CARDIOVASCULAR DISEASE

Insulin sensitizer protects the heart

Heart failure (HF) and atrial fibrillation (AF) frequently coexist and are associated with high morbidity and mortality. Current drugs are limited by poor efficacy and potentially dangerous side effects. Now, writing in *Nature Communications*, Sapra *et al*. demonstrate that the small-molecule hydroximic acid derivative BGP-15 improves cardiac function and reduces arrhythmic episodes in mouse models of progressive HF and AF.

BGP-15 enhances insulin sensitivity in humans and has successfully completed Phase IIb trials in type 2 diabetes. It is a heat shock protein (HSP) co-inducer that is believed to act primarily through activation of HSP70. As preclinical models have implicated a cardioprotective role of HSP70, Sapra *et al*. investigated the therapeutic potential of BGP-15 in HF and AF.

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First, the authors tested the effects of BGP-15 in a transgenic mouse model with a failing heart that was susceptible to AF (HF + AF model). Four weeks of oral BGP-15 treatment attenuated the increase in atrial size and lung weight seen in untreated HF + AF mice, effects that were associated with improved cardiac function and fewer arrhythmic episodes.

BGP-15 exerted similar protective effects in a second mouse model; cardiac-specific muscle-restricted coiled-coil (MURC) transgenic mice (which exhibit dilated cardiomyopathy, HF and cardiac arrhythmias). Treatment of MURC mice with BGP-15 for 4 weeks improved cardiac outcome and attenuated cardiac pathology and molecular abnormalities.

Surprisingly, cardiac HSP70 activity was unaltered in the mouse models following BGP-15 treatment. Furthermore, deletion of HSP70 in HF + AF mice did not affect the ability of BGP-15 to protect the heart. Together, these findings indicated that BGP-15 does not elicit its cardiac effects through HSP70 modulation.

As BGP-15 has also been shown to enhance the actions of membrane-localized receptor proteins, including the insulin receptor, the authors investigated the effects of BGP-15 on the insulin receptor family member IGF1R, which is known to mediate cardiac protection. Indeed, atrial IGF1R phosphorylation was higher in HF + AF mice treated with BGP-15, and cardiac-specific IGF1R overexpression in this mouse model conferred cardiac protection resembling the effects of BGP-15. Interestingly, IGF1R phosphorylation was approximately 60% lower in atrial tissue samples taken from patients who had undergone coronary artery bypass graft surgery and developed AF, compared with samples from patients who maintained sinus rhythm after surgery.

Further mechanistic studies revealed that the disrupted IGF1R signalling in HF + AF mice was likely to be due to elevated atrial levels of the GM3 ganglioside, which decreased cell membrane fluidity and prevented the interaction of calveolin proteins with IGF1R. Notably, BGP-15 attenuated atrial GM3 levels in HF + AF mice and enhanced the content of calveolin proteins.

Given that BGP-15 has already been proven to be safe in humans, these findings support a novel therapeutic approach for patients with HF and AF.

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ORIGINAL RESEARCH PAPER Sapra, G. *et al*. The small-molecule BGP-15 protects against heart failure and atrial fibrillation in mice. *Nature Comm.* http://dx.doi.org/10.1038/ncomms6705 (2014)