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The effects of lidocaine on calcium release and the role of pathways in swine lingual artery contracion induced with agonists

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Introduction

Lidocaine generally relaxes vascular muscle, airway smooth muscle and other smooth muscles, with the mechanism of the direct relaxant effect of lidocaine on smooth muscle potentially caused by an effect on Ca^{2+} mobilization[1]. However, the contraction of vascular smooth muscle is regulated by changes in cytosolic (intracellular) Ca^{2+} levels ($[Ca^{2+}]_i$) and Ca^{2+} sensitivity of contractile elements[2]. Depolarization of the sarcolemma with a high concentration of KCl causes the influx of extracellular Ca^{2+} through voltage-gated Ca^{2+} channels, whereas binding of agonists such as noradrenaline to the receptors causes the release of Ca^{2+} from intracellular Ca^{2+} stores such as the inositol trisphosphate (IP3) channel-operated store or one of the sarcoplasmic stores[3]. Agonists release Ca^{2+} from intracellular Ca^{2+} stores to induce an initial transient contraction (phasic type), followed by activation of Ca^{2+} influx to induce sustained contraction (tonic type)[4].

Aim

Aims of this present study were to investigate the effects of lidocaine on calcium release and the role of pathways in this process in swine lingual artery contraction induced by agonists.

Method

Measurement of isometric tension

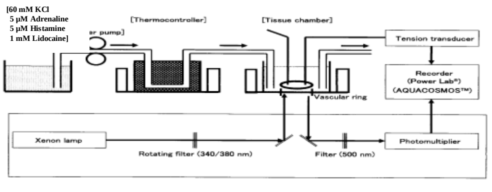
Contractions were detected as increases in isometric tension with the displacement transducer, and signals detected were amplified with a carrier amplifier and recorded with a Powerlab 16/30T data acquisition system. Artery rings were loaded with the Ca^{2+} indicator dye, fura-2.

Measurement of fura-2 fluorescence

Changes in fluorescence intensity of the fura-2-Ca^{2+} complex were monitored using a front-surface fura-2 fluorometer (Aquacosmos, Hamamatsu Photonics K.K., Tokyo, Japan). The ratio of the fluorescence intensity (fluorescence ratio) at 340-nm excitation (F_{340}) to that at 380-nm excitation (F_{380}) was monitored to estimate changes in $[Ca^{2+}]_I$.

Simultaneous measurement of tension and fluorescence ratio

A final 2-min 60 mM KCl perfusion was done after each experiment to confirm that each artery ring had retained intact contractility throughout the experiment. The strength of any contractions and change in $[Ca^{2+}]_i$ in an experiment was normalized to the strength of 60 mM KCl contraction and fluorescence ratio, and expressed as a percentage.



Results

Lidocaine attenuated the contraction and $[Ca^{2+}]_i$ induced by 60 mM KCl or 5 μM adrenaline in a concentration-dependent manner (n=8). The fluorescence ratio was monitored to estimate changes in intracellular Ca^{2+} concentration.

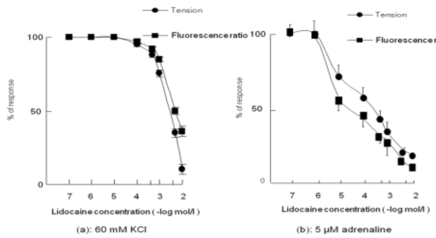


Fig.1 The effects of a variety of lidocaine on swine lingual artery ring contraction induced by a) 60mM Kcladrenaline or b) μM adrenaline

The application of 5 μM adrenaline for 5 min in the absence of extracellular Ca^{2+} caused a transient increase in $[Ca^{2+}]_i$ and tension in Ca^{2+}-free SS salt solution.

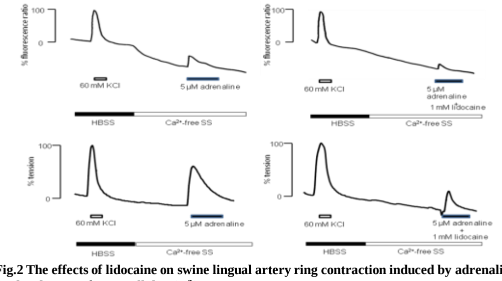


Fig.2 The effects of lidocaine on swine lingual artery ring contraction induced by adrenaline in the absence of extracellular Ca^{2+}

The application of 5 μM histamine for 5 min in the absence of extracellular Ca^{2+} caused a transient increase in $[Ca^{2+}]_i$ and tension in Ca^{2+} free salt solution. The increases in $[Ca^{2+}]_i$ and tension that occurred with the addition of lidocaine were low compared with those that occurred without lidocaine addition.

