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Research article

## Does lindane (gamma-hexachlorocyclohexane) increase the rapid delayed rectifier outward $K^+$ current ( $I_{Kr}$ ) in frog atrial myocytes?

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### Abstract

**Background:** The effects of lindane, a gamma-isomer of hexachlorocyclohexane, were studied on transmembrane potentials and currents of frog atrial heart muscle using intracellular microelectrodes and the whole cell voltage-clamp technique.

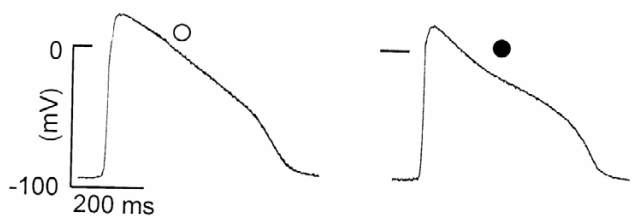
**Results:** Lindane (0.34 microM to 6.8 microM) dose-dependently shortened the action potential duration (APD). Under voltage-clamp conditions, lindane (1.7 microM) increased the amplitude of the outward current ( $I_{out}$ ) which developed in Ringer solution containing TTX (0.6 microM),  $Cd^{2+}$  (1 mM) and TEA (10 mM). The lindane-increased  $I_{out}$  was not sensitive to  $Sr^{2+}$  (5 mM). It was blocked by subsequent addition of quinidine (0.5 mM) or E-4031 (1 microM). E-4031 lengthened the APD; it prevented or blocked the lindane-induced APD shortening.

**Conclusions:** In conclusion, our data revealed that lindane increased the quinidine and E-4031-sensitive rapid delayed outward  $K^+$  current which contributed to the AP repolarization in frog atrial muscle.

### Background

Lindane, a gamma-isomer of hexachlorocyclohexane has largely been used as an insecticide and is widely spread in the environment due to the long life time of the molecule [1]. Absorbed by the respiratory, digestive or cutaneous pathways, it accumulates in tissues in the following order: fat > brain > kidney > muscle > lung > heart > spleen > liver > blood [2]. Lindane stimulates the synaptic transmission of a large number of muscular and nerve preparations, and suppresses the GABA-activated chloride current [3] by interacting with the receptor GABA-chloride channel complex [4]. Due to the similarity between lindane and inositol 1, 4, 5 triphosphate ( $IP_3$ ) [5], it has

been suggested that lindane releases  $Ca^{2+}$  from  $IP_3$ -sensitive intracellular stores in macrophages [6] and smooth myometrial muscle cells [7]. Lindane transiently depolarizes the membrane, opens  $Ca^{2+}$  channels thus increasing the intracellular  $Ca^{2+}$  concentration, and subsequently triggers  $Ca^{2+}$ -activated  $K^+$  current ( $I_{K-Ca}$ ) in human sperm [8]. Lindane (1 microM – 100 microM) does not depress the peak of intracellular  $Ca^{2+}$  transient in guinea pig myocytes, and does not interact directly with the ryanodine receptor  $Ca^{2+}$  release channels from cardiac sarcoplasmic reticulum vesicles [9]. A  $Ca^{2+}$  release from the endoplasmic reticulum, mitochondria and other  $Ca^{2+}$  stores has been reported in the presence of lindane (0.15 mM) in cat



**Figure 1**  
**Effect of lindane on spontaneously beating frog auricular action potential (AP)** AP recorded intracellularly on the same auricle in the standard Ringer solution (white circle) before and 5 min after application of lindane (3.4 microM; black circle).

kidney cells [10]. Lindane (30 microM) has no effect on the L-type  $\text{Ca}^{2+}$  current, but suppresses the activity of large conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels and increases the firing rate of spontaneous action potentials in rat pituitary GH(3) cells [11].

Little is known about the effect of the pesticide on cardiac tissues. The aim of the present work was to study the effect of lindane on the action potential and transmembrane currents of frog auricular heart muscle.

