ORANGE FLAVONOID HESPERETIN PROLONGED ACTION POTENTIAL DURATION AND INHIBITS THE SLOW DELAYED RECTIFIER POTASSIUM CURRENT (I_{Ks}) IN DOG AND RABBIT CARDIAC VENTRICULAR MUSCLE PREPARATIONS AND ISOLATED MYOCYTES

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Hesperetin is the main flavonoid in oranges. Flavonoids are known to reduce cardiovascular mortality, however, their effects on cardiac electrophysiology may have both antiarrhythmic and proarrhythmic consequences as they can attenuate the repolarization reserve.
The present work aimed to study the additive inhibitory effect of Hesperetin on the cardiac action potential repolarization with normal and attenuated repolarization reserve conditions. Hesperetin's effect on transmembrane I_{Ks} and I_{Kr} was also investigated.
Action potentials were recorded using conventional microelectrode techniques. To attenuate the repolarization reserve, Dofetilide 0.1 µM (I_{Kr} blocker) and Veratrine 50 µg (late Na^+ channel activator) were added to the tissue bath. Transmembrane I_{Ks} and I_{Kr} were measured in rabbit myocytes using the whole-cell configuration of the patch-clamp technique.
Hesperetin 10 µM alone has no notable effect on action potential duration (APD), however, during the impaired repolarization reserve, 10 µM Hesperetin caused a significant prolongation of the steady APD (from 466±18 ms to 512±23 ms (n=14), $p<0.05$). In agreement with APD data, a moderate but statistically significant inhibitory effect of 10 µM Hesperetin was observed on the transmembrane I_{Ks} ((n=6), $p<0.05$), without influencing I_{Kr}.
Hesperetin alone has no or negligible effect on APD, therefore, the proarrhythmic risk is low among healthy individuals. However, if the repolarization reserve has been attenuated due to certain pathological conditions such as heart failure or some variable abnormalities such as adverse drug effects, genetic mutations, a high amount of orange juice consumption might lead to moderately increased risk of arrhythmia due to inhibition of I_{Ks} and lengthening of cardiac repolarization.

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