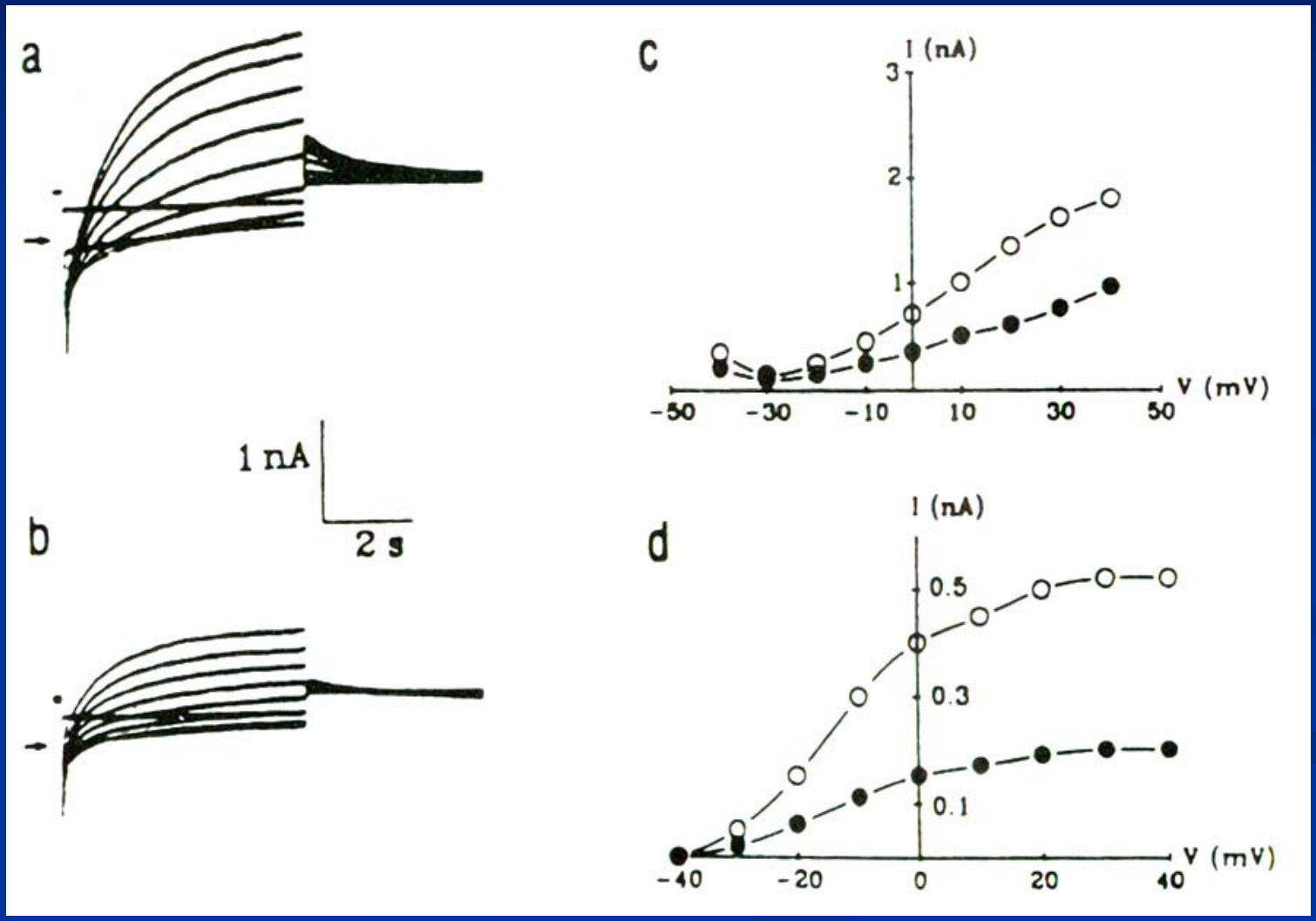
Effect of thaliporphine on cardiac tissues



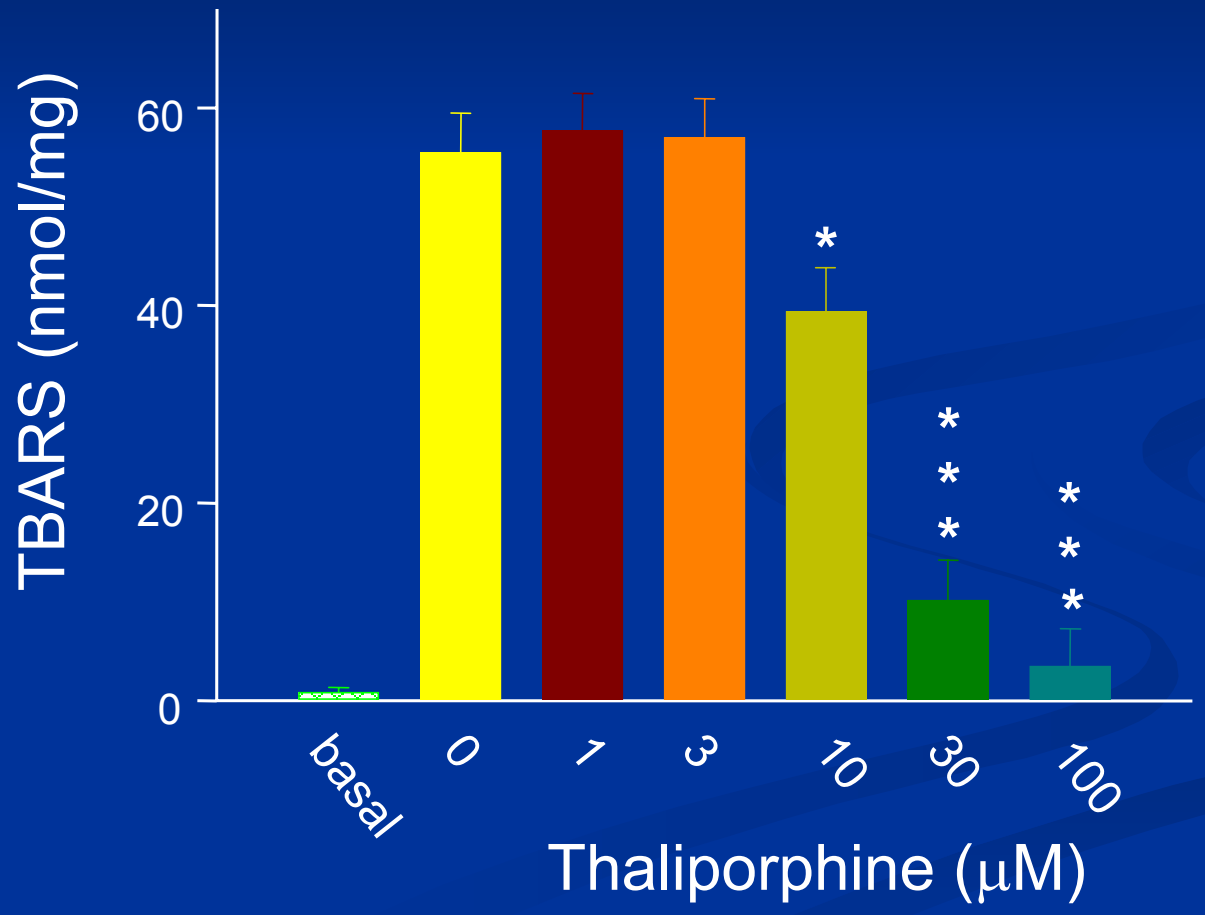
Effect of thaliporphine (10μM) on potassium outward current of rat ventricular cells



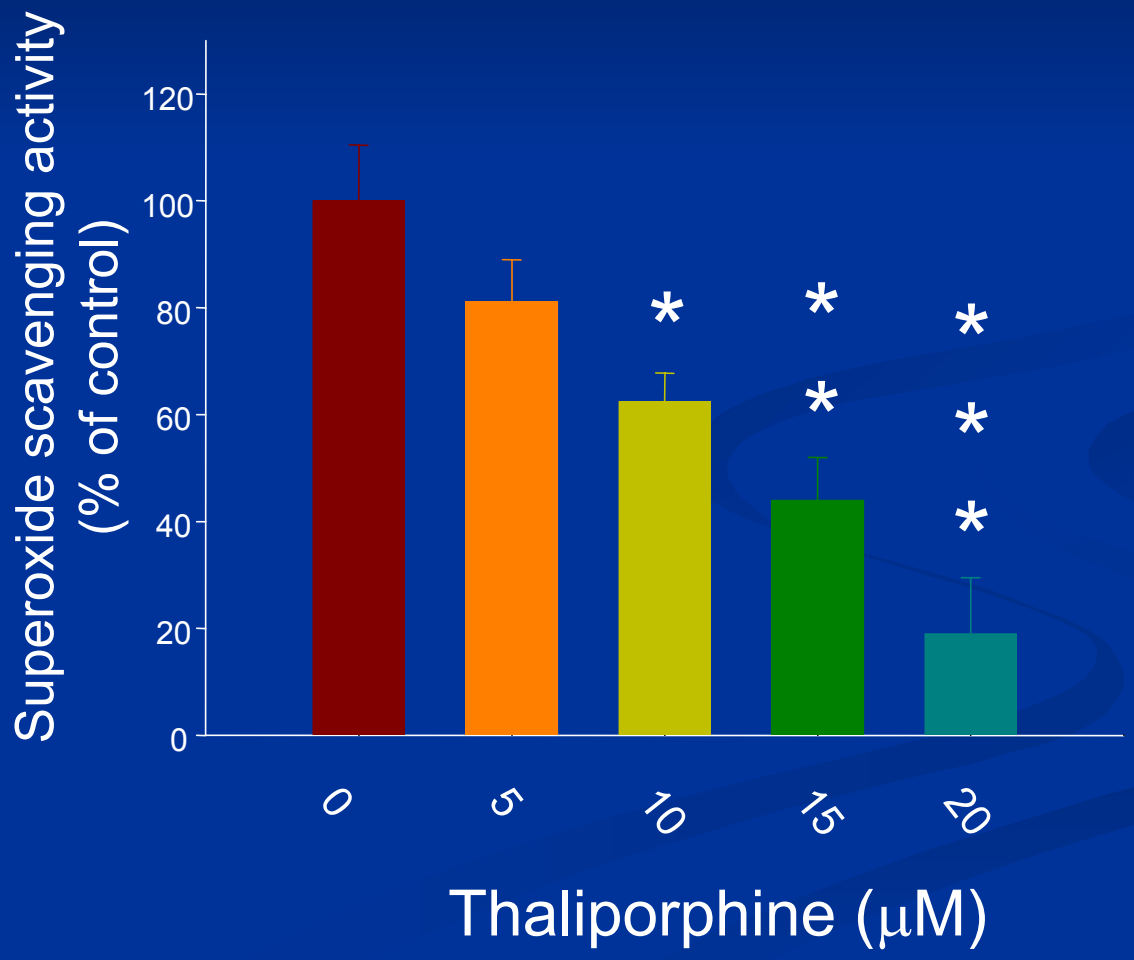
Effect of thaliporphine (10μM) on potassium outward current of GP ventricular cells



Effect of thaliporphine on copper-induced LDL peroxidation



Superoxide anion scavenging activity of thaliporphine



Effect of thaliporphine on ischemia-induced arrhythmias in the in vivo anesthetized rat

	Ventricular tachycardia		Ventricular fibrillation		Mortality (%)
	Incidence (%)	Duration (s)	Incidence (%)	Duration (s)	
Thaliporphine g/kg					
vehicle	100	36.8 ? 8.8	57	32.1 ? 8.9	29
3.5 x 10^{-7}	60	16.1 ? 7.4	20	6.7 ? 4.9	0
3.5 x 10^{-6}	50*	5.7 ? 3.3*	10	0.5 ? 0.5*	0
3.5 x 10^{-5}	10*	0.3 ? 0.3*	0*	0.0 ? 0.0*	0

Values for duration of VT and VF are shown as the mean ? SE of 10-14 rats. *Statistical difference at the level of $p < 0.05$, as compared with the vehicle. Vehicle is 0.01% DMSO in normal saline.