## Results

Intracellular recordings of transmembrane potentials show that the addition of lindane (3.4 microM) to the Ringer solution did not alter the RP, decreased the amplitude of the OS and shortened the plateau duration (Fig. 1). The effects of lindane on the AP were dose-dependent. Table 1 shows that lindane (0.34 microM to 6.8 microM) did not significantly modify RP; lindane (0.34 microM) slightly but significantly ( $P < 0.05$ ) shortened  $\text{APD}_{40}$  and  $\text{APD}_{10}$  by 6% and 3%, respectively.  $\text{APD}_{40}$  and  $\text{APD}_{10}$  shortening was not significantly increased by increasing the lindane concentration to 6.8 microM.  $\text{APD}_0$  was only significantly shortened ( $P < 0.05$ ) in the presence of lindane 3.4 microM in the Ringer solution (Table 1). Under voltage-clamp conditions, the remaining currents recorded in the Ringer solution containing TTX (0.6 microM),  $\text{Cd}^{2+}$  (1 mM) and TEA (10 mM) (control solution) mainly corresponded to the leak current and to the background inward rectifier  $\text{K}^+$  current ( $I_{\text{K1}}$ ) (Fig. 2A). Current-voltage relationships plotted for the current measured at the end of the clamp step potential (V) show that the current was inward ( $I_{\text{in}}$ ) at V more negative than HP and outward ( $I_{\text{out}}$ ) at V more positive than HP (Fig. 2B). The addition of lindane (1.7 microM) to the control solution increased  $I_{\text{out}}$  but did not alter the tail current (Fig. 2A). Current-voltage relationships of Fig. 2B show that lindane (1.7 microM) increased the amplitude of  $I_{\text{out}}$  which developed at membrane potentials more positive than -70 mV. Subse-

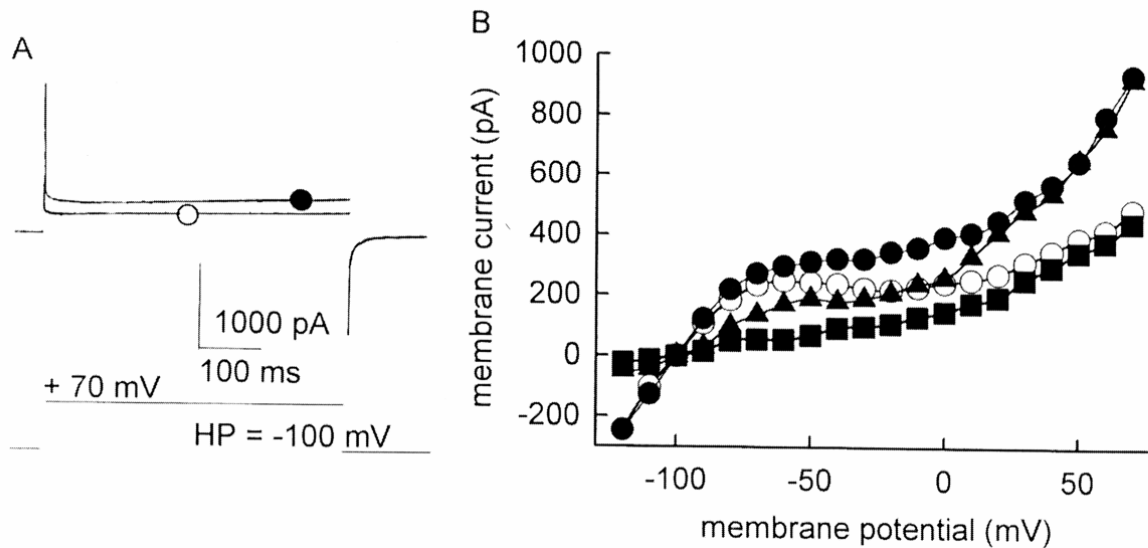
quent addition of  $\text{Sr}^{2+}$  (5 mM) to the control solution containing lindane (1.7 microM) decreased the amplitude of  $I_{\text{out}}$  in the membrane potential range of -120 mV to +30 mV (Fig. 2B), whereas further addition of quinidine (0.5 mM) to the solution containing both, lindane and  $\text{Sr}^{2+}$ , suppressed the remaining  $I_{\text{out}}$  whatever the membrane potential tested (Fig. 2B). Lindane (1.7 microM) increased the magnitude of  $I_{\text{out}}$  which developed when  $I_{\text{K1}}$  was blocked by the addition of  $\text{Ba}^{2+}$  (2 mM) to the control solution (Fig. 3A). Current-voltage relationships show that the lindane-increased  $I_{\text{out}}$  developed at membrane potentials more positive than -20 mV (Fig. 3B). Subsequent addition of E-4031 (1 microM) to the control solution containing lindane blocked the lindane-increased  $I_{\text{out}}$  (Fig. 2A) whatever the membrane potential studied (Fig. 3B). The addition of E-4031 (2 microM) to the Ringer solution did not modify RP but prolonged APD (Fig. 4Aa) and further addition of lindane (3.4 microM) to the solution containing E-4031 (2 microM) did not modify the APD (Fig. 4Ab). Conversely, the addition of E-4031 (2 microM) to the Ringer solution containing lindane (3.4 microM) lengthened  $\text{APD}_0$ ,  $\text{APD}_{40}$  and  $\text{APD}_{10}$  (Fig. 4B).

