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The Presence and Function of TMEM16A in Wistar and Spontaneously Hypertensive Rats

Failure of coronary blood vessels to adequately supply cardiac myocytes with oxygen underlies ischaemic heart disease and ultimately myocardial infarction. Thus it is important to determine the factors that regulate coronary blood flow. Ca^{2+}-activated chloride channels encoded by TMEM16A play a key role in depolarising vascular smooth muscle cell membrane potentials. This can activate voltage-gated Ca^{2+} channels, causing Ca^{2+} influx and contraction of the cell. We show that TMEM16A is present in rat coronary arteries as mRNA and protein. We also show that rat left anterior descending (LAD) coronary artery segments were significantly less able to contract to 300nM U46619 or 1µM 5HT once chloride had been removed from the bathing solution ($n=7$ $p<0.0001$and $n=6$ $p<0.05$ respectively). In line with this, incubation of 10µM MONNA, the novel TMEM16A-specific inhibitor, attenuated U46619/5HT-induced contractions in a wire myograph. EC_{50} values were increased for both vasoconstrictors. In the presence of 10µM MONNA the maximal contractions to U46619 were 19.97%±9.37 of the peak contractions pre-incubation while they were 96.09%±1.56 of those in vehicle controls ($n=8$ $p<0.0001$). Similar results were seen in the 5HT contraction study. Furthermore, in Langendorff perfused rat heart preparations, TMEM16A-specific blockers produced a concentration dependent increase in coronary flow. In hypertensive rats TMEM16A transcript is increased and LAD coronary artery segments are more sensitive to contraction with U46619 and 5HT. 30nM U46619 evoked 0.23±0.06 mN of tension from LAD coronary artery segments of spontaneously hypertensive rats in the wire myograph, while segments from LAD coronary arteries of normotensive rats only produced 0.06±0.03 mN when stimulated with 30nM U46619 ($n=6$ $p<0.05$). Similar effects were seen with 5HT. This increased sensitivity is diminished in the presence of 10µM MONNA. In conclusion TMEM16A is implicated in the regulation of coronary blood flow and contributes to the pathophysiology of hypertension in coronary arteries.