Effect of thaliporphine and L-NAME + thaliporphine on myocardial infarct size caused by occlusion (4 hours) of the left coronary artery

	n	Area at risk (% of ventricle)	Necrotic (% of ventricle)	Necrotic (% of area at risk)
Thaliporphine g/kg				
vehicle	10	45.2 ? 1.0	19.8 ? 2.2	43.9 ? 5.1
3.5 x 10^{-7}	9	47.0 ? 0.6	17.9 ? 2.3	38.1 ? 5.0
3.5 x 10^{-6}	8	46.5 ? 0.9	13.4 ? 1.2*	29.0 ? 2.5*
3.5 x 10^{-5} (1)	11	46.9 ? 0.5	5.0 ? 0.9†	10.7 ? 1.8†
L-NAME g/kg				
1 x 10^{-3}	9	47.5 ? 0.2	21.4 ? 3.5	45.1 ? 7.2
1 x 10^{-3} + (1)	8	47.0 ? 0.4	21.8 ? 4.0	46.5 ? 6.6

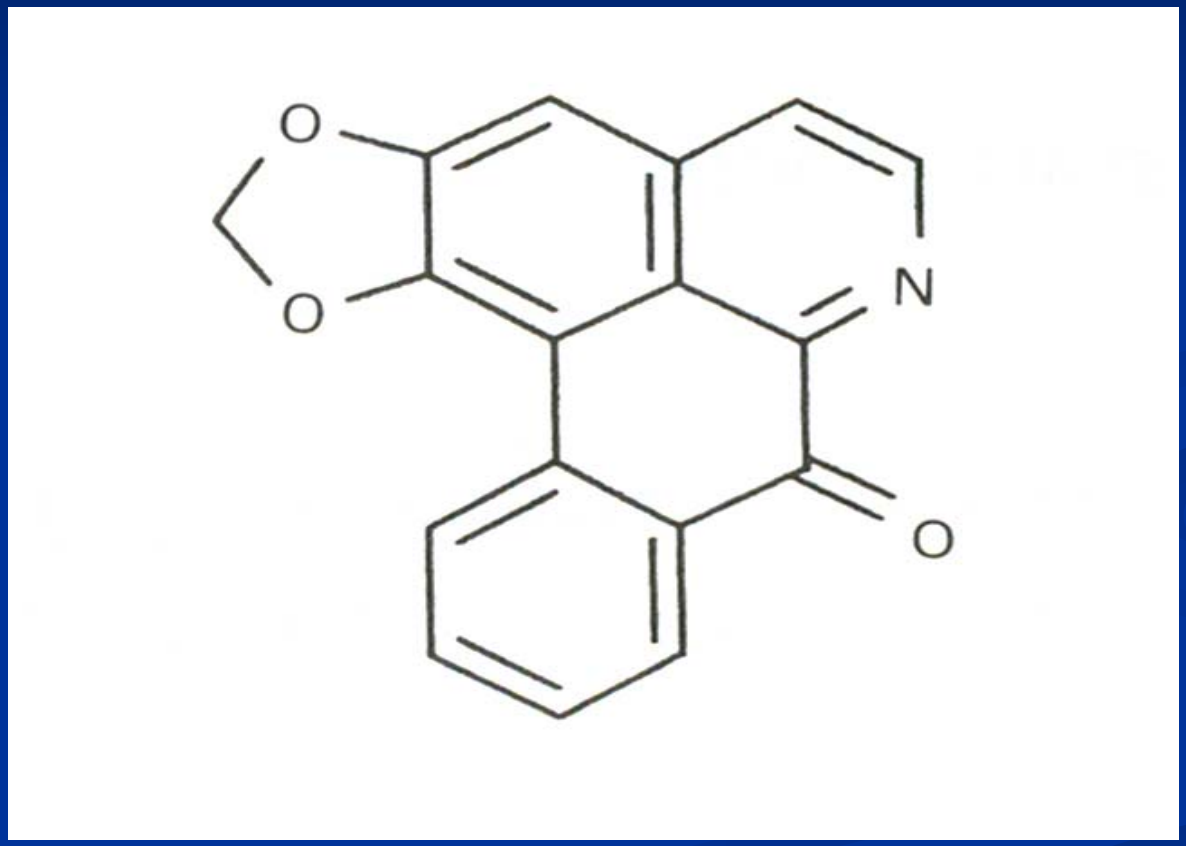
Data are presented as means ? SE; n, number of animals. * $p < 0.05$, † $p < 0.01$, as compared with the vehicle. Vehicle is 0.01% DMSO in normal saline.

Effect of thaliporphine on reperfusion-induced arrhythmias in the in vivo anesthetized rat

	Ventricular tachycardia		Ventricular fibrillation		Mortality (%)
	Incidence (%)	Duration (s)	Incidence (%)	Duration (s)	
Thaliporphine g/kg					
vehicle	100	17.4 ? 5.6	88	92.4 ? 20.5	75
3.5 x 10^{-7}	86	28.6 ? 10.4	86	75.5 ? 15.6	43
3.5 x 10^{-6}	57	14.6 ? 9.1	29*	9.2 ? 8.3*	0*
3.5 x 10^{-5}	75	6.7 ? 2.9	13*	1.3 ? 1.3*	0*

Values for duration of VT and VF are shown as the mean ? SE of 10-14 rats. *Statistical difference at the level of $p < 0.05$, as compared with the vehicle. Vehicle is 0.01% DMSO in normal saline.

Electrophysiological mechanisms for antiarrhythmic efficacy and positive inotropy of liriodenine, a natural aporphine alkaloid from *Fissistigma glaucescens*

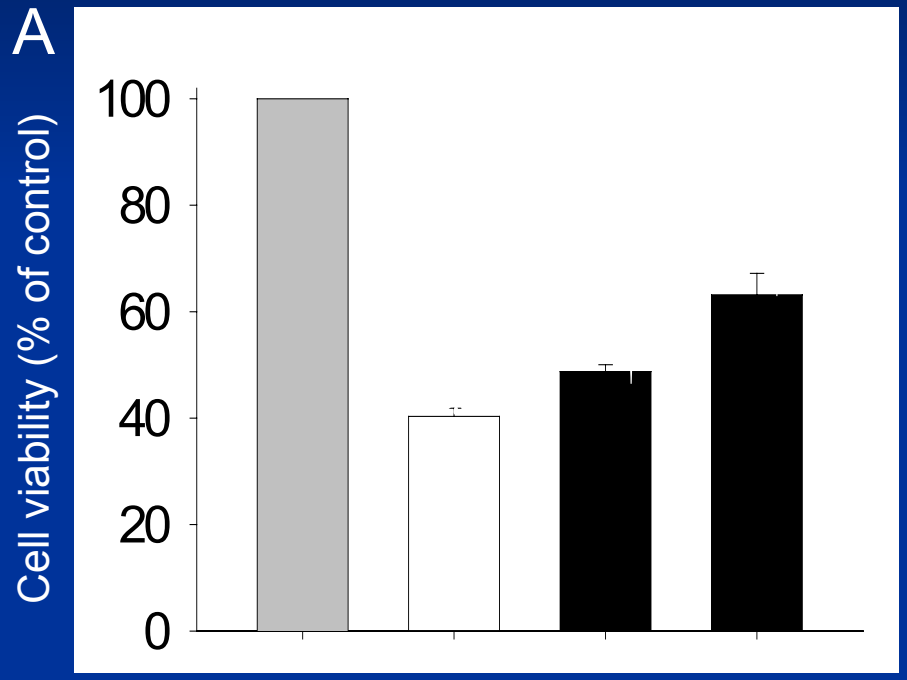


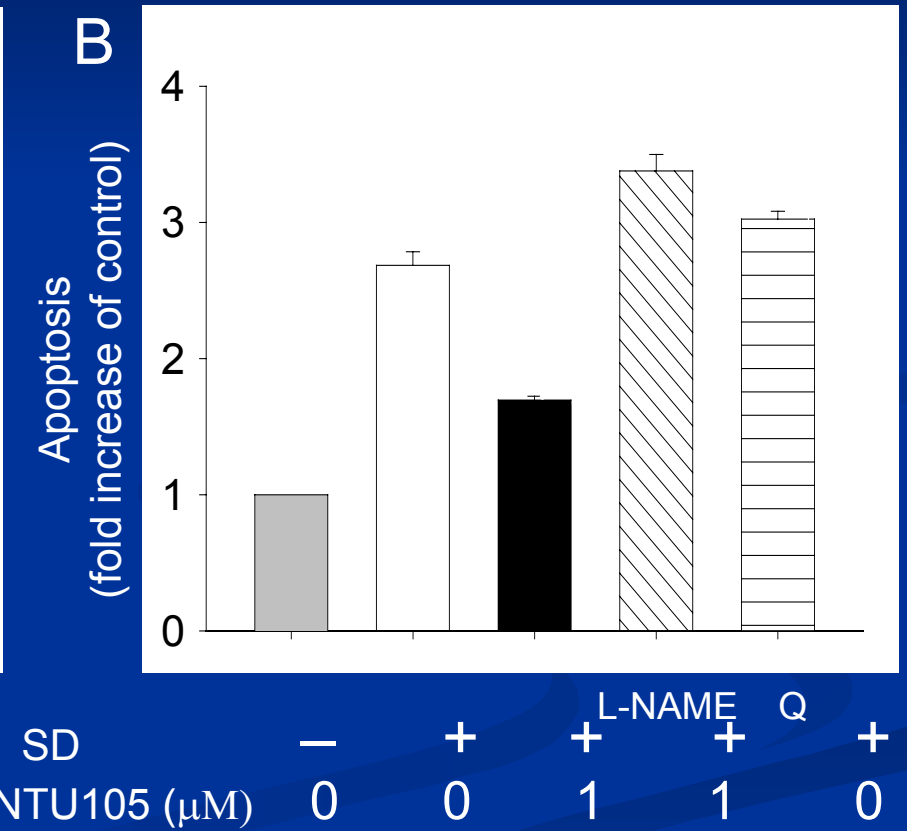
Br. J. Pharmacol. **(1996), 118,** 1571-1583

