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Atrial fibrillation (AF) is the most common cardiac arrhythmia and accounts for substantial morbidity and mortality. Despite decades of research current treatments remain only partially effective, or in the case of ablation, invasive, costly and not effective in some patients. Development of novel, effective and safe therapy for AF has been hampered by the lack of animal models that reflect AF in humans. While some large animal models exhibit aspects of human AF it is difficult to test and develop novel small molecule therapies for AF in these costly and limited models. Ideally, a small animal model that faithfully phenocopies human AF would be an invaluable tool for both understanding the molecular physiology of AF and potentially for identifying and testing novel small molecule therapeutics. Indeed, murine models have proved invaluable in the development of novel therapeutics for cancer, diabetes and obesity. The lack of a mouse model for AF is a barrier to research in this important disease. To address this gap we created doxycycline-inducible transgenic (TG) mice with a mutation (F1759A) of the local anesthetic binding site in human *SCN5A*, the cardiac $\text{Na}_v1.5$ channel gene. Fortuitously these mice exhibit modest atrial enlargement and fibrosis, mitochondrial dysmorphology, frequent, sustained episodes of spontaneous AF, and non-sustained polymorphic ventricular tachycardia, observed as early as 5 weeks of age in the absence of doxycycline. The sustained and spontaneous atrial arrhythmias, an unusual if not unique phenotype in mice, enabled initial explorations of mechanisms of AF using *in vivo* (telemetry), *ex vivo* (optical voltage mapping), and *in vitro* (cellular electrophysiology) techniques. We now propose to use this mouse model to more fully characterize the molecular mechanisms of arrhythmogenesis, to explore whether altered Ca^{2+} homeostasis contributes to the genesis and maintenance of AF, and whether targeting altered Ca^{2+} homeostasis could be an effective treatment of AF. Three Aims are proposed: **Aim 1**: To examine the downstream mechanisms by which increased cytosolic Ca^{2+} increases the propensity of AF. We will test using genetic and pharmacological approaches whether inhibitors of Na^+ - Ca^{2+} exchanger (NCX) and Ca^{2+} -calmodulin dependent kinase (CaMKII) can inhibit AF *in vivo* and spiral waves/rotors *ex vivo*. **Aim 2**: To test the causal link between increased persistent Na^+ current, “leaky” RyR2, and the susceptibility for AF. We will use pharmacological and genetic approaches to inhibit RyR2 leak to see whether it plays a role in AF and whether it may be a novel therapeutic target. **Aim 3**: To test the causal link between mitochondrial dysfunction due to increased persistent Na^+ current and leaky RyR2 channels, and the susceptibility for AF. The proposed studies may identify important links between dysfunctional Na^+ channels, abnormal SR Ca^{2+} release in AF, defective Ca^{2+} -dependent signaling in AF, mitochondrial dysfunction and oxidative overload in AF. Our studies are designed to provide rigorous and robust hypothesis-testing to open new understandings of the molecular bases of AF and to pave the way towards novel, mechanism-based, effective and safe treatments.