## Discussion

The present study shows that micromolar concentrations of lindane shortened the action potential duration APD and increases a quinidine and E-4031-sensitive outward current in frog auricle.

Our data show that the shortening of the duration of the repolarizing phase ( $\text{APD}_{40}$  and  $\text{APD}_{10}$ ) of the AP is the first significant event occurring in response to the application of a lindane concentration as low as 0.34 microM. This effect is then followed by a shortening of the plateau duration  $\text{APD}_0$  which is clearly visible only at a ten times higher concentration.

Voltage-clamp experiments indicate that lindane increases an outward current ( $I_{\text{out}}$ ). This current develops in the presence of TEA, known to block the delayed  $\text{K}^+$  current, in the control solution and under conditions where  $\text{Ca}^{2+}$  current has previously been blocked by  $\text{Cd}^{2+}$ , suggesting that a lindane-increased  $\text{Ca}^{2+}$  influx may not be directly involved in the development of  $I_{\text{out}}$ . The lindane-increased  $I_{\text{out}}$  cannot be attributed to the opening of lindane-induced ionic channels since lindane has been shown to be devoid of ionophoretic properties in planar lipid bilayers [9]. Our data show that the lindane-increased  $I_{\text{out}}$  still persists in the presence of  $\text{Sr}^{2+}$  which is known to block the background  $I_{\text{K1}}$  [12] and  $I_{\text{K-Ca}}$  [13] currents in cardiac tissues. Our findings reveal that quinidine inhibits the effect of lindane on  $I_{\text{out}}$ . Quinidine is an open channel blocker of the cardiac rapid delayed rectifier  $\text{K}^+$  current ( $I_{\text{Kr}}$ ) [14–17]. In addition, they show that micromolar concentrations of E-4031, a specific blocker of  $I_{\text{Kr}}$

**Figure 2**

**Effects of lindane on frog atrial myocytes membrane current** Membrane current was recorded on voltage-clamped frog atrial myocytes bathed in a control Ringer solution containing TTX (0.6  $\mu\text{M}$ ),  $\text{Cd}^{2+}$  (1 mM) and TEA (10 mM). A). Superimposed traces of the current (upper traces) elicited by a 170 mV depolarizing step potential applied from HP = -100 mV (lower trace). (white circle) control solution; (black circle) control solution containing lindane (1.7  $\mu\text{M}$ ) B). Current-voltage relationships plotted for the outward current measured at the end (500 ms) of the clamp potential steps, HP = -100 mV. (white circles) control solution; (black circles) control solution containing lindane (1.7  $\mu\text{M}$ ); (black triangles) control solution containing lindane and  $\text{Sr}^{2+}$  (5 mM); (black squares) control solution containing lindane,  $\text{Sr}^{2+}$  and quinidine (0.5 mM).