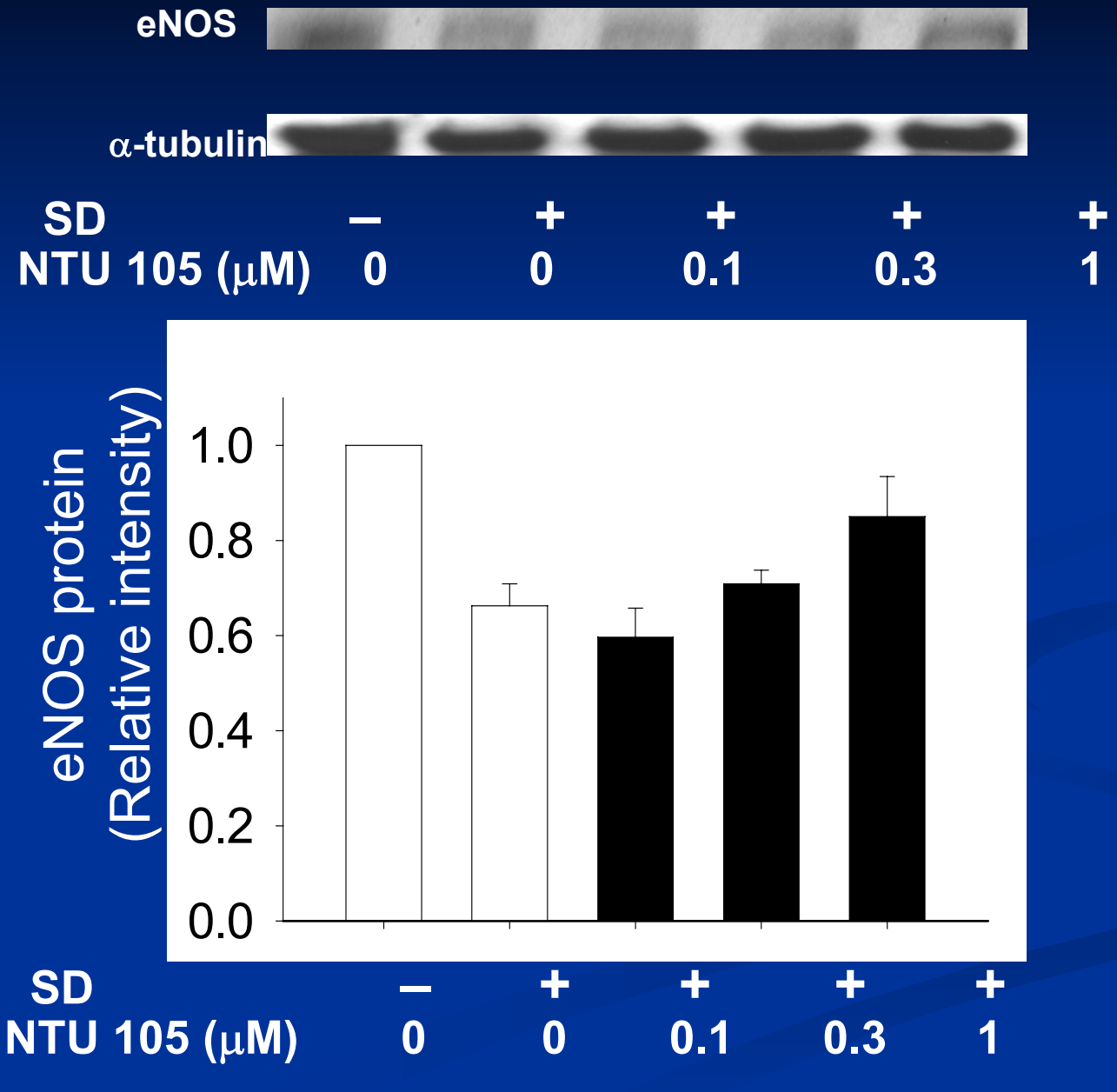
Effect of Liriodenine (NTU-105) on reperfusion-induced arrhythmias in the in vivo anesthetized rat

	VT		VF		Mortality
	Incidence (%)	Duration (s)	Incidence (%)	Duration (s)	(%)
Sham Vehicle (4)	–		–		–
Operated Vehicle (10)	100	65.55 ? 14.76	100	148.94 ? 47.19	80
NTU-105 2.75 x 10^{-9} g/kg (10)	100	52.57 ? 10.80	50	98.07 ? 49.48	40
NTU-105 2.75 x 10^{-8} g/kg (10)	100	35.47 ? 9.37	50	15.87 ? 9.48*	10
NTU-105 2.75 x 10^{-7} g/kg (10)	100	5.55 ? 1.84**	0	0.0 ? 0.0**	0

•[a] Vehicle is 0.1% DMSO in normal saline; (n), number of experiments; values for duration of VT and VF are shown as the mean ?S.E. Statistical difference at the level of * P<0.05 and ** P<0.01, as compared with vehicle.

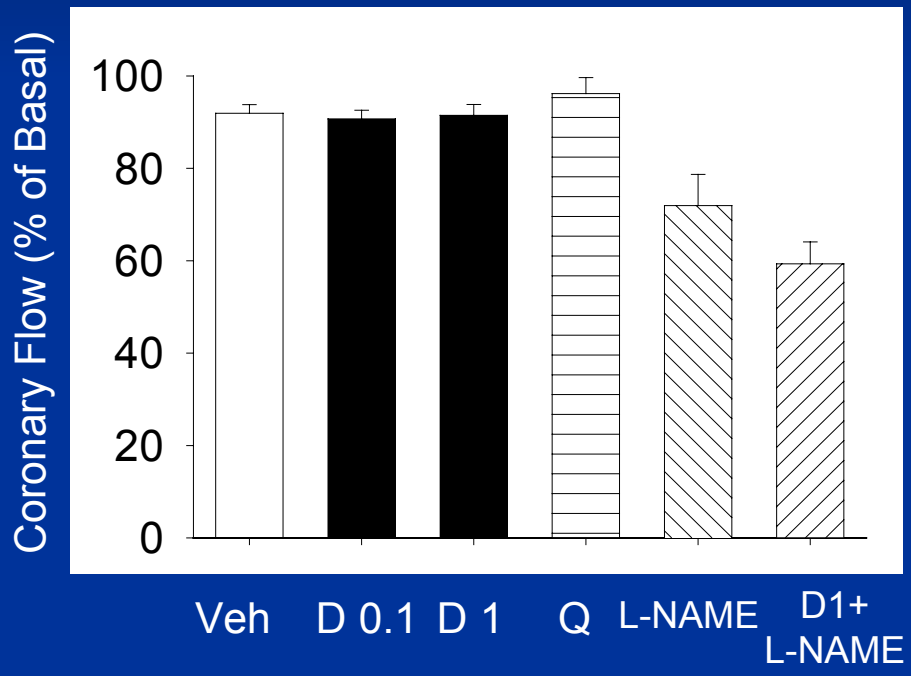

A
Cell viability (% of control)
100
80
60
40
20
0
SD
NTU105 (μM)
–
0
+
0
+
0.1
+
1


B
Apoptosis
(fold increase of control)
4
3
2
1
0
L-NAME
Q
SD
NTU105 (μM)
–
0
+
0
+
1
+
1
+
0

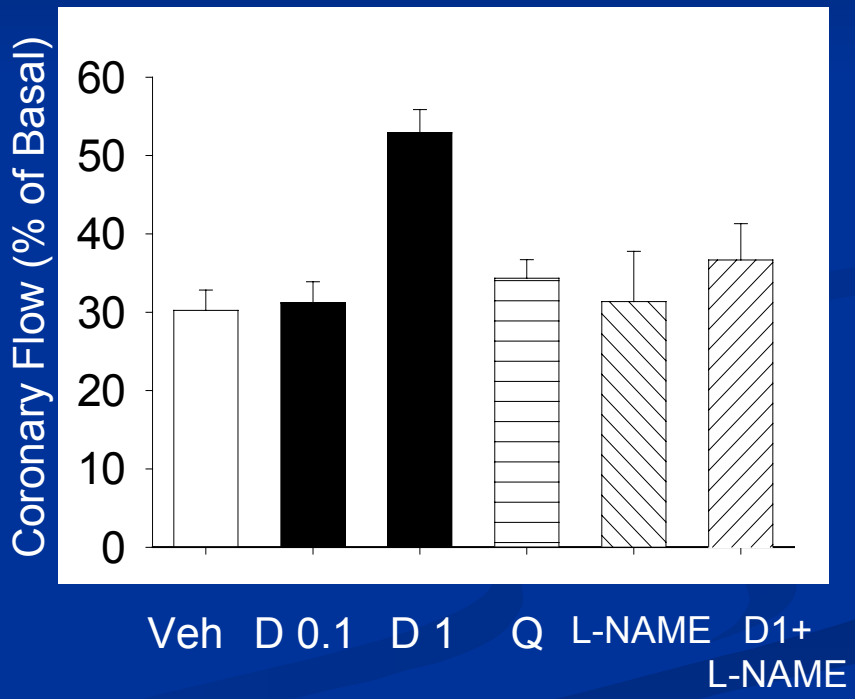

eNOS
α-tubulin
SD – + + + +
NTU 105 (μM) 0 0 0.1 0.3 1
eNOS protein
(Relative intensity)
1.0
0.8
0.6
0.4
0.2
0.0
SD – + + + +
NTU 105 (μM) 0 0 0.1 0.3 1

