Evidence for myocardial synthesis of aldosterone producing myocardial fibrosis in man

Fifteen years ago, the renin–angiotensin–aldosterone system (RAAS) was thought to be only a circulating hormone system. It then became apparent that angiotensins were synthesized in a large number of different tissues within the body. The crucial implication of this is that the culprits, such as angiotensin II, could be made locally in blood vessels and in the myocardium, and that they exerted harmful local effects within these tissues.

In the last 10 years, it has become apparent that angiotensin II is not the only harmful end product of the RAAS. In particular, attention has focused on aldosterone as another harmful end product of the RAAS [1]. Furthermore, a simple rule appears to be that whatever effect has been shown to occur for angiotensin II is subsequently found to occur also with aldosterone. Therefore, it is now apparent that the adrenal cortex is only one of many tissues within the body that can manufacture aldosterone.

Following this theme, it has become clear that the myocardium can synthesize aldosterone locally. In addition, aldosterone production is enhanced in the myocardium of patients with left ventricular (LV) dysfunction [2]. The next crucial question is whether this aldosterone produced locally could have harmful local effects within the myocardium. This is not an easy question to answer, but in this issue of Clinical Science Satoh et al. [3] have produced persuasive evidence that this is likely to be the case.

Satoh et al. [3], using biopsies from human hearts, showed not only that aldosterone synthase (CYP11B2) expression was increased in patients with heart failure, but also that there was a correlation between this expression and the amount of collagen in the myocardial tissue biopsy. Although correlations can never prove a cause-and-effect relationship, this is still persuasive, if not conclusive, evidence that local myocardial synthesis of aldosterone could actually produce local myocardial fibrosis.

The main question now needing to be addressed is what are the mechanisms whereby aldosterone produces myocardial fibrosis. It could be a direct effect of aldosterone on fibrosis, or perhaps due to aldosterone producing LV hypertrophy (LVH); fibrosis is a by-product of most LVH. On the other hand, it could also be because aldosterone produces endothelial dysfunction and a vasculopathy, which lead to tissue injury and local microinfarcts that then undergo reparative fibrosis [4]. Of course, it could be a combination of all of these factors (Scheme 1).

Another key issue is the link between salt and aldosterone. In animal studies, both salt and aldosterone have been shown to be required to produce myocardial fibrosis. It could therefore be that fibrosis occurs only when the aldosterone level is inappropriately high for an individual’s salt intake. This could be why the harmful effect of aldosterone has been seen most readily in heart failure, since such patients have an inappropriately high level of aldosterone for their salt status.

In conclusion, it now appears likely that aldosterone produced locally in the myocardium is responsible for producing myocardial fibrosis, which gives even more impetus towards investigating the clinical consequences of aldosterone blockade in cardiovascular disease in man.

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REFERENCES