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RESEARCH NEWS

A range of activators for cardiac I_{Ks} channels

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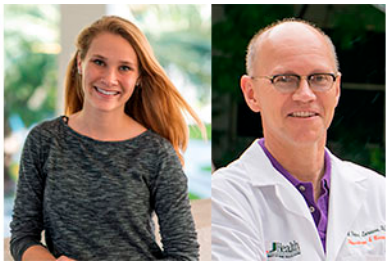
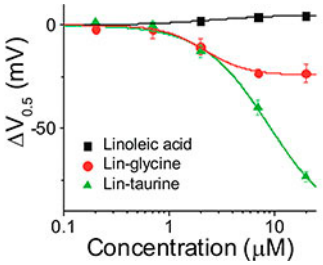
***JGP* study suggests that varying the head group of polyunsaturated fatty acids could enable personalized treatments for long QT syndrome.**

Voltage-gated I_{Ks} channels mediate outward K^+ currents that help to repolarize cells and terminate action potentials in the ventricles of the heart. Mutations in the I_{Ks} channel can therefore delay repolarization and ventricle relaxation, resulting in long QT syndrome (LQTS). The severity of this disease can vary greatly, with some mutations causing only mild symptoms while others pose a high risk of sudden cardiac arrest and death. Yet current treatments for LQTS, such as β blockers, are based on a one-size-fits-all approach. In this issue of *JGP*, Bohannon et al. suggest that, by activating I_{Ks} channels to various extents, polyunsaturated fatty acids (PUFAs) with different head groups might provide more personalized treatment options to LQTS patients (1).

Peter Larsson and colleagues have previously shown that PUFAs with negatively charged head groups can modify the activity of I_{Ks} channels by inserting their hydrophobic tails into the cell membrane in such a way that the head group can electrostatically attract positively charged residues in the channel's voltage-sensing domain, thereby shifting the voltage-dependence of channel activation (2,3). The head group can also attract a lysine residue in the pore domain, increasing the channel's maximum conductance (4). "We wondered whether we could improve the ability of PUFAs to activate I_{Ks} channels by changing the number or type of negative charges within the head group," says Larsson, a professor at the Miller School of Medicine, University of Miami.

Larsson and colleagues, including first author Briana Bohannon, first compared PUFAs with either glycine or taurine head groups and found that, though both can left-shift the voltage dependence of I_{Ks} activation, taurine-containing PUFAs are roughly twice as effective as their glycine-containing counterparts. "Both are expected to have one negative charge, but their pK_as are very different," Larsson explains. "Taurine has a much lower pK_a and is completely unprotonated at physiological pH, whereas more than 50% of glycine head groups should be protonated at pH 7.4."





Briana Bohannon (left), Peter Larsson (center), and colleagues reveal that PUFAs with distinct head groups can differentially activate the cardiac I_{Ks} channels that terminate ventricular action potentials, raising the prospect of personalized treatments for LQTS. The graph (right) shows that, compared with linoleic acid (black), linoleoyl glycine (red) moderately shifts the voltage dependence of I_{Ks} activation, whereas linoleoyl taurine (green) has a much greater effect, largely because of its lower pK_a.

Increasing the number of potential negative charges did not enhance the effects of PUFAs on I_{Ks} channels. Again, however, head groups with lower pK_as shifted the voltage dependence of channel activation more strongly than head groups with higher pK_as. In contrast, the effect of PUFAs on maximum conductance appears to be independent of head group pK_a values.

Taken together, Bohannon et al.'s results demonstrate that different PUFAs can have a range of effects on I_{Ks} activity. The researchers found that both linoleoyl glycine and linoleoyl taurine can restore the activity of I_{Ks} channels carrying an LQTS-causing mutation. In the future, however, patients with severe loss-of-function mutations may be best treated with PUFAs carrying taurine head groups, while patients with milder symptoms are treated with glycine-containing PUFAs.

Intriguingly, Bohannon et al. also found that PUFAs can still activate I_{Ks} channels when applied to cells in combination with physiologically relevant concentrations of albumin, a serum protein that binds to PUFAs and other fatty acids and carries them through the bloodstream. "So this is a proof of concept that, even in the presence of albumin, there are enough free PUFA molecules to bind and activate the channels," Larsson says. This raises the possibility that orally administered PUFAs might be able to successfully reach the heart tissue of LQTS patients via the bloodstream.

This is all a long way off, Larsson cautions, but his team have already embarked on the next step, investigating whether PUFAs are safe and effective in animal models of LQTS.

References

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