[14,15], prolong the APD in frog auricle, are able to prevent or to reverse the APD shortening induced by lindane and in addition suppressed the lindane-increased  $I_{\text{out}}$ . These observations indicate that  $I_{\text{Kr}}$  participates to the AP repolarization in frog auricular cells, as in mammalian cardiac tissues [18,19]. This current is sensitive to quinidine and E-4031 but, as reported in rabbit ventricular cells [20], it is not sensitive to  $\text{Sr}^{2+}$  or  $\text{Ba}^{2+}$ . The data also reveal that lindane increases  $I_{\text{Kr}}$ . The mechanism by which lindane increases  $I_{\text{Kr}}$  is probably not the result of a direct activation of the channel  $I_{\text{Kr}}$ , believed to be encoded by the human *ether-a-go-go* related gene (HERG) [21–25], and which is involved in long QT syndrome, a cardiac disorder characterized by syncope, seizure and sudden death which can be congenital, idiopathic or iatrogenic [26]. HERG  $\text{K}^+$  channel regulation depends on protein-kinase (PK)-dependent pathways. In guinea pig ventricular myocytes, the shift of the activation of HERG  $\text{K}^+$  channel induced by phorbol ester involves a PKA-dependent pathway [27]. A PKC-dependent pathway links a G protein-coupled receptor that activates phospholipase C to modulate the Herg channel in *Xenopus* oocytes co-expressing the channel and tyrotropin releasing hormone receptor [28]. According to Heath and Terrar [29],  $I_{\text{Kr}}$  is thought to be regulated by PKC which is activated by beta-adrenoceptors stimulation in guinea-pig ventricular myocytes. Lindane activates

PKC activity in rat brain and liver tissues [30]. In addition, it has been shown that dynamic regulation of the Herg  $\text{K}^+$  channels may be achieved via receptor-mediated changes in phosphatidyl inositol bisphosphate (PIP2) concentrations; elevated PIP2 accelerated activation and slowed inactivation kinetics [31]. But single exposure of rats to lindane (100 mg / kg) did not cause any significant change in phosphoinositide levels in erythrocyte membrane and cerebrum 2 or 24 h after exposure [32].

### Conclusions

In conclusion, the results presented show for the first time that the rapid delayed outward current  $I_{\text{Kr}}$ , involved in the repolarization of the cardiac AP, is increased by micromolar concentrations of lindane and may be responsible for the alterations of the AP duration induced by the pesticide. Although the mechanism by which lindane may increase  $I_{\text{Kr}}$  remains to be elucidated, the consequences of the effect of lindane on  $I_{\text{Kr}}$  are of toxicological interest since this current is involved in cardiac disorder.

### Materials and methods

Experiments were performed at 20–21°C on quiescent whole auricle isolated from frog heart and on myocytes isolated enzymatically from the auricle.

**Table 1: Effect of lindane on spontaneously beating frog atrial action potential (AP) AP was recorded using intracellular microelectrodes before and after successive and cumulative addition of lindane to the Ringer solution (control).**

Treatments	RP (mV)	OS (mV)	APD <sub>0</sub> (ms)	APD <sub>40</sub> (ms)	APD <sub>10</sub> (ms)
control	-90.3 ± 2.0	24.3 ± 1.2	162 ± 9	450 ± 13	532 ± 13
lindane 0.34 microM	-90.0 ± 1.5	23.1 ± 1.3	157 ± 8	422 ± 5*	514 ± 6*
lindane 1.7 microM	-91.9 ± 1.1	26.9 ± 1.4	154 ± 8	420 ± 5	510 ± 5
lindane 3.4 microM	-91.8 ± 1.0	20.7 ± 1.3	128 ± 7 <sup>+</sup>	424 ± 6	507 ± 5
lindane 6.8 microM	-92.7 ± 1.7	18.0 ± 1.7	111 ± 12	423 ± 7	501 ± 9

(RP) resting membrane potential; (OS) amplitude of the overshoot; (APD<sub>0</sub>) duration of the AP measured at 0 mV; (APD<sub>40</sub>) and (APD<sub>10</sub>) duration of the AP measured at a membrane potential + 40 mV and + 10 mV higher than RP, respectively. The data are mean values ± s. e. mean of 12 AP recorded from 2 different atriums. *P* < 0.05: \* lindane 0.34 microM versus control; <sup>+</sup> lindane 3.4 microM versus lindane 0.34 microM.

