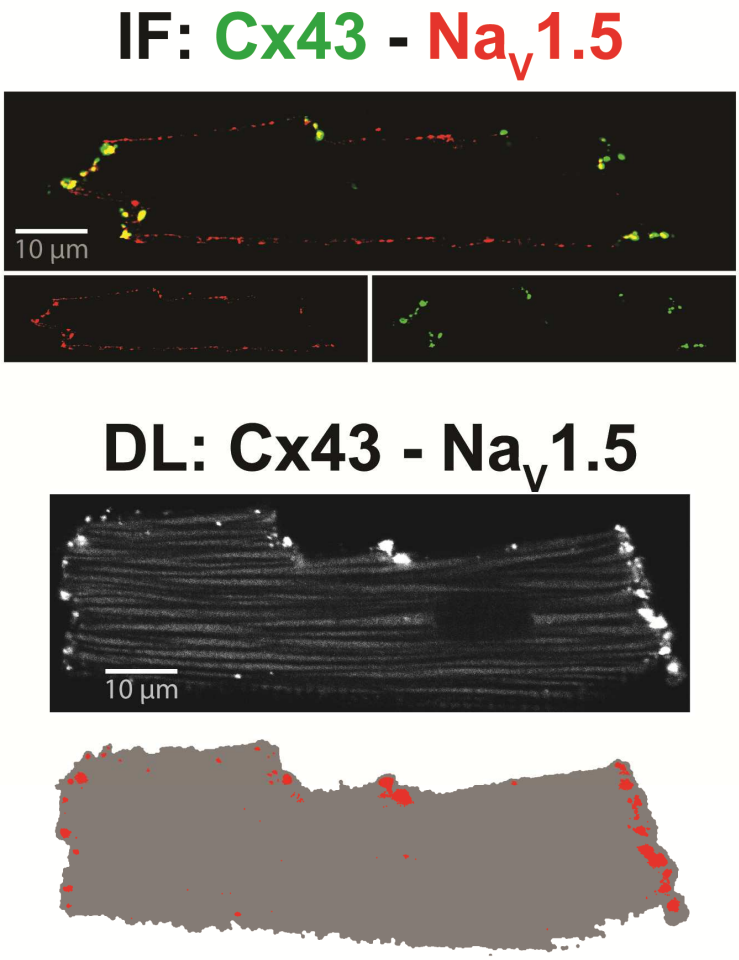
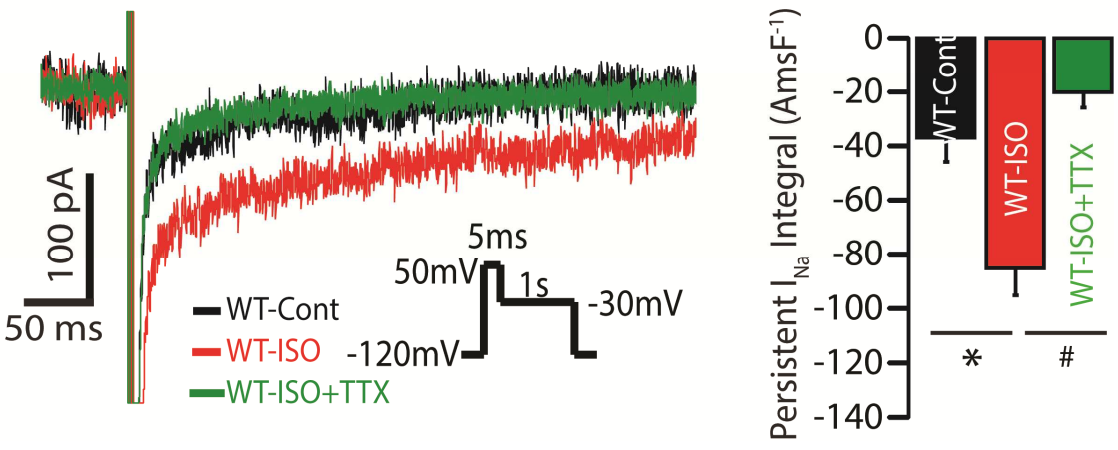
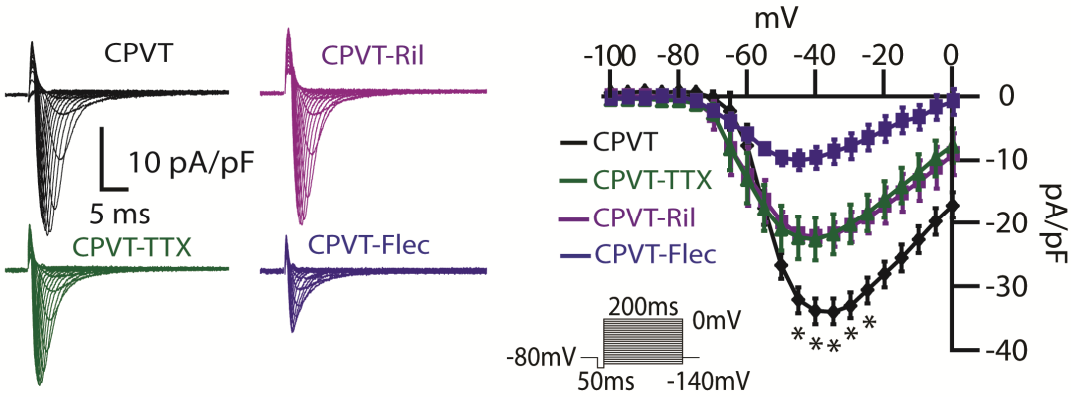
Supplemental Figure 1