D: NTU-105

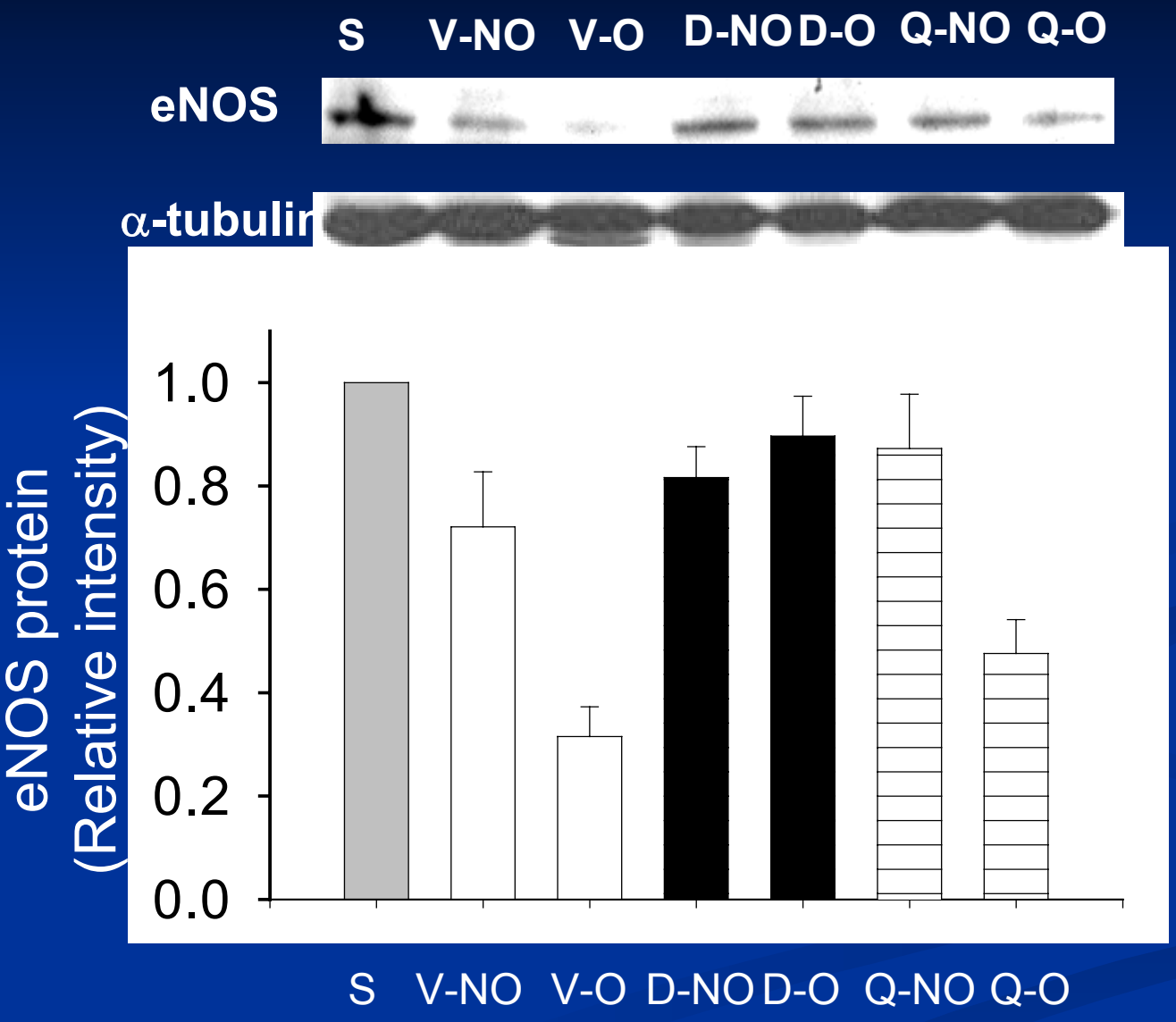
A


Coronary Flow (% of Basal)
100
80
60
40
20
0
Veh
D 0.1
D 1
Q
L-NAME
D1+ L-NAME

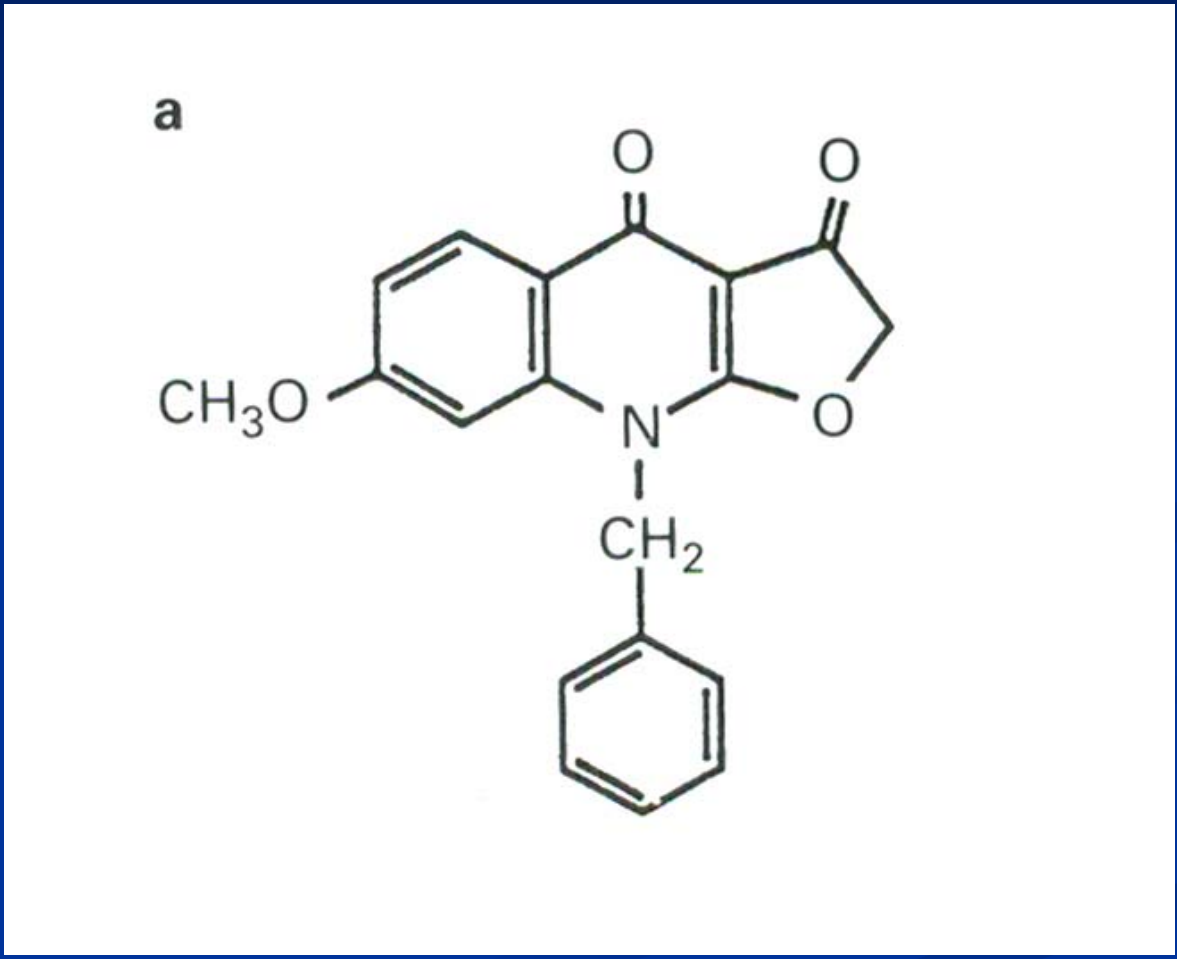
B


Coronary Flow (% of Basal)
60
50
40
30
20
10
0
Veh
D 0.1
D 1
Q
L-NAME
D1+ L-NAME

D: NTU-105

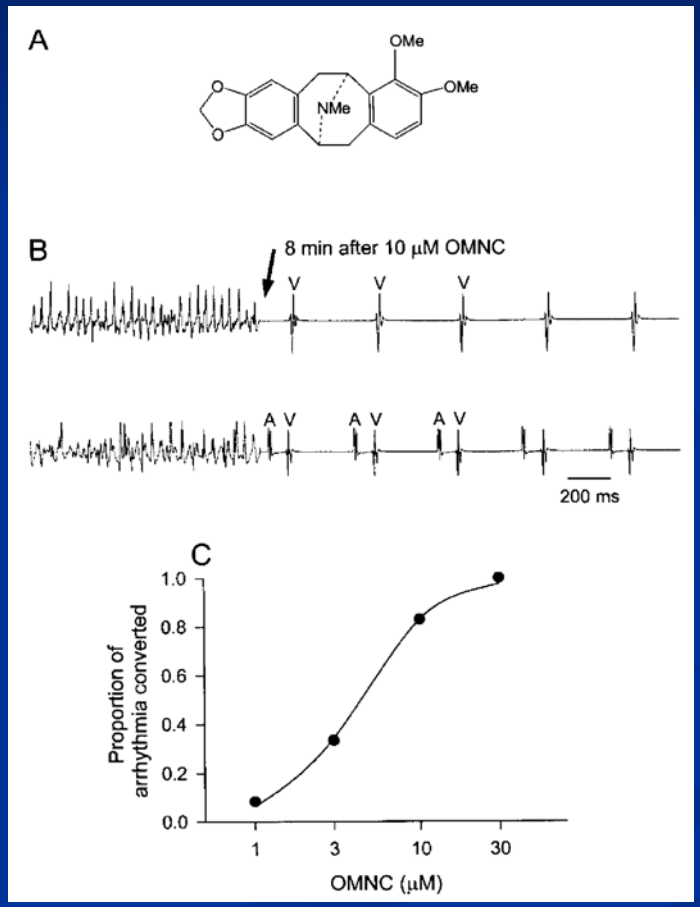

S
V-NO
V-O
D-NO
D-O
Q-NO
Q-O
eNOS
α-tubulin
eNOS protein
(Relative intensity)
1.0
0.8
0.6
0.4
0.2
0.0
S
V-NO
V-O
D-NO
D-O
Q-NO
Q-O