### Solutions

The composition of the frog standard Ringer solution was (mM): NaCl, 110.5; CaCl<sub>2</sub>, 2; KCl, 2.5; HEPES-NaOH buffer, 10; pH 7.35. The Ca<sup>2+</sup>-free solution, used for cells isolation, was obtained by simple Ca<sup>2+</sup> removal and contained 600 mU / ml type I collagenase (Sigma) and 1.5 mU / ml type XIV protease (Sigma). Tetrodotoxin (TTX; 0.6 microM; Sankyo, Japan) and CdCl<sub>2</sub> (1 mM) were added to the standard solution to inhibit the peak Na<sup>+</sup> current (I<sub>Na</sub>) and L-type Ca<sup>2+</sup> current (I<sub>Ca</sub>), respectively. Tetraethylammonium (TEA, Sigma-Aldrich Chimie, Saint Quentin Fallavier, France), quinidine (Sigma-Aldrich Chimie) were used to block delayed K<sup>+</sup> current; E-4031 (Alamone, Jerusalem, Israel) was used to inhibit the rapid delayed outward current; SrCl<sub>2</sub> (5 mM) and BaCl<sub>2</sub> (2 mM) to block the inward rectifying K<sup>+</sup> current (I<sub>K1</sub>) and the Ca<sup>2+</sup>-activated K<sup>+</sup> current (I<sub>K-Ca</sub>). Lindane (Merck, GmbH) was dissolved in acetone.

### Recordings of membrane potentials

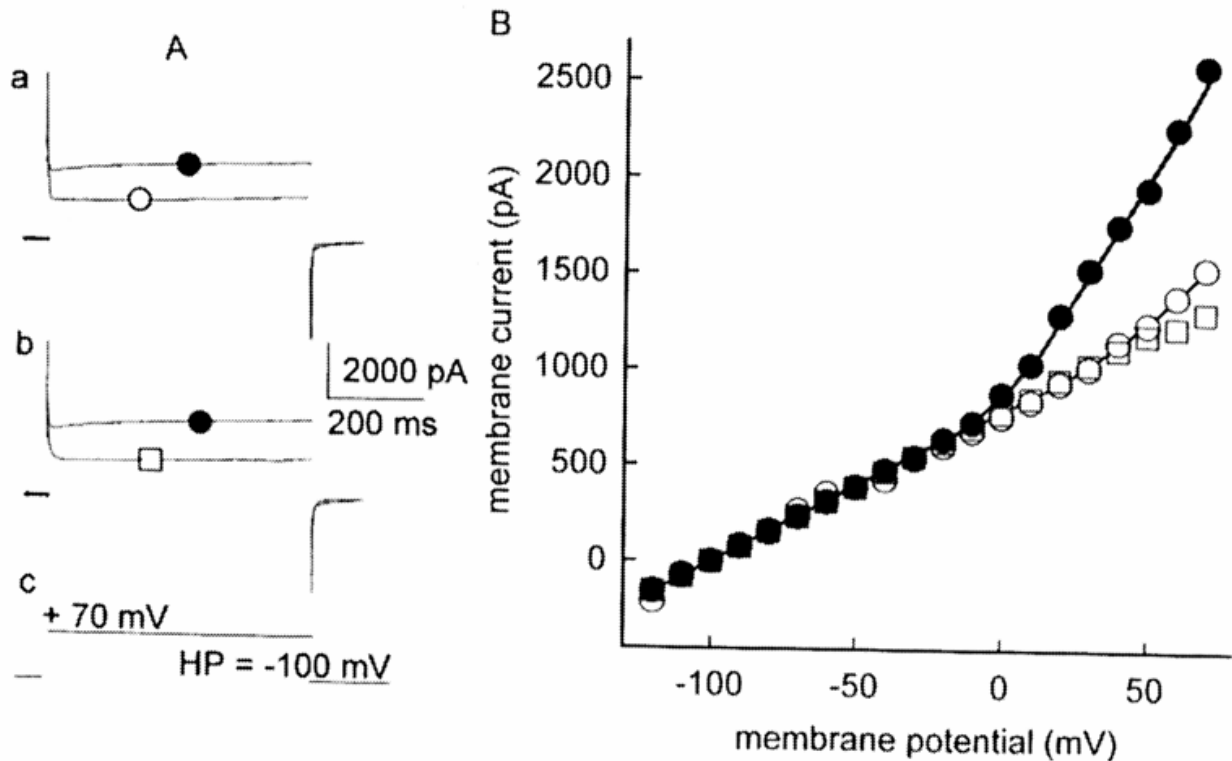
Spontaneously beating action potentials (AP) were recorded on quiescent whole auricle, by means of intracellular microelectrodes used in the "floating mode". The tip length (less than 5 mm) of conventional glass microelectrodes (filled with 3 M KCl, 25–30 Mohms resistance, tip potential less than ± 3 mV) was connected to the input stage of the differential voltage follower by means of a thin Ag / AgCl wire. The following AP parameters were measured: RP: resting membrane potential; OS: overshoot, AP duration (APD): APD<sub>0</sub> duration of the plateau measured at 0 mV; APD<sub>40</sub> and APD<sub>10</sub>: duration of the AP at the end of the plateau and of the repolarization phase were measured at a membrane potential + 40 mV and + 10 mV higher than RP, respectively [33].