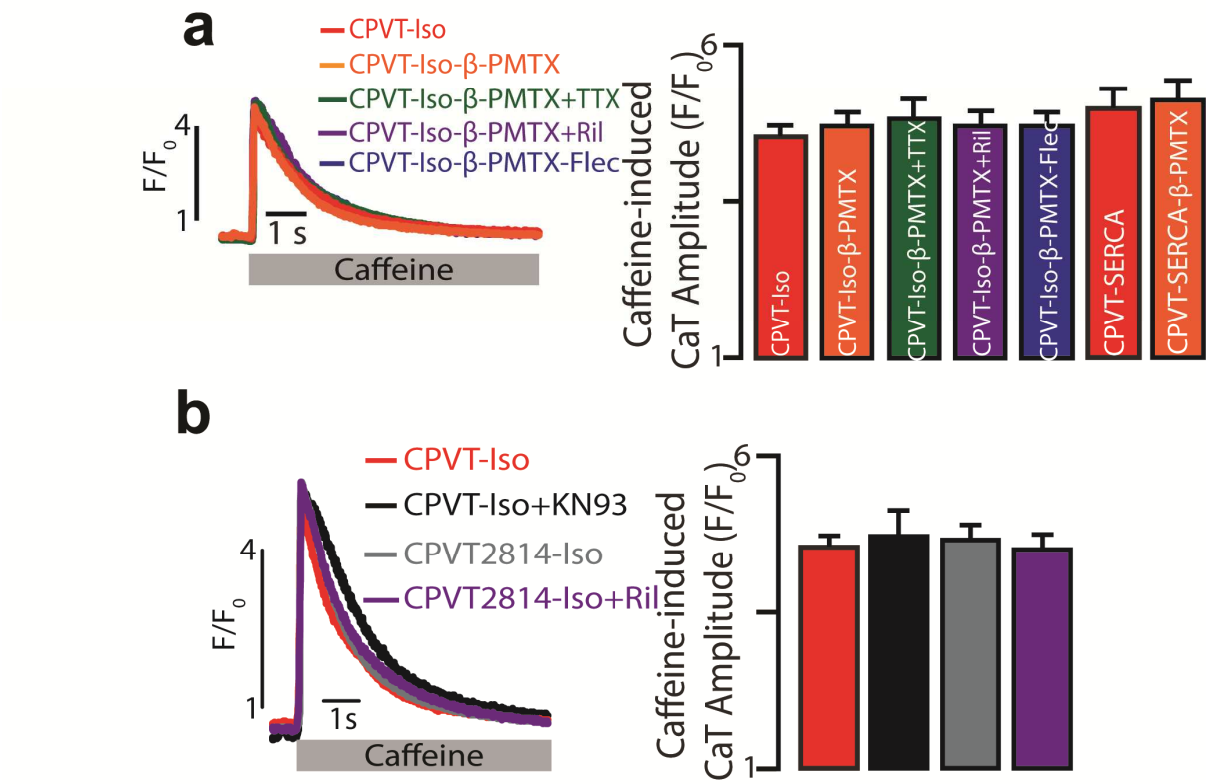
Supplemental Figure 2



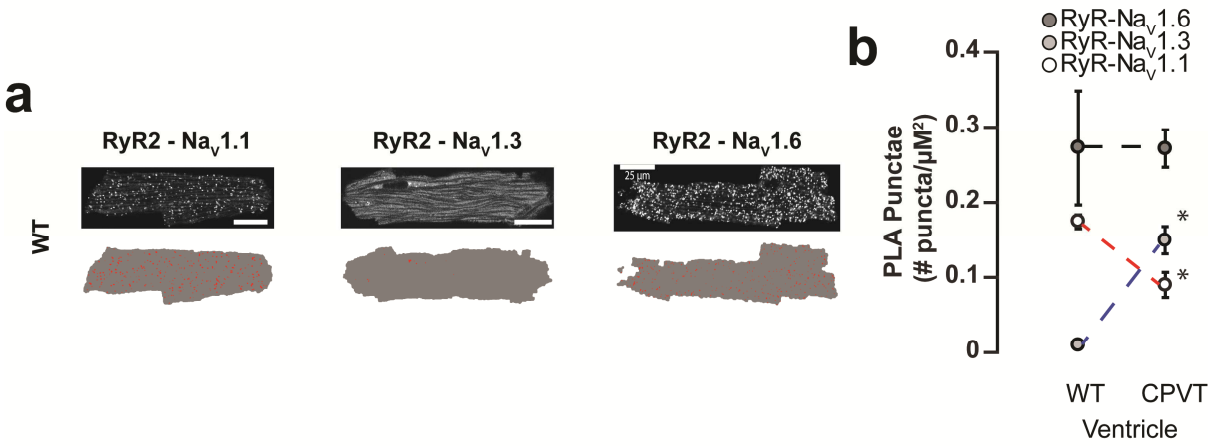
Supplemental Figure 3



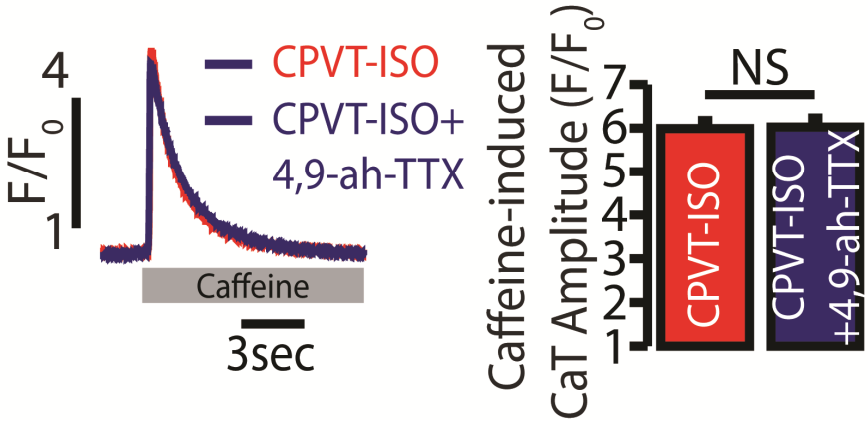
Supplemental Figure 4



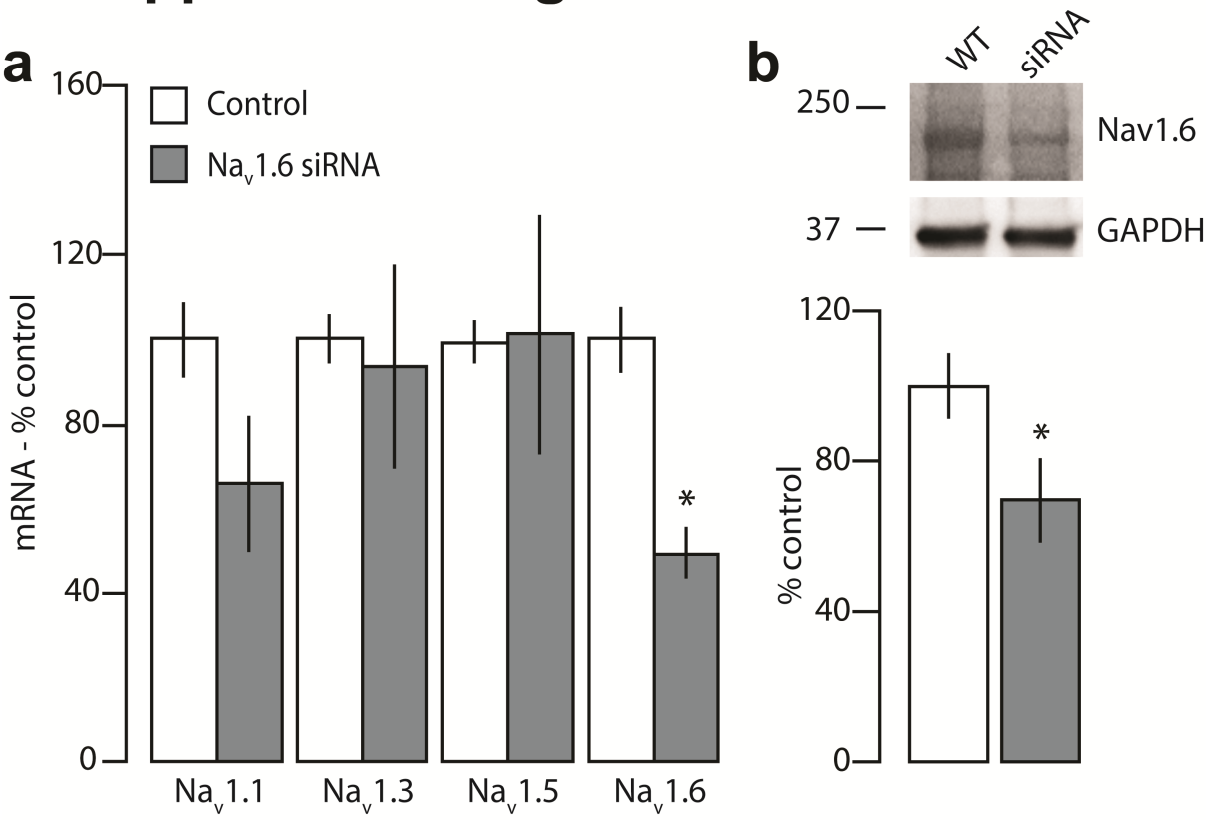
Supplemental Figure 5



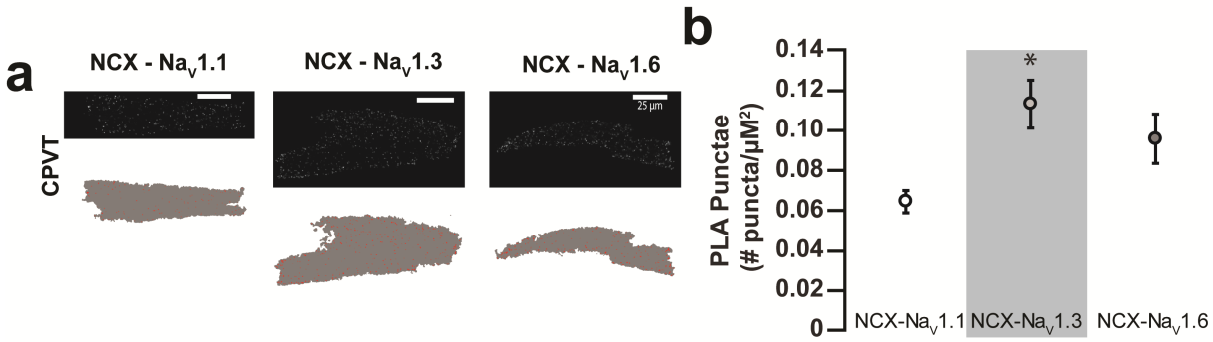
Supplemental Figure 6



Supplemental Figure 7



Supplemental Figure 8



Although triggered arrhythmias including catecholaminergic polymorphic ventricular tachycardia (CPVT) are often caused by increased levels of circulating catecholamines, the mechanistic link between β-adrenergic receptor (AR) stimulation and the subcellular/molecular arrhythmogenic trigger(s) is unclear. Here, we systematically