The family of G-protein-coupled heptahelical receptors are widely distributed in the human body. Of special clinical importance are $\beta$-adrenoceptors, which mediate the effects of the sympathetic nervous system. In the heart, they induce, at least to a large extent, the inotropic effects of catecholamines. They confer signals from their ligands to the cell, and this signal transduction process classically runs via G-proteins to downstream effectors. The best investigated effector is the enzyme adenyl cyclase (AC), which catalyses the conversion of ATP to cAMP. Increases in cAMP levels are thought to lead mainly to activation of cAMP-dependent protein kinases (PKA). In turn, PKA increases the phosphorylation state of target proteins in the cardiac cell like the L-type Ca$^{2+}$ channels, phospholamban, and other proteins (see Fig. 1). Some of these phosphorylation events increase the Ca$^{2+}$ content of the cardiomyocytes, in this way not only elevating force but also hastening relaxation.

A central tenet was hitherto that these $\beta$-adrenoceptors are localised exclusively to the sarcolemma, the outer membrane of the cardiac cell. Indeed, in the last decades, purification protocols for the sarcolemma used the presence of $\beta$-adrenoceptors (and activity of AC) as a criterion for the purity of plasma membrane preparations (see e.g. [2]). In contrast, it has been claimed for many years that cAMP levels are compartmentalised in the cell [3]. For instance, different agonists that elevated force to a comparable level (forskolin versus isoproterenol) increased cAMP to 10-fold higher levels [4]. Moreover, immunohistological evidence for these compartments of cAMP (and PKA) has been presented (for review see [3]). These observations, however, are at odds with the idea that $\beta$-adrenoceptors are solely located at the cell surface. Indeed, it now appears as though this assumption was a very crude approximation.

See article by Boivin et al. [1] (pages 69–78) in this issue.
In a series of elegant experiments, Boivin et al. [1] present convincing evidence for the presence and functional role of β-adrenoceptors on the nuclear membrane. Immunohistochemical data clearly demonstrated β1- and β3-adrenoceptors, as well as G-proteins and ACs, in the nuclear membrane. The pharmacological stimulation of β3-adrenoceptors in nuclear preparations from the heart was linked to increased gene transcription. It remains unclear whether β2-adrenoceptors are really absent from the nuclei or simply below the current level of detection; their absence would further increase the complexity of the β2-adrenoceptor system.

Work from several groups has shown that, as a matter of principle, some G-protein-coupled receptors are located at the nuclear membranes of several non-cardiac cell types and exert functional effects in the nucleus [5,6]. Moreover, some G-protein-coupled receptors, such as those for endothelin, are located at the nuclear membrane of cardiac cells [7]. Receptors located at the nuclear membrane may have roles in nuclear signalling like regulation of nuclear transport, gene expression, and nuclear envelope formation. Previous ligand binding studies were able to detect β-adrenoceptors in isolated nuclei from neonatal rat cardiomyocytes. However, one can never exclude cellular contaminants in neonatal cell preparations and, therefore, that work may have been overlooked [8]. Nuclear membranes contain well-known components for regulation of the Ca2+ equilibrium like Ca2+-ATPase pumps [9] or ryanodine-sensitive Ca2+ release channels [10]. Hence, nuclear β-adrenoceptors may in part regulate the Ca2+ content of the nucleus.

One puzzling question stemming from these data is what would be the ligand of nuclear adrenoceptors. Classically, it has been thought that catecholamines act on the sarcolemma receptor and do not penetrate the outer membrane due to their high polarity. However, as the authors cite in their discussion, there are transport mechanisms in the sarcolemma similar to uptake 2 that may elevate the cytosolic concentration of catecholamines [8]. One can speculate that minute but relevant amounts of catecholamines are even synthesized de novo in the cardiac cell.

It is a well-established fact that β1-adrenoceptors are down-regulated in heart failure [11]. Another open question arising from the work of Boivin et al. [1] is whether the expression of β1-adrenoceptors in the nucleus is likewise down-regulated in the failing heart and whether this might in part explain the concomitant changes in gene expression in heart failure. Moreover, is it possible that the beneficial effects of β-adrenoceptor blockers in the treatment of heart failure [12] are partially mediated by their direct action on nuclear β-adrenoceptors? At least, lipophilic β-adrenoceptor blockers like propranolol are known to enter the cell to a considerable extent. This was hitherto considered to be of no real consequence.

In summary, we are continuously learning new and exciting facts related to the cardiac role of β-adrenoceptors.

References