Iptakalim: a new or just another KCO?

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This editorial refers to ‘Kₐₜₚ activation prevents progression of cardiac hypertrophy to failure induced by pressure overload via protecting endothelial function’ by S. Gao et al.,³ pp. 444–456, this issue.

Cardiac hypertrophy, especially left ventricular hypertrophy (LVH), is a major compensatory mechanism in response to pressure overload derived from hypertension. Also, tissue remodelling through LVH is known to lead to heart failure if the increased workload is sustained over a long period of time. In a nutshell, hypertension can result in hypertrophy which, if sustained, leads to heart failure. Hypertension is also a risk factor for vascular accidents leading to ischaemia.

Endothelial cell (dys)function has been shown to play important roles in the pathophysiological events related to the establishment and progression of hypertensive heart disease. Nitric oxide (NO) production by endothelial cells inhibits the progression of cardiac hypertrophy, whereas endothelin generation promotes hypertrophy.¹ Actually, the imbalance between these two systems is one of the underlying causes of cardiac tissue remodelling. Antihypertensive drugs that increase NO generation or that inhibit endothelin production have been shown to decrease cardiac hypertrophy (mostly by decreasing LVH), thus preventing heart failure induced by a pressure overload.²

However, despite intense research, drugs able to ameliorate hypertension and, at the same time, protect against the associated heart diseases are still lacking. A promising candidate in this area is iptakalim, a recently developed channel opener (KCO) that has been shown to be antihypertensive in different models of hypertension in rats, dogs, and humans.³,⁴

This issue of Cardiovascular Research brings an interesting contribution to the field of hypertension and heart disease, uncovering some new properties of iptakalim. Gao et al.⁵ show that iptakalim possesses antihypertrophic properties, preventing the progression of LVH to heart failure induced by pressure overload. They also show that iptakalim helps maintain several haemodynamic parameters, such as heart rate, blood pressure, and ventricular function. Additionally, iptakalim reduces myocardial and perivascular fibrosis as well as mRNA expression of two important molecular markers of heart failure, atrial natriuretic peptide, and B-type natriuretic peptide. Their most interesting results concern the signalling pathway that might underlie the whole-organ effects. Gao et al. show that iptakalim treatment substantially increases serum content of NO and decreases that of endothelin-1 protein. These data parallel an increase in the content of endothelial NO synthase and a decrease in endothelin-converting enzyme. The results suggest that iptakalim’s effects on cardiac hypertrophy induced by pressure overload occur through the maintenance of the balance between the NO and endothelin signalling systems. Based on previous studies, they claim that iptakalim protects endothelial function by preferential activation of the SUR2B/Kir6.1 subtype of plasma membrane Kₐₜₚ channels (cellKₐₜₚ or sarcKₐₜₚ in muscle tissues) expressed in the endothelium.³,⁶,⁷

As often is the case, new questions are expected to arise from solid research. The present work by Gao et al. raises several questions that must be addressed concerning iptakalim’s intracellular effects. Several articles point to a link between mitochondrial Kₐₜₚ channels (mitoKₐₜₚ) activity and hypertrophy. Diazoxide, a mitoKₐₜₚ agonist, has been shown to inhibit phenylephrine-induced hypertrophy.⁶ The mitoKₐₜₚ antagonist 5-hydroxydecanoate (5HD) has been shown to block the inotropic effects of calcium and other known inotropic drugs, such as ouabain or dobutamine.⁹ These data strongly support the hypothesis that mitoKₐₜₚ activity is intrinsically involved in the intracellular signalling pathways leading to hypertrophy. Additionally, the protection afforded by iptakalim against MPP⁺ or H₂O₂ is abolished by 5HD, which suggests that iptakalim’s protective mechanisms occur via mitoKₐₜₚ activation.¹⁰,¹¹ Indeed, all cardioprotective KCOs described thus far have been shown to be mitoKₐₜₚ agonists. Cardioprotective protocols such as ischaemic pre- or postconditioning also operate via mitoKₐₜₚ opening.¹²–¹⁴ However, Gao et al. claim that cardioprotective doses of iptakalim do not open cardiac muscle mitoKₐₜₚ. Even though no data are shown, the unpublished data regarding mitoKₐₜₚ activity were obtained using techniques that are not sensitive enough for that purpose.¹²,¹⁴–¹⁷ which could lead to misleading interpretations. For
example, activation of mitoK<sub>ATP</sub> would result in increased K<sup>+</sup> flux into the matrix, thereby slightly decreasing membrane potential. To compensate for this ΔV decrease, respiration would increase (and not decrease, as claimed). As briefly stated above, there is some evidence that iptakalim does activate mitoK<sub>ATP</sub> and that mitoK<sub>ATP</sub> is part of the antihypertrophic signalling system. Thus, iptakalim’s effect upon mitoK<sub>ATP</sub> must be the focus of future research.

On the other hand, it is well known that activation of sarcK<sub>ATP</sub> in muscular tissue (as well as the heart) results in trophic signalling system. Thus, iptakalim’s effect upon mitoK<sub>ATP</sub> agonist.

References

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