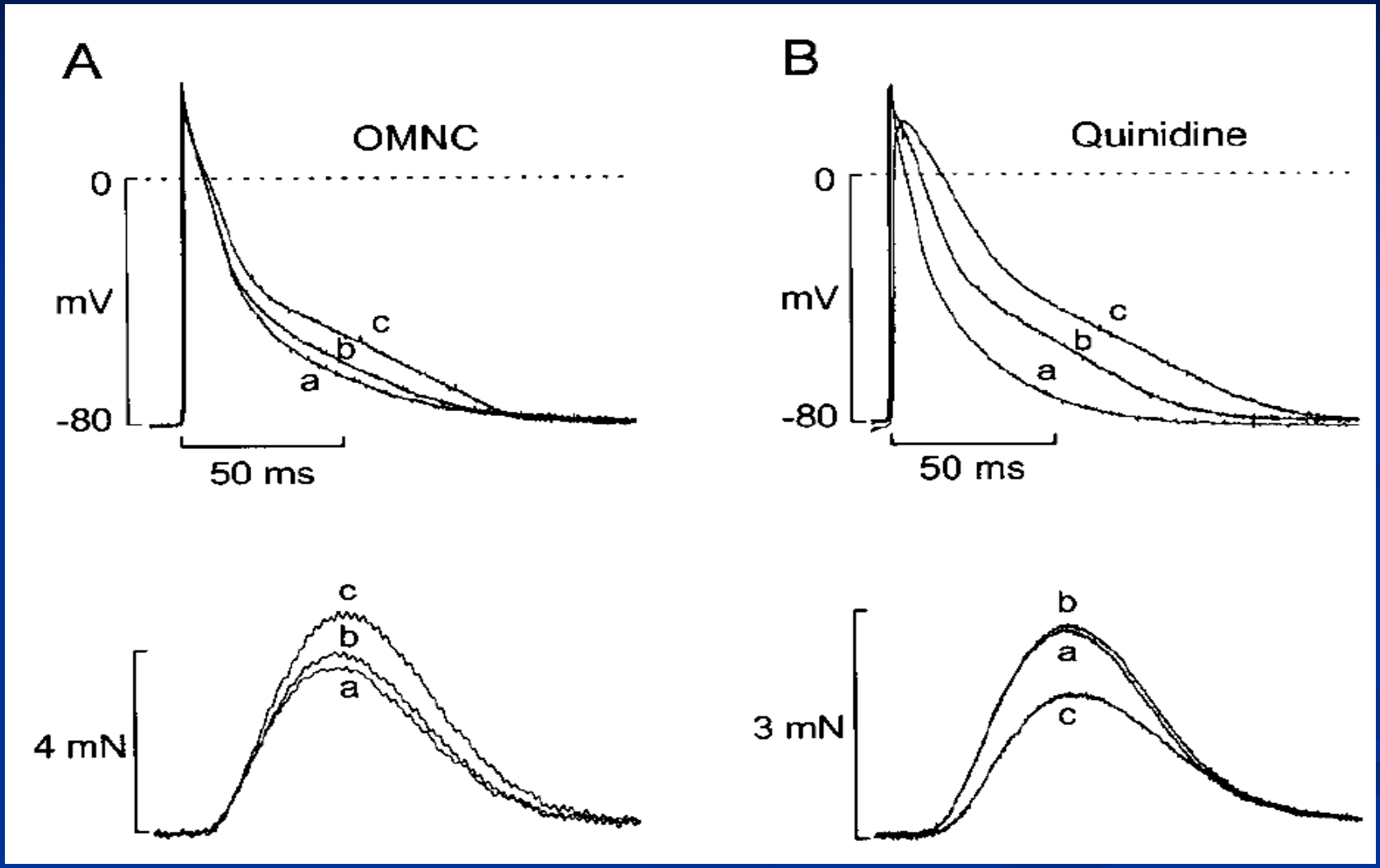
Electrophysiological basis for the antiarrhythmic action and positive inotropy of HA-7, a furoquinoline alkaloid derivative, in rat heart



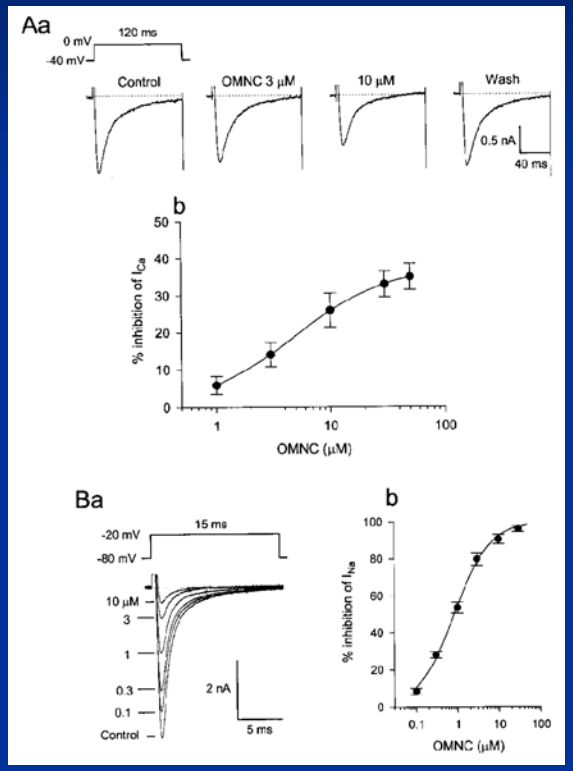
British Journal Pharmacology **(1997)122**, 1285-1298

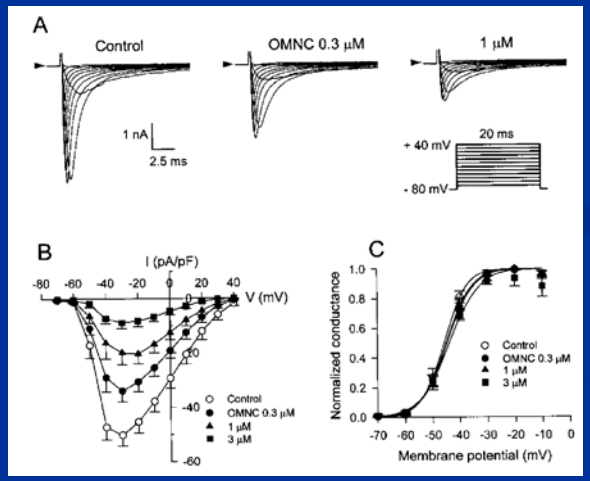
Cardiac electrophysiologic and antiarrhythmic actions of a pavine alkaloid derivative, *O*-methyl-neocaryachine, in rat heart

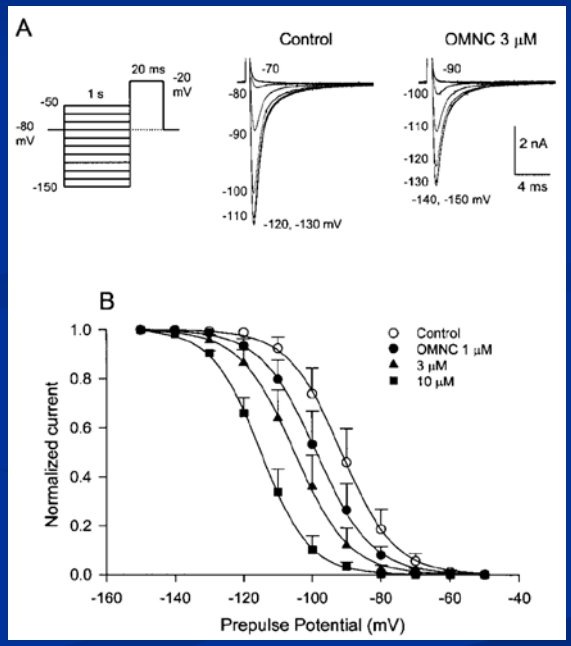



A
OMNC
0
mV
-80
c
b
a
50 ms
B
Quinidine
0
mV
-80
c
b
a
50 ms
c
b
a
4 mN
b
a
c
3 mN

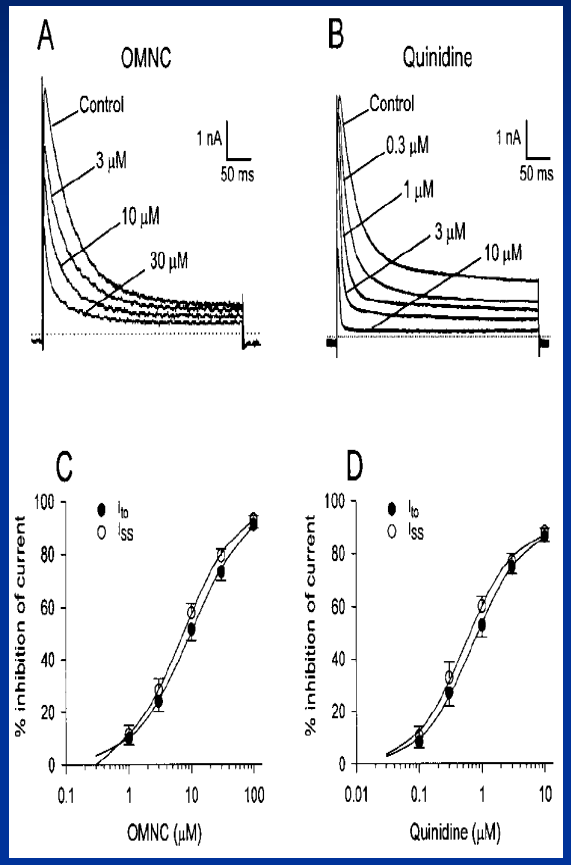
Effect of OMCN on INa

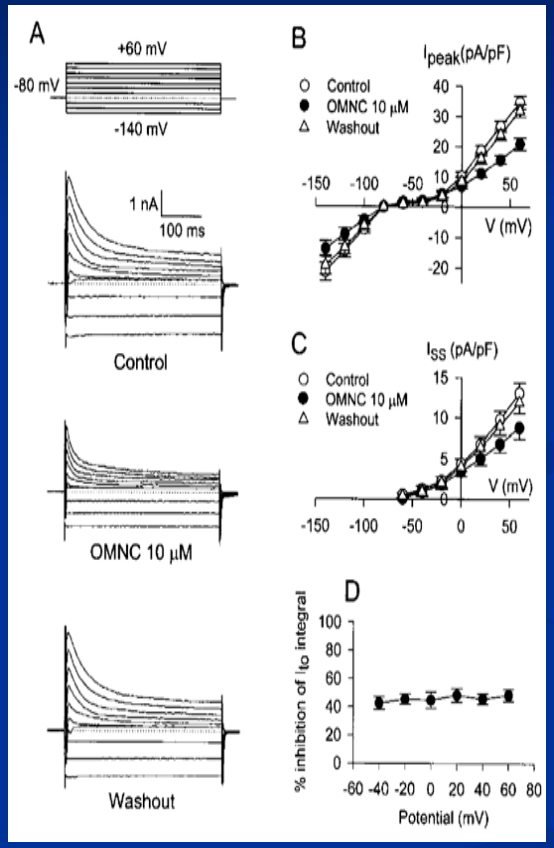


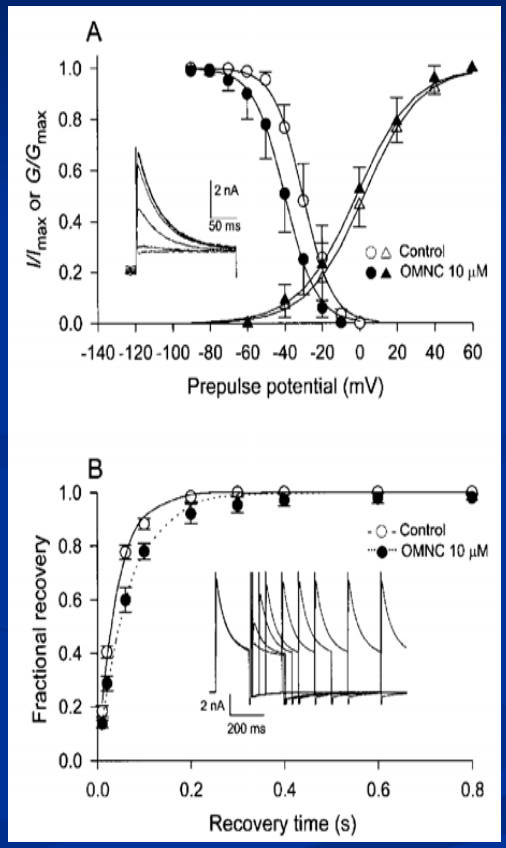




Effect of OMCN on potassium currents







Original Paper

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Ionic Mechanisms for the Antiarrhythmic Action of Cinnamophilin in Rat Heart