investigated the subcellular and molecular consequences of β-AR stimulation in the promotion of catecholamine-induced cardiac arrhythmias. Using mouse models of cardiac calsequestrin-associated CPVT, we demonstrate that a subpopulation of Na^+ channels, mainly the neuronal Na^+ channels nNa_v, colocalize with RyR2 and Na^+/Ca^{2+} exchanger (NCX) are a part of the β-AR-mediated arrhythmogenic process. Specifically, augmented Na^+ entry via nNa_v in the settings of genetic defects within the RyR2 complex and enhanced sarcoplasmic reticulum (SR) Ca^{2+}-ATPase (SERCA)-mediated SR Ca^{2+} refill is both an essential and a necessary factor for the arrhythmogenesis. Furthermore, we show that augmentation of Na^+ entry involves β-AR-mediated activation of CAMKII subsequently leading to nNa_v augmentation. Importantly, selective pharmacological inhibition as well as silencing of $Na_v1.6$ inhibit myocyte arrhythmic potential and prevent arrhythmias *in vivo*. Taken together, these data suggest that the arrhythmogenic alteration in Na^+/Ca^{2+} handling evidenced ruing β-AR stimulation results, at least in part, from enhanced Na^+ influx through nNa_v. Therefore, selective inhibition of these channels and $Na_v1.6$ in particular can serve as a potential antiarrhythmic therapy.

- Catecholaminergic polymorphic ventricular tachycardia (CPVT) is often caused by increased levels of circulating catecholamines; however, the mechanistic link between β-adrenergic receptor (AR) stimulation and the subcellular/molecular arrhythmogenic trigger(s) is unclear.
- In both CPVT and wild type mice, a subpopulation of Na^+ channels (neuronal Na^+ channels; nNa_v) colocalize with RyR2 and Na^+/Ca^{2+} exchanger (NCX).
- Augmented Na^+ entry via nNa_v and enhanced sarcoplasmic reticulum (SR) Ca^{2+}-ATPase (SERCA)-mediated SR Ca^{2+} refill are both essential and necessary for CPVT.
- Augmentation of Na^+ entry involves β-AR-mediated activation of Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII).
- Selective pharmacological blockade as well as silencing of $Na_v1.6$ inhibit myocyte arrhythmic potential and prevent arrhythmias *in vivo*.