Ebner *et al.: Intrinsic Activity*, 2019; **7**(Suppl.1):A3.10
doi:10.25006/IA.7.S1-A3.10
published online: 11 September 2019

INTRINSIC ACTIVITY

Joint Meeting of the Austrian Neuroscience Association (16th ANA Meeting) and the Austrian Pharmacological Society (25th Scientific Symposium of APHAR)

Innsbruck, 25–27 September 2019

MEETING ABSTRACT

A3.10

Pharmacological profile of the bradycardic agent ivabradine on human cardiac ion channels

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Background: Ivabradine lowers the heart rate by inhibition of hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels mediating the 'funny' pacemaker current I_f in the sinoatrial node. It is clinically approved for the treatment of heart failure and angina pectoris. Due to its proposed high selectivity for I_f, administration of ivabradine is not associated with the side effects commonly observed following the application of other heart rate-lowering agents. Recent evidence, however, has shown significant affinity of ivabradine towards human $K_V11.1$ (human ether-a-go-go-related gene, hERG) potassium channels. Despite the inhibition of $K_V11.1$ channels by ivabradine, cardiac action potential (AP) duration and heart rate-corrected QT interval (QT_c) of the human electrocardiogram were not prolonged. We thus surmised that compensatory mechanisms might counteract the drug's inhibitory action on $K_V11.1$.
Methods: The effects of ivabradine on human $K_V11.1$ and $K_V7.1$ potassium, $Ca_V1.2$ calcium, and $Na_V1.5$ sodium channels, heterologously expressed in tsA201 cells, were studied in the voltage-clamp mode of the whole-cell patch-clamp technique. In addition, changes in action potential parameters of human induced pluripotent stem cell (iPSC)-derived cardiomyocytes upon application of ivabradine were studied with current-clamp experiments.
Results: Ivabradine exhibits significant affinity towards cardiac ion channels other than HCN. We demonstrate for the first time inhibition of human voltage-gated $Na_V1.5$ sodium channels at therapeutically relevant concentrations. Within this study we also confirm recent findings of human $K_V11.1$ inhibition by low µM concentrations of ivabradine and observed no prolongation of ventricular-like APs in cardiomyocytes derived from iPSCs.
Discussion: Our results provide an explanation why ivabradine, despite its affinity for $K_V11.1$ channels, does not prolong the cardiac AP and QT_c interval. Furthermore, our results suggest the inhibition of voltage-gated $Na_V1.5$ sodium channels to underlie the recent observations of slowed atrioventricular conduction by increased atrial–His bundle intervals upon administration of ivabradine.
Acknowledgements: This work was funded by the "Österreichische Muskelforschung" (ÖMF) supported by the "Harley Davidson Charity Fonds" (AP00845OFF/KP00845OFF) to X.K., and the Austrian Science Fund (FWF, P30234-B27) to K.H.
Keywords: ivabradine – S16257 – human – cardiac ion channels – induced pluripotent stem cells

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