Design of a photo-activatable ivabradine to enable light induced block of HCN current in tissues

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HCN channels are expressed as four different subtypes (HCN1-4) both in the heart and in the nervous system. They are activated by membrane hyperpolarization and are responsible of a cation non-selective, depolarizing current which contributes to the generation and modulation of rhythmic activity, dendritic integration, and transmission of synaptic potentials. Misregulation of HCN channel activity has been linked to neurological disorders, including pain and epilepsy, and heart failure making HCN channels relevant target for pharmacological modulation. Currently, the only HCN channel blocker used in clinic is Ivabradine. However, ivabradine poorly discriminates among HCN subtypes, limiting its use in clinics and research. On the other hand, the high degree of conservation of the Ivabradine binding site in HCN subtypes makes it hard to develop subtype specific Ivabradine analogues. Therefore, we have designed and synthetized a caged version of Ivabradine (BrHQ-Iva) that can be released by light. This was achieved by quaternarization of its amine nitrogen with 8-bromo-7-hydroxy-2-quinolinylmethyl as a photocleavable protecting group with the aim to enable the one-photon or two-photon light-induced release of Ivabradine in living cells. Our patch clamp experiments both in HCN1-expressing HEK cells and on native HCN currents in L5 neurons from mouse brain slices show that BrHQ-Iva is ineffective in dark even when provided at high doses (100 mM) and activates upon exposure to light, from UV (370 nm) to blue (440 nm). BrHQ-Iva represents a new tool for blocking HCN current at high spatial resolution and paves the way for the development of treatments that inhibit HCN activity without undesired side effects. 1896-Pos S5-S6 interactions important for the electromechanical coupling in HCN