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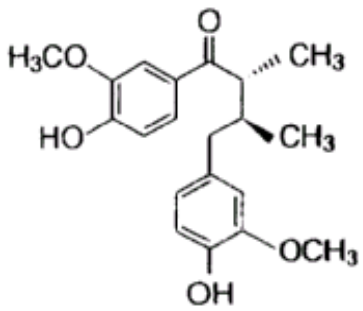
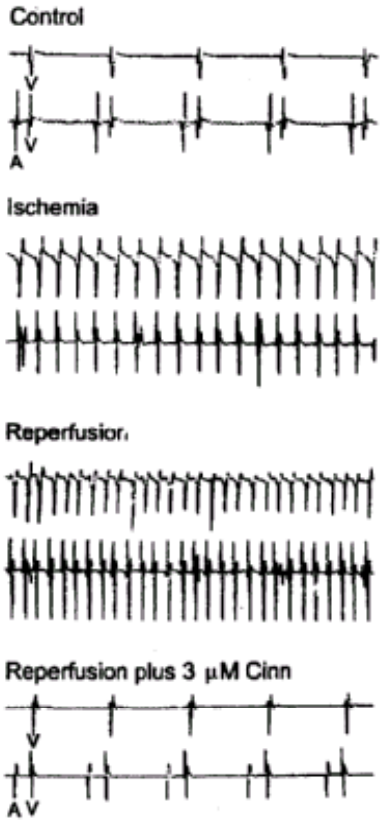


Fig. 1. Chemical structure of Cinn.



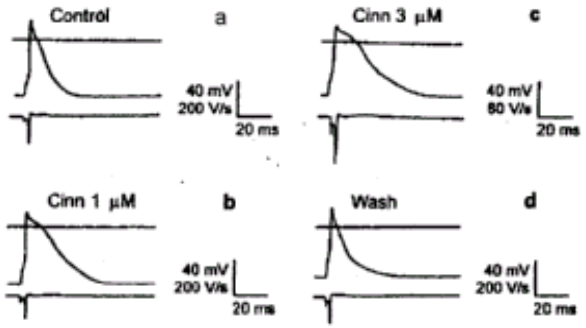
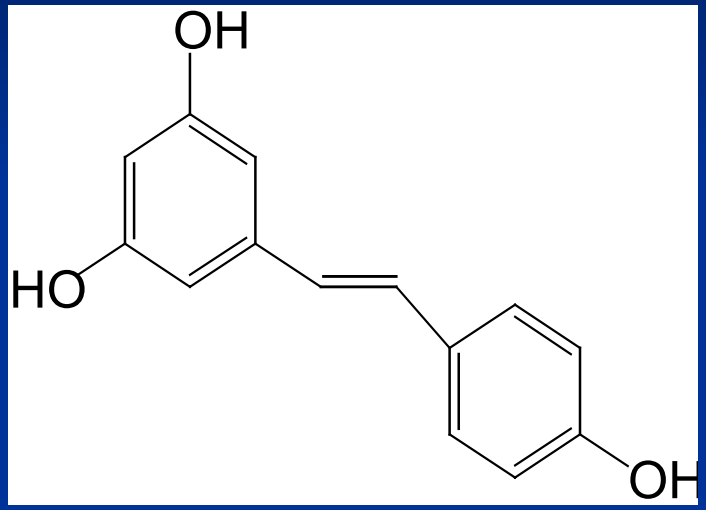
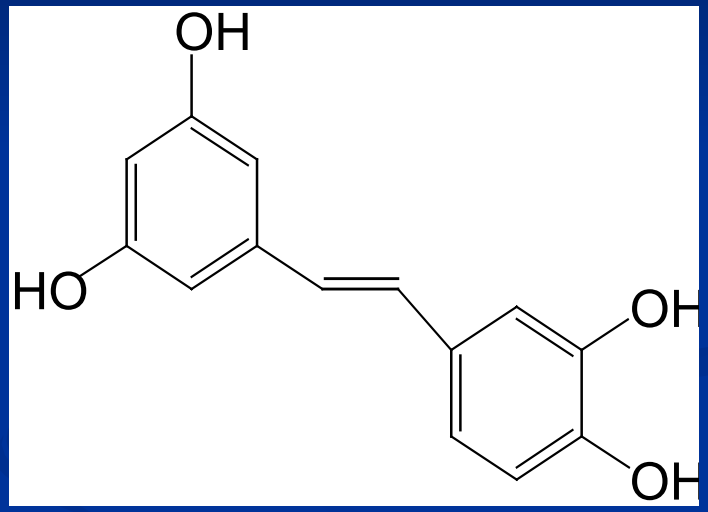


Fig. 2. Representative cardiac electrogram recorded from a low atrial recording electrode (lower panel) and a ventricular recording electrode (upper panel). Typical recordings obtained in control, ischemia, reperfusion and reperfusion plus treatment with 3 μ*M* Cinn. The ventricular tachycardia induced by ischemia-reperfusion was converted to normal sinus rhythm 3 min after cinnamophilin. A = Atrial depolarization; V = ventricular depolarization.

Fig. 3. Effects of Cinn on action potentials in the rat ventricular cell. **a–d** Action potentials (upper curve) and V_{max} (lower curve) in control, in the presence of 1 and 3 μ*M* Cinn and after washout of Cinn, respectively. The frequency of stimulation was 0.2 Hz.



