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CARDIOVASCULAR DISEASE

Spice might protect the heart


DIGITAL VISION

The heart has the ability to adapt to increased stress by undergoing hypertrophy, but if sustained, heart failure may ensue. Now, two studies in the *Journal of Clinical Investigation* show that the dietary compound curcumin can block such hypertrophy through the inhibition of p300-histone acetyltransferase (p300-HAT) activity, indicating a novel potential strategy for the prevention of heart failure.

Curcumin is a natural polyphenolic compound responsible for the yellow colour of the curry spice turmeric, and is widely used in alternative medicine. With potential antitumour, antioxidant and anti-inflammatory actions, clinical studies for various disorders including cancer, rheumatoid arthritis and inflammatory bowel disease have already been conducted. Previous studies have also shown that curcumin suppresses histone acetylation by specifically inhibiting activity of the key regulator of histone acetylation p300-HAT. With histone acetylation having an important role in the progression of cardiac hypertrophy and heart failure, the authors proposed that curcumin may be an effective therapeutic agent for heart failure.

To test their theory, both groups first assessed the ability of curcumin to prevent hypertrophy *in vitro*. Indeed, curcumin pretreatment prevented the α-adrenergic receptor agonist, phenylephrine (PE), from inducing hypertrophy and increased expression of the hypertrophic markers, atrial and brain naturetic peptide (ANP and BNP), in rat ventricular cardiomyocytes. In addition, PE-induced acetylation of histones H3 and H4 was also markedly blocked by specific inhibition of p300-HAT activity. Importantly, acetylation and DNA binding of the hypertrophy-responsive transcription factor GATA4 — an important mediator of hypertrophic gene expression — were also reduced.

Next, Li and colleagues analysed the effects of curcumin in two mouse models of cardiac hypertrophy: PE infusion and aortic branching (AB) surgery (a model of pressure overload). Curcumin pretreatment prevented hypertrophy and reduced histone acetylation in both models. Specifically, p300-HAT activity was inhibited, with no effect on histone deacetylase activity. In addition, the marked induction of GATA4 acetylation and DNA-binding activity observed with PE and AB was completely absent in curcumin-pretreated mice. Furthermore, the development of two prominent features of cardiac hypertrophy and the progression to heart failure (inflammation and fibrosis) was also blocked, as indicated by suppressed NF-κB and TGFβ–SMAD signalling, respectively. Importantly, in addition to these preventative actions, curcumin was also shown to be capable of reversing established cardiac hypertrophy following PE or AB.

Morimoto and colleagues went on to demonstrate the potential of curcumin therapy using two animal models of heart failure, in which curcumin administration was started after the development of left ventricular (LV) hypertrophy or dilatation (at the stage of chronic heart failure). In the salt-sensitive Dahl rat model of hypertension, curcumin preserved LV systolic function, reduced wall thickness, decreased levels of BNP and inhibited hypertension-induced increases in myocardial cell diameter, perivascular fibrosis and GATA4 acetylation. Similar effects were observed in a surgical rat model of myocardial infarction.

Studies of curcumin in trials in other diseases have so far been inconclusive, which in part might be due to issues such as low bioavailability of the formulations used. Addressing such issues, together with further studies to better understand the effects of curcumin, might lead to the development of novel therapeutic approaches targeting pathological cardiac hypertrophy.

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ORIGINAL RESEARCH PAPERS Li, H.-L. *et al.* Curcumin prevents and reverses murine cardiac hypertrophy. *J. Clin. Invest.* **118**, 879–893 (2008) | Morimoto, T. *et al.* The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. *J. Clin. Invest.* **118**, 868–878 (2008)