Electrical remodeling is a crucial aspect of the general process of cardiac remodeling associated with left ventricular hypertrophy and heart failure [1], and it is thought to contribute to an increased risk of ventricular fibrillation and sudden cardiac death. Angiotensin II has long been recognized as a major factor in cardiac remodeling in a variety of cardiovascular and non-cardiovascular diseases—from hypertension to diabetes [2]. Two receptor subtypes for angiotensin II have been identified in the heart, AT1 and AT2, which apparently share two features: the endogenous ligand and the gross molecular structure, belonging both to the seven transmembrane-domain receptor family [3]. Because of its well-documented action on myocyte hypertrophy, collagen deposition, aldosterone production, and many other functions, the AT1 receptor has long monopolized the attention of researchers [4]. Experimental observations have provided the rationale for development and clinical use of angiotensin receptor blockers (ARB), with the aim of offering a better protection than angiotensin-converting enzyme inhibitors (ACE-I) against angiotensin II by directly blocking AT1. Due to the activity of peptidases other than ACE (e.g., chymase) that convert angiotensin I to angiotensin II, ACE-I block less than 15% of the total production of angiotensin II in the heart.

The number of patients receiving ACE-I is much larger than that corresponding to those treated with ARB; nevertheless, it is generally agreed that AT1 blockade may represent a safe and valuable option that can reduce mortality and adverse cardiovascular events in a variety of clinical settings [5].

From a pharmacological point of view, the two classes of drugs (ACE-I or ARB) have different profiles mainly because AT1 antagonists leave intact the interaction of angiotensin II with the sibling receptor, AT2. The implications of this fact are unknown, since the effect of AT2 stimulation on cardiac tissue remains largely unexplored.

In this issue, Caballero et al. [6] are the first to attempt to investigate the effects of AT2 stimulation on cellular cardiac function from an electrophysiological point of view. They found something unexpected: To understand why their results are surprising, it is necessary to go one step back, to the electrophysiological actions mediated by angiotensin II via AT1 stimulation.

1. Angiotensin receptors and electrophysiological remodeling

In animal models of cardiac hypertrophy and failure, AT1 antagonists (as well as ACE-I) prevent or even reverse cardiac electrophysiological remodeling [7]. These data are in agreement with the clinical evidence of a protection against sudden cardiac death in patients treated with ARB [8]. The effect on remodeling seems to be due to the prevention or reversal of the prolongation of the action potential, which occurs in all cardiomyopathies and is strictly related to the lengthening of the QT interval observed in the ECG. The ionic basis of electrical remodeling involves the repolarizing potassium currents: the transient outward current, Ito, appears to be an obligatory link between the angiotensin II effect and prolongation of the action potential. Ito is finely regulated by angiotensin II: Indeed, the molecular and functional expression of transient outward current(s) is depressed in cardiac hypertrophy and failure [1,9]. This effect is reversed by long-term treatment with AT1 antagonists [7]. The transcription factors activated by myocardial hypertrophy (GATA and FOG2) also control the expression of the Kv4.2 gene [10], whose product is one of the proteins coding for Ito channels. The role of Ito as an electrophysiological target of angiotensin II is shown by data obtained in other pathophysiological settings. AT1 stimulation is associated with Ito downregulation in type-1 diabetes in rats and...
with a parallel action potential prolongation [11]. The same mechanism seems to underlie the transmural gradient of \( I_{\alpha} \) density in the canine ventricle and the related difference in action potential profile between endocardium and epicardium [12]: endocardial cells, where \( I_{\alpha} \) is small, develop a large \( I_{\alpha} \) as found in epicardial cells in the presence of the AT1 antagonist losartan. Vice versa, epicardial cells are “converted” into endocardial myocytes by incubation with angiotensin II. This transcriptional or post-transcriptional modulation of \( I_{\alpha} \) channel proteins by angiotensin II has been attributed to the well-known signaling that occurs downstream of the AT1 receptor.

The AT2 receptor has long been considered not only the “younger sibling” of AT1, but also its opponent. In a variety of cells types, AT2 exert contrasting effects (reviewed in Ref. [13]), including an increase in outward potassium currents in cultured neurons [14]. These results, in the absence of similar studies in cardiac cells, could have led to the belief that AT2 stimulation in the myocardium causes an increase in potassium currents.

The paper by Caballero et al. [6] shows that this is not the case: AT2 stimulation causes a 20% decrease in \( I_{\alpha} \) and a corresponding action potential prolongation in rat ventricular myocytes. Interestingly, the AT2-mediated decrease in \( I_{\alpha} \) was observed only in the perforated-patch configuration, probably because the conventional whole-cell configuration of the patch-clamp technique altered the intracellular milieu and the signaling pathway. Their results demonstrated that one of the intracellular steps between the AT2 receptor and the \( I_{\alpha} \) channel involves the activation of the serine/threonine phosphatase type 2A (PP2A) that may act by dephosphorylating the channel and decreasing current amplitude. Moreover, by transfecting Kv4.2 channels into CHO cells, Caballero et al. identified this channel protein as the target (or one of the targets) of angiotensin II via AT2 stimulation.

2. Physiological and clinical implications and open questions

This paper raises a number of interesting questions. Some of these, such as the species dependence and the role of this pathway in modulating other cardiac channels, will likely be answered soon by further investigation. However, other aspects will require more intensive research.

Keeping in mind that angiotensin II contributes to the regulation of potassium channels in the evolution of the so-called “cardiac memory” [15], the physiological implications of AT2 stimulation on \( I_{\alpha} \) channels should be addressed (e.g., does the transient, acute inhibition of \( I_{\alpha} \) by locally released angiotensin II play a role in regulating beat-to-beat action potential duration?) Furthermore, the role of AT2 stimulation during chronic treatment with ARB should be investigated by clarifying whether (i) the acute effect is maintained over time and (ii) the electrophysiological effects in hypertrophied or failing myocytes are similar to those described by Caballero et al. [6] in normal myocardial cells. Until then, it will be difficult to speculate as to the possible clinical implications of AT2-mediated electrophysiological effects. However, the results by Caballero et al. should be kept in mind when looking at clinical data that compare treatment with ACE-I and ARB.

References