Characterization of a novel hERG potassium channel isoform upregulated in schizophrenia patients

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Background: Recently, Weinberger and colleagues found an association between a single nucleotide polymorphism (SNP) in the second intron of the KCNH2 gene and schizophrenia (Huffaker *et al.*, 2009). The KCNH2 SNP results in increased expression of an alternatively spliced isoform of the human ether-a-go-go-related (hERG 1A) potassium channel (referred to as hERG 3.1) in the prefrontal cortex and hippocampus. Intriguingly, the vast majority of antipsychotics, which block dopamine receptors as their major therapeutic mechanism, also inhibit hERG K^+ channels. This raises the possibility that, in patients who have increased levels of hERG 3.1, treatment with antipsychotics could exacerbate, or ameliorate, symptoms of the disease. Accordingly, the aim of this study was to characterize the gating properties of the novel hERG 3.1 isoform and investigate the effects of antipsychotic drugs on this isoform.

Methods: hERG K^+ channel currents were recorded from CHO cells, stably expressing hERG 1A or transiently transfected with the hERG 3.1 isoform, using the whole-cell voltage clamp technique.

Results & Conclusions: hERG channels can exist in one of three main gating states, a closed state, an open state or an inactivated state. Transitions between theses states are voltage dependent.

hERG 3.1 displays the same voltage dependence of channel activation as the 1A isoform, but has a voltage dependence of channel inactivation that is 8mV shifted to more positive potentials when compared to the hERG 1A isoform. While the rates of channel activation are not statistically different for both isoforms, the rates of deactivation are faster across the tested voltage range by almost an order of magnitude. This faster channel deactivation leads to an overall "loss of function" effect and less flux of potassium ions across the cell membrane. Applying of the known state dependent hERG blocker Haloperidol has a significantly lowered affinity for the 3.1 isoform compared to the 1A isoform.

The clinical significance of reduced hERG block in patients with increased levels of the hERG 3.1 isoform remains to be determined.

Huffaker SJ, Chen J, Nicodemus KK, Sambataro F, Yang F, Mattay V, Lipska BK, Hyde TM, Song J, Rujescu D, Giegling I, Mayilyan K, Proust MJ, Soghoyan A, Caforio G, Callicott JH, Bertolino A, Meyer-Lindenberg A, Chang J, Ji Y, Egan MF, Goldberg TE, Kleinman JE, Lu B, Weinberger DR. (2009) *Nature Medicine* **15**: 509-518.