Editorial

Iptakalim: a new or just another KCO?

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Cardiac hypertrophy, especially left ventricular hypertrophy (LVH), is a major compensatory mechanism in response to pressure overload derived from hypertension. Also, tissue remodeling 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 ischemia.

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. Actually, the imbalance between these two systems is one of the underlying causes of cardiac tissue remodeling. 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.

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 K⁺ channel opener (KCO) that has been shown to be antihypertensive in different models of hypertension in rats, dogs, and humans.

This issue of *Cardiovascular Research* brings an interesting contribution to the field of hypertension and heart disease, uncovering some new properties of iptakalim. Gao and coworkers 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 hemodynamic 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 signaling pathway that might underlie the whole-organ effects. Gao and coworkers 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 signaling systems. Based on previous studies, they claim that iptakalim protects endothelial function by preferential activation of the SUR2B/Kir6.1 subtype of plasma membrane K\text{ATP} channels (cellK\text{ATP}, or sarcK\text{ATP} in muscle tissues) expressed in the endothelium. \(^4,6,7\)

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 K\text{ATP} channels (mitoK\text{ATP}) activity and hypertrophy. Diazoxide, a mitoK\text{ATP} agonist, has been shown to inhibit phenylephrine-induced hypertrophy. \(^8\) The mitoK\text{ATP} 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 mitoK\text{ATP} activity is intrinsically involved in the intracellular signaling pathways leading to hypertrophy. Additionally, the protection afforded by iptakalim against MPP\(^+\) or H\text{2}O\text{2} is abolished by 5HD, which suggests that iptakalim’s protective mechanisms occur via mitoK\text{ATP} activation. \(^10,11\) Indeed, all cardioprotective KCOs described thus far have been shown to be mitoK\text{ATP} agonists. Cardioprotective protocols such as ischemic pre- or postconditioning also operate via mitoK\text{ATP} opening. \(^12-14\) However, Gao and coworkers claim that cardioprotective doses of iptakalim do not open cardiac muscle mitoK\text{ATP}. Even though no data are shown, the unpublished data regarding mitoK\text{ATP} 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\text{ATP} would result in increased K\(^+\) flux into the matrix, thereby slightly decreasing membrane potential. To compensate for this \(\Delta\Psi\) decrease, respiration would increase (and not decrease, as claimed \(^5\)). As briefly stated above, there is some evidence that iptakalim does activate mitoK\text{ATP}, and that mitoK\text{ATP} is part of the antihypertrophic signaling system. Thus, iptakalim’s effect upon mitoK\text{ATP} must be the focus of future research.

On the other hand, it is well known that activation of sarcK\text{ATP} in muscular tissue (as well as the heart) results in action potential duration (APD) shortening due to the
ionic changes resulting from channel opening. Thus, if iptakalim acts upon sarcK$_{ATP}$ and not mitoK$_{ATP}$, as suggested by Gao and coworkers, it must result in APD shortening. However, no such evidence is yet present in the cardiovascular-related iptakalim literature.

From the data published in this and other related papers, it does seem that iptakalim is a drug that deserves a chance in the battle against cardiac diseases in the clinical setting. However, as mentioned above, all cardioprotective KCO (as well as cardioprotective interventions such as pre- and postconditioning) have thus far been shown to act upon mitoK$_{ATP}$, not sarcK$_{ATP}$. Therefore, until further proof is provided, it might be safer to bet that iptakalim is just another mitoK$_{ATP}$ agonist.

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References
