NOS1AP polymorphisms reduce NOS1 activity and interact with prolonged repolarization in arrhythmogenesis

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NOS1AP SNPs correlate with QT prolongation and cardiac sudden death in patients affected by long QT syndrome type 1 (LQT1). NOS1AP targets NOS1 to intracellular effectors. We hypothesize that NOS1AP SNPs cause NOS1 dysfunction and this may converge with prolonged action potential duration (APD) to facilitate arrhythmias.

Aims: To test 1) the effects of NOS1 inhibition and their interaction with prolonged APD in a guinea pig cardiomyocyte (GP-CMs) LQT1 model; 2) whether pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from LQT1 patients differing for NOS1AP variants and mutation penetrance display a phenotype compatible with NOS1 deficiency.

Methods and Results: In GP-CMs NOS1 was inhibited by SMTC (or L-VNIO); LQT1 was mimicked by I_{Ks} blockade (JNJ203) and β-adrenergic stimulation (isoproterenol). hiPSC-CMs were obtained from symptomatic (S) and asymptomatic (AS) KCNQ1-A341V carriers, harboring the minor and major alleles of NOS1AP SNPs (rs16847548 and rs4657139) respectively. In GP-CMs: NOS1 inhibition prolonged APD, enhanced I_{CaL} and I_{NaL}, slowed Ca^{2+} decay and induced delayed afterdepolarizations. Under action-potential clamp, switching to shorter APD suppressed "transient inward current" events induced by NOS1 inhibition and reduced cytosolic Ca^{2+}. In S (vs AS) hiPSC-CMs: APD was longer and I_{CaL} larger; NOS1AP and NOS1 expression and colocalization were decreased.

Conclusions: the minor NOS1AP alleles are associated with NOS1 loss of function. The latter likely contributes to APD prolongation in LQT1 and converges with it to perturb Ca^{2+} handling. This establishes a mechanistic link between NOS1AP SNPs and aggravation of the arrhythmia phenotype in prolonged repolarization syndromes.