Vitamin A for the heart: progress for cardiac hypertrophy regression?

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MOST OFTEN, hypertrophy of the heart is the response to a variety of stimuli such as arterial hypertension, ischemia, or valvular heart disease to name only a few. However, cardiac growth may also result from sarcomeric gene mutations (6). A common feature and therefore hallmark of cardiac hypertrophy is increased left ventricular weight through which the heart tries to compensate increased wall tension (Laplace’s law). Unfortunately, chronic stress for the heart also involves a remodeling process including fibrosis, apoptosis, and finally chamber dilatation progressing to congestive heart failure (6) with poor prognosis. In a large number of animal models for cardiac hypertrophy—but also in human heart disease—activation of the renin-angiotensin aldosterone system (RAAS) was found to play a major role in the pathophysiology of hypertrophy as well as in the progression to heart failure. Although RAAS inhibitors, e.g., angiotensin-converting enzyme (ACE) inhibitors or angiotensin type 1 receptor (AT1) blockers, are clinically widely used, medicine is far from healing this complex disease. Also, the recently clinically introduced renin inhibitors (e.g., aliskiren) can block the RAAS at the very beginning of its signaling cascade; however, completely novel approaches to target additional stress pathways and thus the progression of cardiac hypertrophy and heart failure are urgently needed. In recent years, several new hypertrophic signaling pathways were found and further investigated (5, 6, 9), but only a few approaches were experimentally studied to inhibit the circulus vitiosus found in these cardiac diseases (6, 12).

Retinoic acid is a derivative and active metabolite of vitamin A known to modulate cardiac structure and function. So far, a handful of experimental studies suggest that retinoic acid suppresses morphological changes of the heart and alterations in gene expression associated with hypertrophy induced by endothelin, angiotensin II, and phenylephrine (10, 11, 13) and attenuates ventricular remodeling after myocardial infarction (7). In their article in the American Journal of Physiology-Heart and Circulatory Physiology, Choudhary et al. (1) extend our knowledge by investigating all-trans retinoic acid in hypertrophy development of the heart in a pressure overload rat model. The authors elegantly show in a series of carefully conducted experiments that pressure overload leads to the well-known cardiac remodeling process and upregulation of RAAS components but suggest for the first time that addition of retinoic acid is able to prevent these maladaptive effects over a treatment range of 5 mo.

Using histological techniques, echocardiography, and invasive hemodynamic measurements, the authors show that cardiac hypertrophy and fibrosis occur and that this is associated with decreased systolic as well as diastolic left ventricular function. While retinoic acid seems to be able to prevent hypertrophy in vivo as well as malfunction of the heart, it has no convincing effect when left ventricular weight is assessed postmortem. Also, it remains unclear from the present report whether hypertrophy can be reversed in a sense of re-remodeling since retinoic acid treatment was already started before pressure overload was even induced. This would be clinically very interesting, since most patients present themselves to the physician with an already existing hypertrophy.

Although it is important to show these in vivo data, it would also be important to see whether the main effect of retinoic acid to inhibit cardiac hypertrophy was actually due to preventing myocyte growth per se or rather due to preventing hyperplasia of fibroblasts (10) or a combination of both. In this context it is of interest that although fibrosis was prevented by Liu et al. (3) in spontaneously hypertensive rats previously, no effect of retinoic acid on left ventricular weight was observed. This may suggest that in case of increased afterload (1, 10) retinoic acid may primarily be of benefit through a decrease in cardiac fibrosis rather than decreasing myocyte size, but this notion must be investigated further. In contrast, at least for cultured neonatal myocytes (e.g., Ref. 13) smaller myocyte size has been shown, but it remains unclear whether this is also true for adult cardiac myocytes.

The role of retinoic acid specifically in cardiac myocytes is important insofar as myocardial malfunction may also result from myocyte dysfunction due to disturbed intracellular Ca cycling (e.g., impaired sarcoplasmic reticulum (SR) Ca storing ability, increased SR Ca leak, decreased Ca transient amplitudes), alterations of protein expression (e.g., decreased SR Ca ATPase, increased Na/Ca exchanger), and even alterations in protein phosphorylation (e.g., increased ryadonine receptor phosphorylation) of single cardiac myocytes as shown in many animal studies as well as in human hearts (e.g., Ref. 4). It would be most interesting to see whether this is also evident in the present model and whether retinoic acid is actually able to reverse these effects of possible altered excitation-contraction coupling. On the other side, the beneficial effects for cardiac contractility presented in the present study may be due solely to decreased cardiac fibrosis as mentioned above, which also explains the benefits for systolic as well as diastolic function.

But what may be the underlying signaling pathways for these in vivo findings? How does retinoic acid prevent remodeling? It was previously reported (8) that retinoic acid inhibits hypertrophic pathways in neonatal cardiac myocytes through binding to specific receptors called retinoid acid receptors (RAR)/retinoid X receptors (RXR), which upregulate specific phosphatases [mitogen-activated protein kinase phosphatase (MKP)-1 and MKP-2] and inhibit extracellular signal-regulated kinase (ERK)1/2, c-Jun NH2-terminal kinase (JNK), and phosphatases [mitogen-activated protein kinase phosphatase (MKP)-1 and MKP-2] and inhibit extracellular signal-regulated kinase (ERK)1/2, c-Jun NH2-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAP kinase) through dephosphorylation. Especially through inhibition of the MAP kinase pathway, hypertrophy may be prevented. In addition, the present report suggests that activation of RAR/RXR may suppress the massively activated RAAS during aortic banding. This can be concluded from the decreased expression of angiotensinogen, renin, and ACE in the presence of retinoic acid, which suppresses the activation of RAAS in this context.
acid. Also, angiotensin II [as well as brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP)] was found to be decreased in the blood. However, it remains unclear why angiotensin II as well as BNP and ANP are increased at all during the first 3 days (already in the presence of retinoic acid) and only from day 7 on can angiotensin II be suppressed by retinoic acid. Maybe the increase in ACE2 expression needs a few days until angiotensin II can be converted to ANG-(1–7), which then leads to the antiproliferative effects. Since angiotensin II was shown to massively increase fibroblast proliferation (2, 10), inhibition of this pathway may mainly be responsible for the decrease in cardiac fibrosis.

In summary, an important role of retinoic acid has become increasingly evident, as indicated by the present and previous reports. New studies investigating the role of retinoic acid in cardiac hypertrophy in vivo may be triggered to study its effects after hypertrophy is induced and what the role specifically for adult cardiac myocytes and intracellular Ca homeostasis as well as additional signaling pathways may be. This may very well result in novel therapeutic approaches to treat cardiovascular disease.

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