Resveratrol

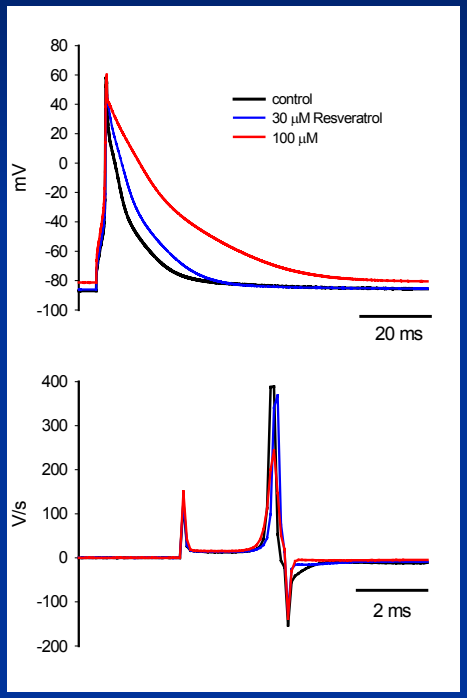


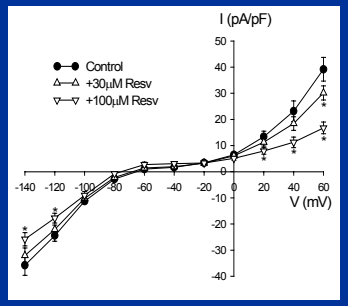
Astringinin

Effect of resveratrol in rat ventricular myocyte

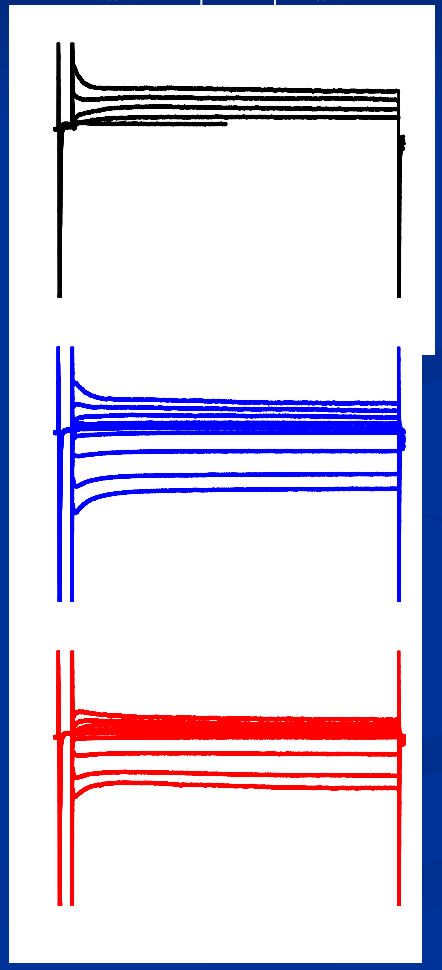
0.1 mM EGTA in K^+ internal solution

A

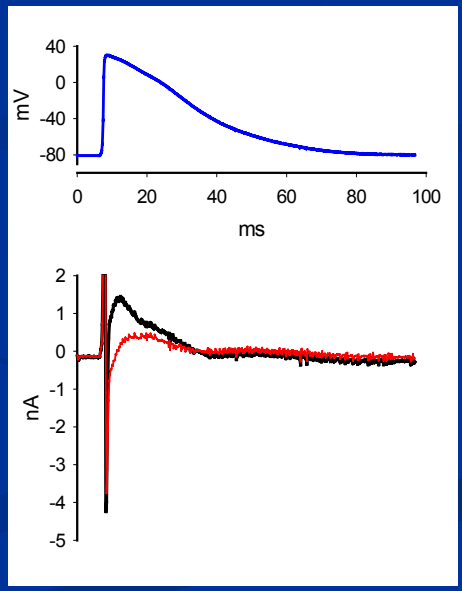




B

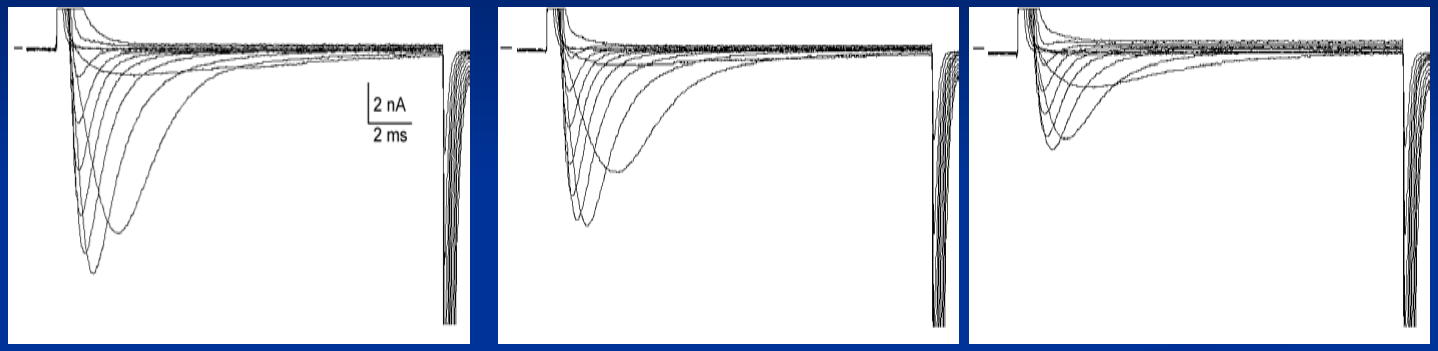


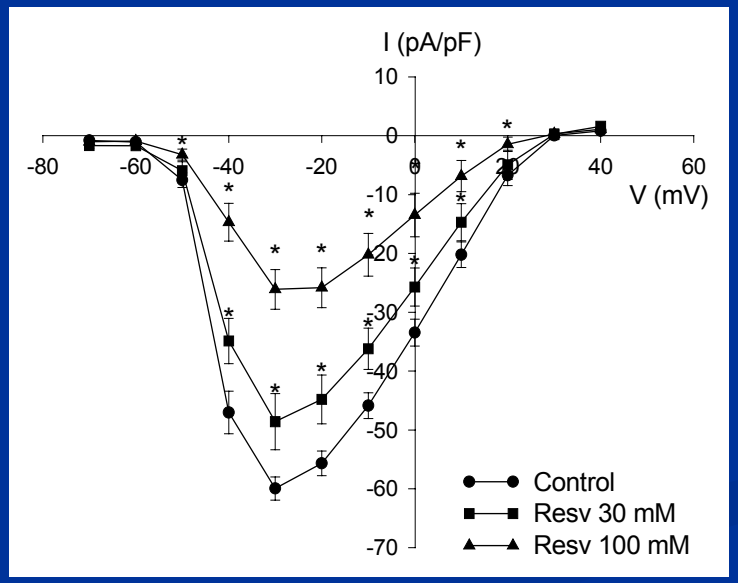
C Action-potential clamp

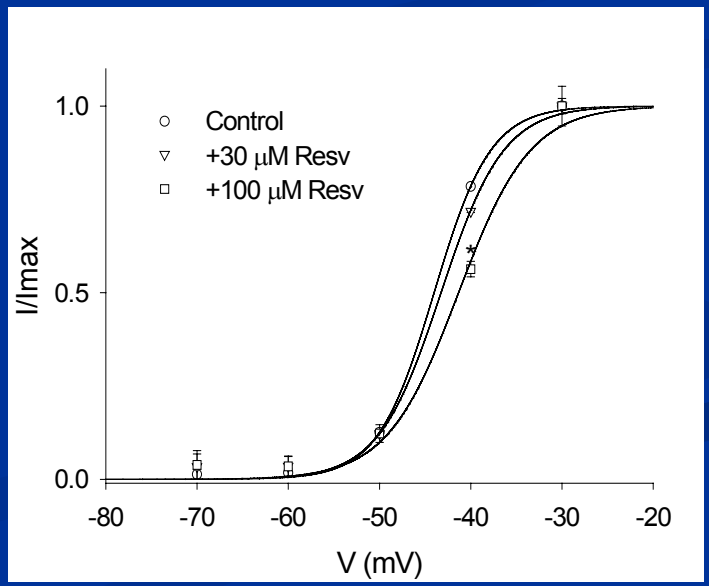


Resveratrol

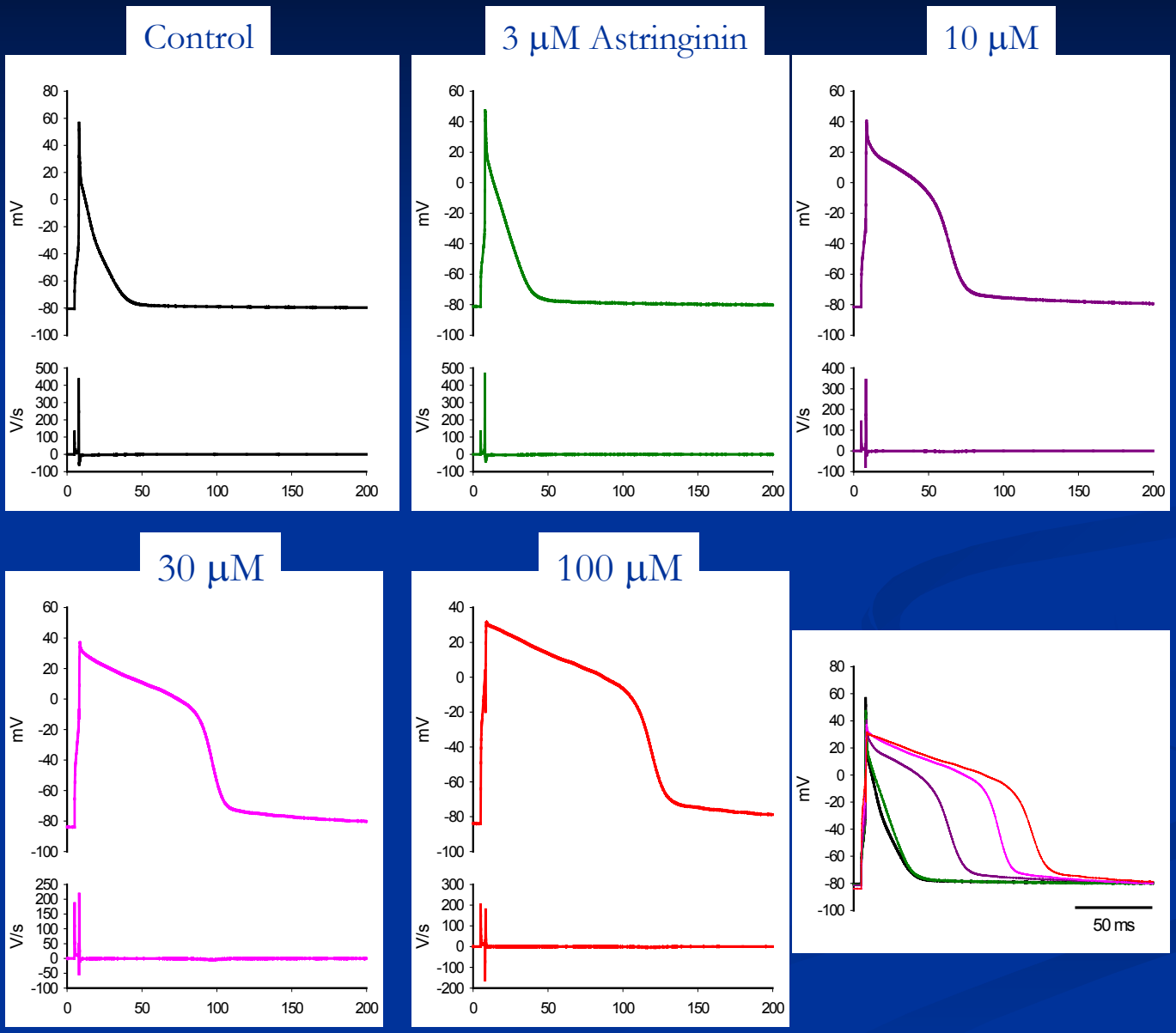
Control | 30 μM | 100 μM

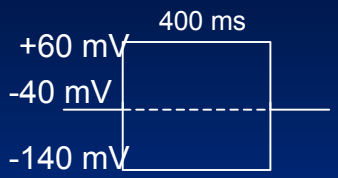


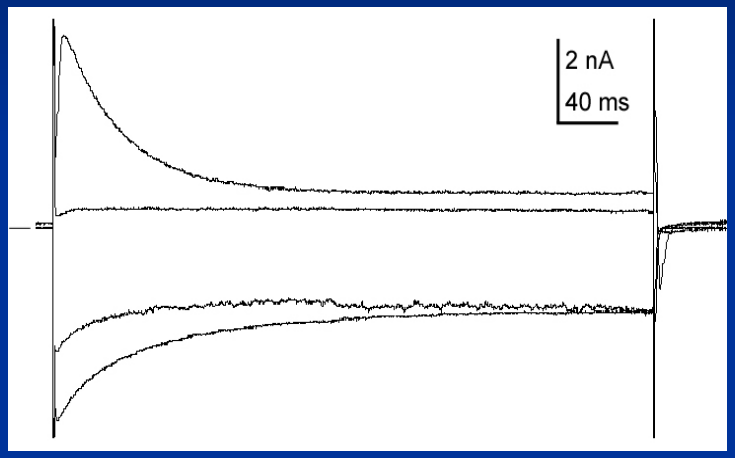


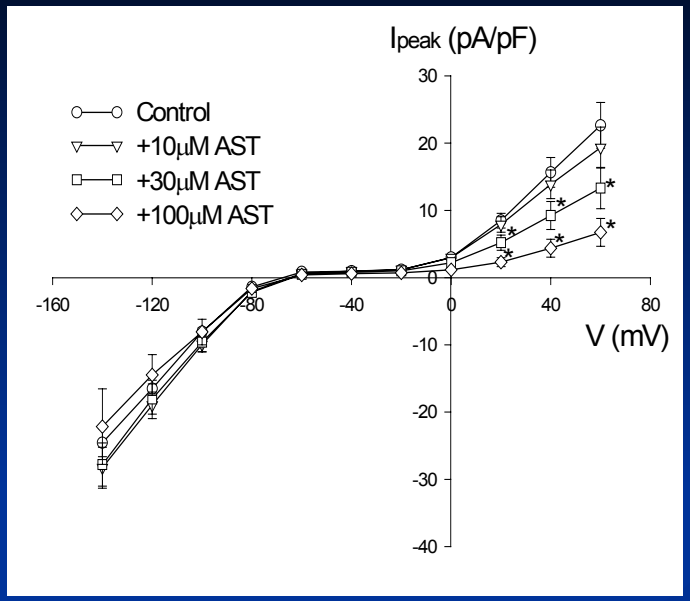


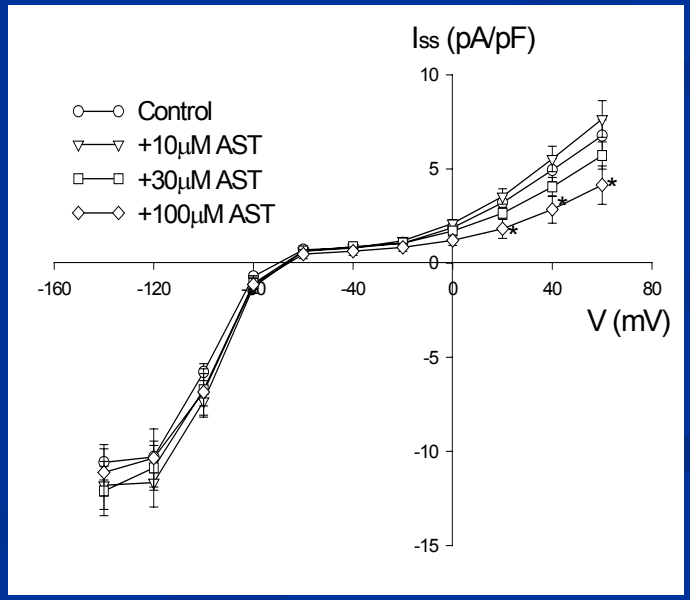
Effect of astringinin on the action potential of rat ventricular myocyte