### Recordings of membrane currents

Membrane currents were recorded on single myocytes dispersed by enzymatic digestion of the auricle of frog heart [34]. After isolation of the auricle from the heart, the ex-

ternal epithelial sheet surrounding the auricular tissue was carefully detached and removed. The epithelial-free auricle was then pinned at the bottom of an isolating chamber in which the solutions used for the dissociation were maintained at 30°C and gently stirred with a small magnet. The auricle was successively bathed for 30 min : i) in a Ca<sup>2+</sup>-free Ringer solution, ii) in a Ca<sup>2+</sup>-free Ringer solution containing ethylene glycol tetra acetic acid (EGTA) neutralised with NaOH (0.1 mM), iii) in a Ca<sup>2+</sup>-free Ringer solution then, iv) in a Ca<sup>2+</sup>-free solution containing collagenase and protease. All solutions were filtered and oxygenated. When the tissue was digested, the auricle was rinsed twice (10 min) with a Ca<sup>2+</sup>-free Ringer solution and then bathed in a standard Ringer solution and kept at 4°C. Before experimentation, cells were dispersed in a Petri dish (outer diameter 33 mm, depth 10 mm, Corning, New-York, USA) filled with Ringer solution (1 ml) by gently shaking the digested auricle. Patch clamp pipettes (Propper Manufacturing glass, id 1.2 mm, wall 0.2 mm, resistance 1.5 to 2.5 Mohms) were filled with a solution containing (mM); KCl, 150; Na<sub>2</sub>-creatine phosphate, 5; ATP, 5; EGTA neutralised with KOH, 5; HEPES (KOH) buffer, 10; pH = 7.3. The cell current was monitored using an Axopatch 220B amplifier feedback amplifier (Axon Instruments, Foster City, USA). Starting from a holding potential (HP) of -100 mV, the membrane potential (V) was displaced in rectangular steps of 10 mV at a rate of 0.2 Hz. Positive potentials correspond to depolarization, positive currents correspond to outward current [34].

Transmembrane potentials and currents were recorded with a Labmaster acquisition card (DMA 100 OEM, Dipsi, Cachan, France), driven by Acquis 1 software linked to the mass storage of a desk computer (AT 80486 DX 33), and displayed on an oscilloscope Nicolet 310 (Nicolet, Madison, WI, USA).

