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COMMENTARY

Regulation of cardiac Na–Ca exchange activity by selective tyrosine kinase inhibition

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Cardiac performance is regulated by a number of different phosphorylation-dependent mechanisms affecting a wide range of cellular processes. Some of the best-studied examples of signaling pathways that produce acute functional responses in the heart involve the activity of serine/threonine kinases such as protein kinase A and protein kinase C. It has also been recognized for some time that tyrosine kinases play an important role in cardiac function, although they have perhaps been more often associated with signaling mechanisms involved in regulating metabolism or growth and differentiation. However, this picture is beginning to change in light of more recent evidence that modulation of tyrosine kinase activity can also produce acute functional responses, including changes in both electrical and mechanical activity.

Ion channels have been identified as frequent targets of tyrosine kinase activity in many different cell types, including cardiac myocytes (Davis *et al*., 2001). Supporting evidence has come from studies demonstrating that functional changes occur in direct response to activation of receptors linked to tyrosine kinase-dependent signaling pathways. Pharmacologic inhibition of tyrosine kinase and tyrosine phosphatase activity has also been used to demonstrate that basal tyrosine phosphorylation plays an important role in affecting functional responses.

Although changes in ion channel activity can affect the force of contraction, there is also evidence that tyrosine kinases may alter contractility by other mechanisms. Liew *et al*. (2003) recently reported that the phytoestrogen genistein can enhance cardiac myocyte contraction by a mechanism associated with its ability to inhibit tyrosine kinase activity. At least part of the explanation for genistein's effect on cardiac muscle contraction was attributed to its capacity to inhibit Na–Ca exchange (NCX) activity and attenuate extrusion of cytosolic Ca^{2+}. If this effect on NCX is truly due to inhibition of tyrosine kinase activity, it suggests that basal tyrosine phosphorylation stimulates the exchanger. At first glance, this observation would seem to be at odds with a new study in the current issue of the *British Journal of Pharmacology*. Missan & McDonald (2004) report that the tyrosine kinase inhibitors tyrphostin A23 and tyrphostin A25 stimulate membrane current generated by NCX in cardiac myocytes, suggesting that basal tyrosine phosphorylation actually inhibits the exchanger. Missan and McDonald also find that the effect of these tyrphostins does not appear to be mimicked by genistein. The question then is how can these apparently incongruous results be reconciled?

Species or even gender-dependent differences in the sensitivity of NCX to tyrosine kinase inhibitors such as genistein may explain some of the apparent discrepancies (Liew *et al*., 2004). However, another intriguing possibility is that in cardiac myocytes NCX may actually be regulated by two tyrosine kinase-dependent mechanisms: one that stimulates NCX and is sensitive to inhibition by genistein, and a second that inhibits NCX and is sensitive to inhibition by tyrphostins. While this might seem unnecessarily complicated, pharmacologically distinct tyrosine kinase activities with opposing effects have been reported to regulate other acute functional responses in cardiac myocytes (Du *et al*., 2004). The only apparent incongruity then would be the inability of Missan and McDonald to detect an inhibitory effect of genistein, but this could be explained by the fact that there was minimal NCX activity under basal conditions in their experiments. It was only after exposure to the active tyrphostin analogues that NCX activity could be detected.

These new findings highlight NCX as another possible target for tyrosine kinase signaling pathways in the heart. They also raise several crucial questions, such as what are the tyrosine kinases that are involved and how do they regulate NCX activity?

References

DAVIS, M.J., WU, X., NURKIEWICZ, T.R., KAWASAKI, J., GUI, P., HILL, M.A. & WILSON, E. (2001). Regulation of ion channels by protein tyrosine phosphorylation. *Am. J. Physiol. Heart Circ. Physiol.,* **281,** H1835–H1862.

DU, X.L., GAO, Z., LAU, C.P., CHIU, S.W., TSE, H.F., BAUMGARTEN, C.M. & LI, G.R. (2004). Differential effects of tyrosine kinase inhibitors on volume-sensitive chloride current in human atrial myocytes: evidence for dual regulation by Src and EGFR kinases. *J. Gen. Physiol.,* **123,** 427–439.

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LIEW, R., MACLEOD, K.T. & COLLINS, P. (2003). Novel stimulatory actions of the phytoestrogen genistein: effects on the gain of cardiac excitation–contraction coupling. *FASEB J.,* **17,** 1307–1309.

LIEW, R., STAGG, M.A., CHAN, J., COLLINS, P. & MACLEOD, K.T. (2004). Gender determines the acute actions of genistein on intracellular calcium regulation in the guinea-pig heart. *Cardiovasc. Res.,* **61,** 66–76.

MISSAN, S. & MCDONALD, T.F. (2004). Cardiac Na^+–Ca^{2+} exchanger current induced by tyrphostin tyrosine kinase inhibitors. *Br. J. Pharmacol.,* **143,** 943–951.

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