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Blocking an ion channel with a bioengineered peptibody

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Abstract

Novel ion channels blocking modalities are needed for the development of the next generation of safer and more effective antiarrhythmic pharmacotherapies. As a proof of concept, we engineered and produced an ion channel blocking peptibody, that targets the acetylcholine activated inward rectifier potassium current (IKACh). The peptibody was engineered as a fusion protein between the human IgG1 Fc fragment fusion protein and TertiapinQ, a 21 amino acid European honey bee venom that inhibits IKACh. We tested the hypothesis that the peptibody is a more potent blocker of IKACh compared to TertiapinQ.

Methods: We used patch clamp, multiple electrode arrays (MEA) and whole animal electrophysiology to evaluate the peptibody's effectiveness in blocking IKACh in vivo and in vitro.

Results: The peptibody was purified from the culture supernatant of transfected Expi293F cells as a 56 KDa dimer. In human embryonic kidney cells transfected with Kir3.1 and Kir3.4, the molecular correlates of IKACh, patch clamp showed that the IC50s of IKACh block were 20 pM for the peptibody versus 10 nM for TertiapinQ. In anesthetized male SD rats, 10 second electrical stimulation of the right vagus (2ms, 4V square pulses) at frequencies between 4 and 28 Hz caused a progressive, frequency dependent increase in the RR interval due to parasympathetically mediated activation of IKACh. Jugular vein injection of 1 ml peptibody at 2.1M abolished the slowing of the heart rate due to vagal stimulation. Conversely, 1 ml of 2.1M of control IgG1 Fc fragment had no effect. In order to test the specificity of the peptibody, we quantified the repolarization duration of spontaneously-beating induced human pluripotent stem cells derived ventricular cardiomyocytes in the presence and absence of the peptibody, using MEA. The peptibody at 1, 10, and 100 pM did not modify repolarization durations.

Conclusions: Engineered ion channel-specific peptibodies can be powerful and highly potent ion channel blockers and have the potential to be developed into novel antiarrhythmic modalities.

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