**Figure 3**

**Effects of E-4031 on the lindane-induced outward current** Membrane current was recorded on voltage-clamped frog atrial myocytes bathed in a control Ringer solution containing TTX (0.6  $\mu\text{M}$ ),  $\text{Cd}^{2+}$  (1  $\text{mM}$ ), TEA (10  $\text{mM}$ ) and  $\text{Ba}^{2+}$  (2  $\text{mM}$ ). A). Superimposed traces of the current elicited by a 170 mV depolarizing step potential applied from HP = -100 mV (c) before and after lindane (1.7  $\mu\text{M}$ ) application (traces a) and subsequent addition of E-4031 (1  $\mu\text{M}$ ) to the solution containing lindane (traces b); (white circle) control solution; (black circle) control solution containing lindane; (white square) control solution containing lindane and E-4031. B). Current-voltage relationships plotted for the outward current measured at the end (500 ms) of the clamp potential steps, HP = -100 mV. (white circles) control solution; (black circles) control solution containing lindane (1.7  $\mu\text{M}$ ); (white squares) control solution containing lindane and E-4031 (1  $\mu\text{M}$ ).

**Statistical analysis of data**

Numerical data are expressed as mean values  $\pm$  s. e. mean,  $n$  corresponds to the number of preparations tested. The data were analyzed using the paired Student's  $t$ -test using Sigmaplot software (Jandel, Erkrath, Germany) and differences were considered significant at  $P < 0.05$ .

**List of abbreviations**

AP: action potential

APD: action potential duration

APD<sub>0</sub>: duration of the plateau measured at 0 mV

APD<sub>40</sub>: duration of the AP at the end of the plateau measured at a membrane potential + 40 mV higher than RP

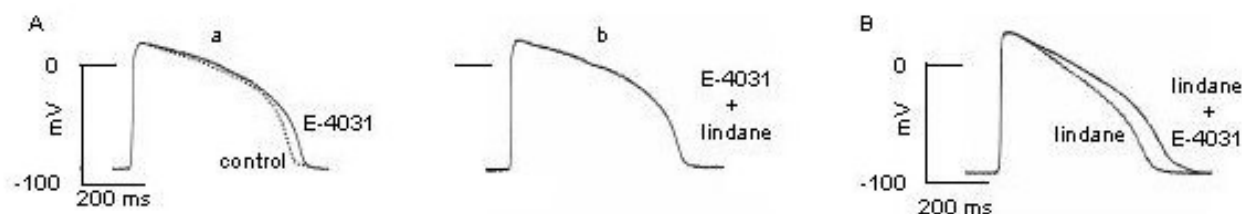
APD<sub>10</sub>: duration of the AP at the end of the repolarization phase measured at a membrane potential + 10 mV higher than RP

EGTA: ethylene glycol tetra acetic acid

HP: holding potential

IP<sub>3</sub>: inositol 1, 4, 5 triphosphate

I<sub>K-Ca</sub>: Ca<sup>2+</sup>-activated K<sup>+</sup> current



**Figure 4**  
**Effects of E-4031 (1 microM) and lindane (3.4 microM) on the action potential (AP).** Superimposed traces of the AP recorded on frog auricle using intracellular microelectrodes. A. a): AP recorded before and after addition of E-4031 to the Ringer solution; b) further addition of lindane to the solution containing E-4031. B). AP recorded in the Ringer solution containing lindane before and after further addition of E-4031.

$I_{in}$ : inward current

$I_{K1}$ : inward rectifying  $K^+$  current

$I_{out}$ : outward current

$I_{Kr}$ : rapid delayed outward current

microM: micromolar

mM: millimolar

mm: millimeter

ms: millisecond

mV: millivolt

mU / ml: milliunit per milliliter

OS: overshoot

pA: picoampere

PIP2: phosphatidyl inositol bisphosphate

PK: protein kinase

RP: resting membrane potential

TEA: tetraethylammonium

TTX: tetrodotoxin

V: clamp step potential

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