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Symposium

Arrhythmias caused by abnormal Ca^{2+} homeostasis and the treatment strategies

Nagomi Kurebayashi¹

¹*Department of Pharmacology, Juntendo University School of Medicine*

Type 2 ryanodine receptor (RyR2) is the Ca^{2+} release channel on the ER and plays a pivotal role in EC-coupling in the heart. Abnormal activation of RyR2 has been implicated in arrhythmogenic diseases. For example, in heart failure, chronic phosphorylation of RyR2 can contribute to enhanced Ca^{2+} leak from ER. In addition, mutations in RyR2 are reported to cause arrhythmogenic diseases such as catecholaminergic polymorphic ventricular tachycardia (CPVT) and long QT syndrome (LQTS). In most cases spontaneous Ca^{2+} release from ER via activated RyR2 is thought to trigger arrhythmia. We have recently established a procedure for functional evaluation of the arrhythmogenic RyR2 mutations using HEK293 expression system. Furthermore, we identified several compounds that suppress RyR2 activity via high-throughput screening using the HEK293 system. Because some of them suppressed abnormal Ca^{2+} signals in mouse cardiomyocytes, RyR2 inhibitors may be promising as novel anti-arrhythmic drugs.