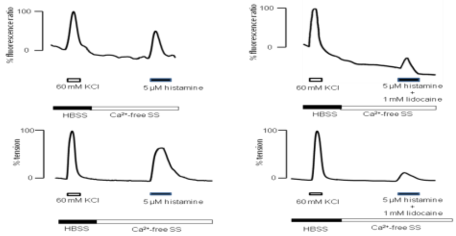


Fig.3 The effects of lidocaine on swine lingual artery ring contraction induced by histamine in the absence of extracellular Ca^{2+}

The application of 5 μM caffeine for 5 min in the absence of extracellular Ca^{2+} caused a transient increase in $[Ca^{2+}]_i$ and tension in Ca^{2+}-free salt solution. The increases in $[Ca^{2+}]_i$ and tension that occurred with the addition of lidocaine were the same as those that occurred without lidocaine addition.

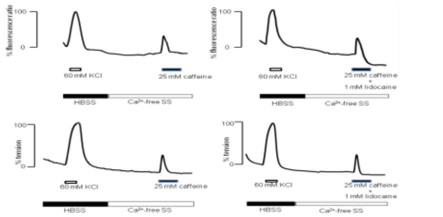


Fig.4 The effects of lidocaine on swine lingual artery ring contraction induced by caffeine in the absence of extracellular Ca^{2+}

The application of 5 μM adrenaline for 15 min in the presence of extracellular Ca^{2+} caused $[Ca^{2+}]_i$ and tension to develop slowly to peak strength. Treatment with 1 mM lidocaine 5 min before and during the application of adrenaline significantly inhibited the increases in $[Ca^{2+}]_i$ and tension induced by the application of adrenaline.

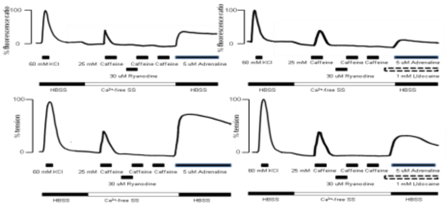


Fig.5 The effects of lidocaine on swine lingual artery ring contraction induced by adrenaline in the presence of extracellular Ca^{2+} after depletion of extracellular Ca^{2+} stores

The effect of lidocaine on swine lingual artery ring contraction induced with agonists in the presence or absence of extracellular Ca^{2+}. Values represent the mean ± SEM. $[Ca^{2+}]_i$: intracellular concentration of Ca^{2+}.
*** denotes a significant difference compared with the value obtained without lidocaine addition.**

	Adrenaline without lidocaine $[Ca^{2+}]_i$ (%)	Adrenaline without lidocaine Tension (%)	Adrenaline with lidocaine $[Ca^{2+}]_i$ (%)	Adrenaline with lidocaine Tension (%)
Adrenaline in the absence of extracellular Ca^{2+}	35 ± 2	76 ± 1	14 ± 2*	37 ± 2*
Histamine in the absence of extracellular Ca^{2+}	71 ± 2	69 ± 2	21 ± 3*	16 ± 1*
Caffeine in the absence of extracellular Ca^{2+}	42 ± 2	42 ± 2	42 ± 3	40 ± 2
Adrenaline in the presence of extracellular Ca^{2+} after depletion of intracellular Ca^{2+}	39 ± 2	83 ± 2	23 ± 3*	37 ± 2*

Discussion and Conclusion

Lidocaine depressed the increase in $[Ca^{2+}]_i$ and tension induced with KCl and adrenaline in a concentration-dependent manner, and depressed the increase in these induced with adrenaline and histamine. In contrast, lidocaine did not depress the increase in $[Ca^{2+}]_i$ and tension induced by caffeine in the absence of extracellular Ca^{2+}. However, lidocaine did depress the increase in $[Ca^{2+}]_i$ and tension induced with adrenaline in the presence of extracellular Ca^{2+} after depletion of the intracellular Ca^{2+} store. Therefore, it was suggested that lidocaine depressed the increase in Ca^{2+} via IP_3 channel-operated Ca^{2+} channels and and Ca^{2+}-induced Ca^{2+} release (CICR), that lidocaine did not attenuate CICR in KCl- and agonist-induced smooth muscle contraction, and that lidocaine depressed the increase of Ca^{2+} influx from extracellular Ca^{2+} through receptor-activated Ca^{2+} channels (RACC) or nonselective cation channels. Further investigation is needed into whether the intracellular Ca^{2+} store is a single compartment in the lingual artery

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