400 ms
+60 mV
-40 mV
-140 mV


2 nA
40 ms


Ipeak (pA/pF)
Control
+10μM AST
+30μM AST
+100μM AST
30
20
10
0
-10
-20
-30
-40
-160
-120
-80
-40
0
40
80
V (mV)


Iss (pA/pF)
Control
+10μM AST
+30μM AST
+100μM AST
10
5
0
-5
-10
-15
-160
-120
-40
0
40
80
V (mV)

Effect of Astringinin on Ischemia-Induced Arrhythmias in the in Vivo Anesthetized Rat

Astringinin (g/kg)	Ventricular tachycardia		Ventricular fibrillation		
	Incidence (%)	Duration (s)	Incidence (%)	Duration (s)	Mortality (%)
0 (vehicle)	100	38.1 ± 7.3	73	31.5 ± 12.4	36
2.5×10^{-6}	100	32.4 ±10.0	29	15.7 ± 10.2	29
2.5×10^{-5}	50*	10.4 ± 3.2*	29	13.3 ± 6.2*	0
2.5×10^{-4}	44*	5.7 ± 3.1*	11*	1.1 ± 1.1*	0

Values for duration of VT and VF are shown as the means ± SE of 7-11 rats. Vehicle is 0.01% DMSO in normal saline.

*Statistical difference at the level of $p<0.05$

Effect of Astringinin on Reperfusion-Induced Arrhythmias in the in Vivo Anesthetized Rat

	Ventricular tachycardia		Ventricular fibrillation		
Astringinin (g/kg)	Incidence (%)	Duration (s)	Incidence (%)	Duration (s)	Mortality (%)
0 (vehicle)	100	11.4 ± 5.3	100	87.0 ± 16.0	70
2.5×10^{-7}	63	14.5 ± 5.9	50	29.6 ± 18.7	25
2.5×10^{-6}	30	3.3 ± 2.3	10*	9.5 ± 9.5*	10*
2.5×10^{-5}	25	6.0 ± 3.9	0*	0.0 ± 0.0*	0*

Values for duration of VT and VF are shown as the means ± SE of 8-10 rats. Vehicle is 0.01% DMSO in normal saline. *Statistical difference at the level of $p<0.05$

Conclusion

A. Antiarrhythmic mechanisms include
   - Inhibition of ion channels
   - Preservation of eNOS activity
   - Antioxidant activity

B. Inhibition of ventricular fibrillation is correlated with the survival rate in animals

Conclusion

C. Inhibition of VT or VF don't necessarily lead to parallel decrease in myocardial injury or infarction.

D. Agents with antioxidant and ion channel blocking activities don't always have better cardioprotective action in ischemia and ischemia/reperfusion animals .

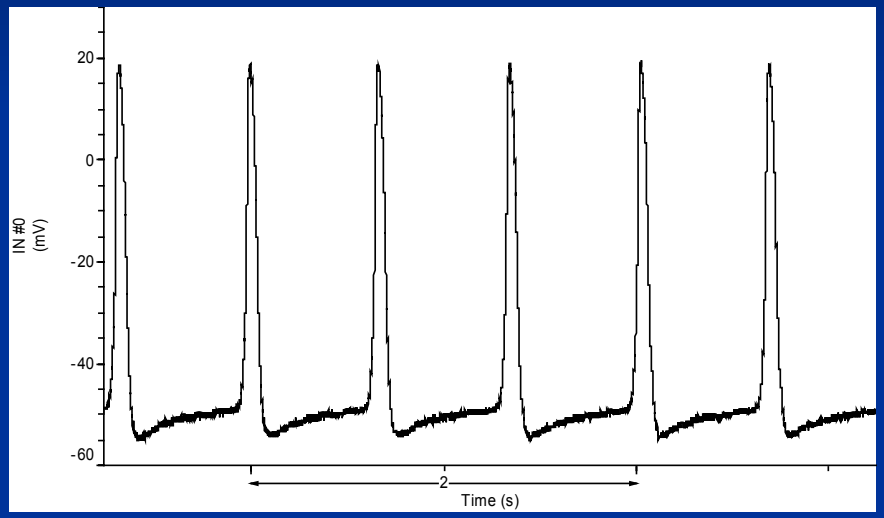
Conclusion

E. Agents with both eNOS preservation and ion channel modulating activities have better protective action

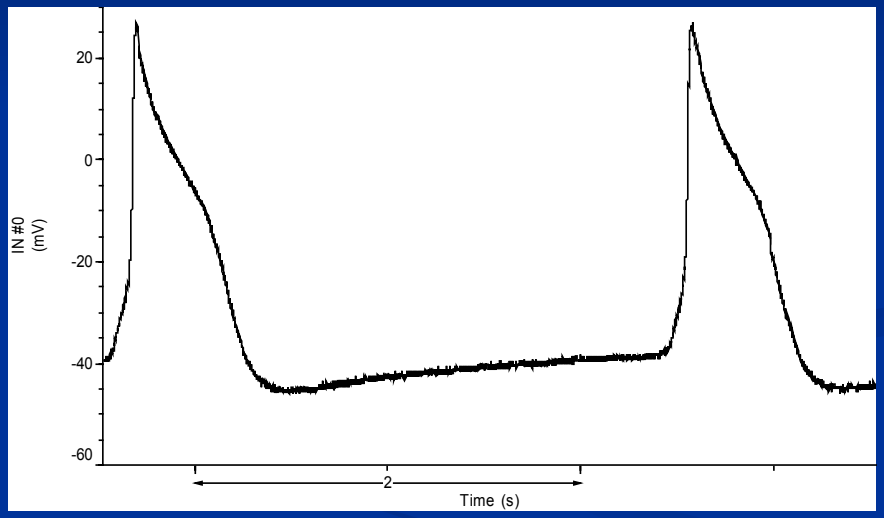
F. Both alkaloids and non-alkaloids can be a possible lead compounds as a useful myocardial protective agents

Effect of E4031 on spontaneous action potential of HL-1 cell

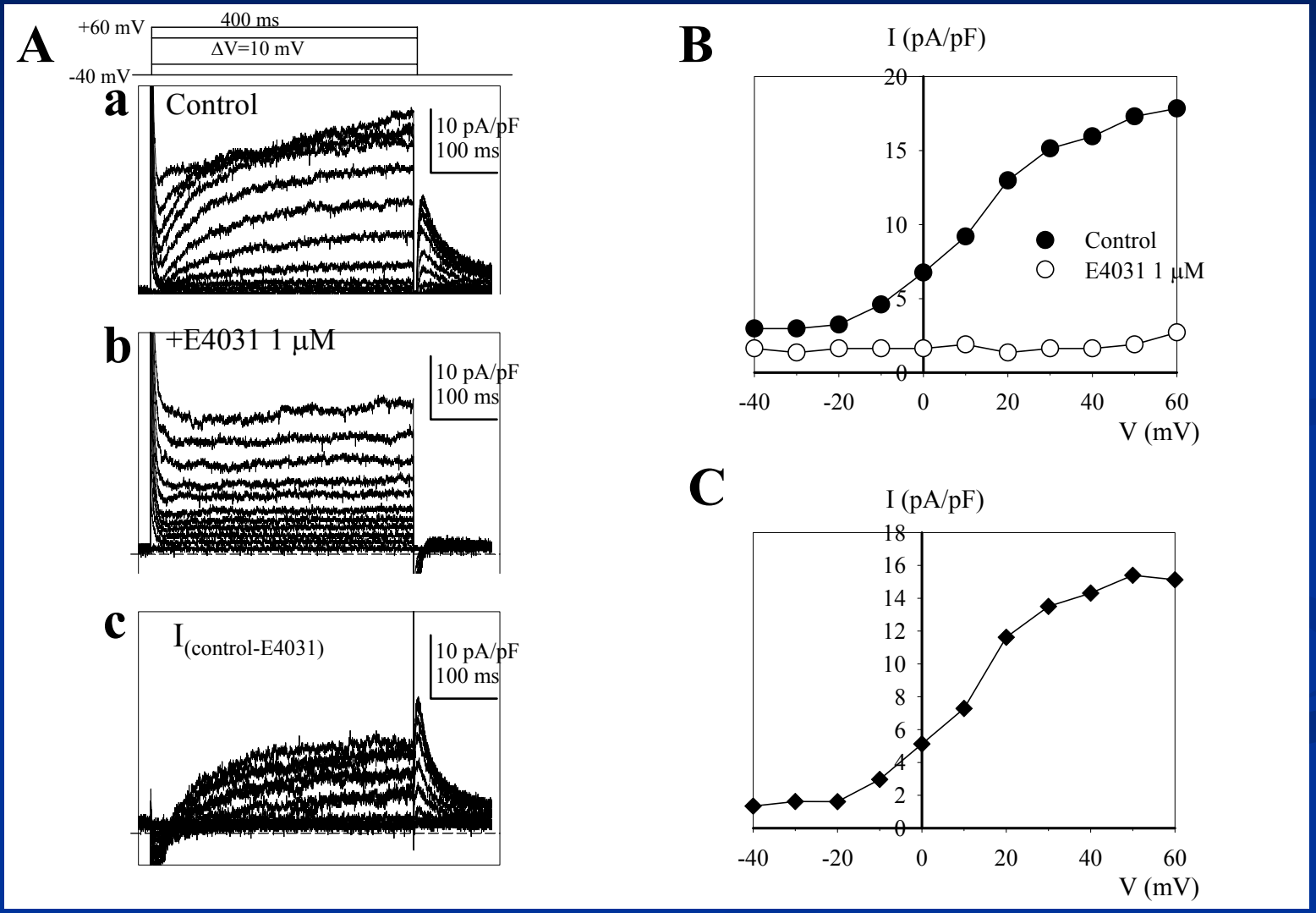
Control



E4031 1 μM



The characteristics of IKr in HL-1 cell



Thank you for your attention