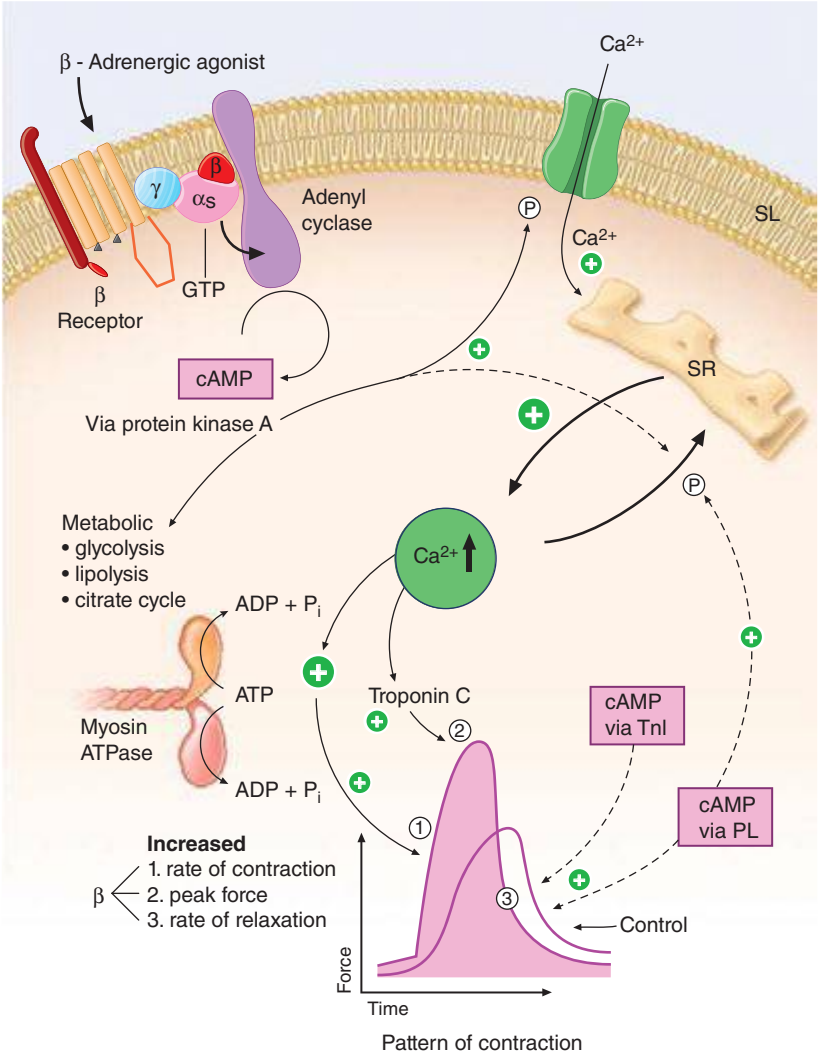

FIGURE 265e-6 Signal systems involved in positive inotropic and lusitropic (enhanced relaxation) effects of β-adrenergic stimulation. When the β-adrenergic agonist interacts with the β receptor, a series of G protein–mediated changes leads to activation of adenylyl cyclase and the formation of cyclic adenosine monophosphate (cAMP). The latter acts via protein kinase A to stimulate metabolism (***left***) and phosphorylate the Ca^{2+} channel protein (***right***). The result is an enhanced opening probability of the Ca^{2+} channel, thereby increasing the inward movement of Ca^{2+} ions through the sarcolemma (SL) of the T tubule. These Ca^{2+} ions release more calcium from the sarcoplasmic reticulum (SR) to increase cytosolic Ca^{2+} and activate troponin C. Ca^{2+} ions also increase the rate of breakdown of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (Pi). Enhanced myosin ATPase activity explains the increased rate of contraction, with increased activation of troponin C explaining increased peak force development. An increased rate of relaxation results from the ability of cAMP to activate as well the protein phospholamban, situated on the membrane of the SR, that controls the rate of uptake of calcium into the SR. The latter effect explains enhanced relaxation (lusitropic effect). P, phosphorylation; PL, phospholamban; TnI, troponin I. *(Modified from LH Opie: Heart Physiology: From Cell to Circulation, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004. Reprinted with permission. Copyright LH Opie, 2004.)*

The Ca^{2+} released from the SR then diffuses toward the myofibrils, where, as already described, it combines with troponin C (Fig. 265e-6). By repressing this inhibitor of contraction, Ca^{2+} activates the myofilaments to shorten. During repolarization, the activity of the Ca^{2+} pump in the SR, the SR Ca^{2+} ATPase ($SERCA_{2A}$), reaccumulates Ca^{2+} against a concentration gradient, and the Ca^{2+} is stored in the SR by its attachment to a protein, *calsequestrin*. This reaccumulation of Ca^{2+} is an energy (ATP)-requiring process that lowers the cytoplasmic $[Ca^{2+}]$ to a level that inhibits the actomyosin interaction responsible for contraction, and in this manner leads to myocardial relaxation. Also, there is an exchange of Ca^{2+} for Na^{+} at the sarcolemma (Fig. 265e-7), reducing the cytoplasmic $[Ca^{2+}]$. Cyclic AMP–dependent PKA phosphorylates the SR protein *phospholamban*; the latter, in turn, permits activation of the Ca^{2+} pump, thereby increasing the uptake of Ca^{2+} by the SR, accelerating the rate of relaxation, and providing larger quantities of Ca^{2+} in the SR for release by subsequent depolarization, thereby stimulating contraction.

Thus, the combination of the cell membrane, transverse tubules, and SR, with their ability to transmit the action potential and release and then reaccumulate Ca^{2+}, plays a fundamental role in the rhythmic contraction and relaxation of heart muscle. Genetic or pharmacologic alterations of any component, whatever its etiology, can disturb these functions.

CONTROL OF CARDIAC PERFORMANCE AND OUTPUT

The extent of shortening of heart muscle and, therefore, the stroke volume of the ventricle in the intact heart depend on three major influences: (1) the length of the muscle at the onset of contraction, i.e., the preload; (2) the tension that the muscle is called on to develop during contraction, i.e., the afterload; and (3) the contractility of the muscle, i.e., the extent and velocity of shortening at any given preload and afterload. The major determinants of preload, afterload, and contractility are shown in Table 265e-2.

THE ROLE OF MUSCLE LENGTH (PRELOAD)

The preload determines the length of the sarcomeres at the onset of contraction. The length of the sarcomeres associated with the most forceful contraction is ~2.2 μm. This length provides the optimum configuration for the interaction between the two sets of myofilaments. The length of the sarcomere also regulates the extent of activation of the contractile system, i.e., its sensitivity to Ca^{2+}. According to this concept, termed *length-dependent activation*, myofilament sensitivity to Ca^{2+} is also maximal at the optimal sarcomere length. The relation between the initial length of the muscle fibers and the developed force has prime importance for the function of heart muscle. This relationship forms the basis of Starling's law of the heart, which states that within limits, the force of ventricular contraction depends on the end-diastolic length of the cardiac muscle; in the intact heart, the latter relates closely to the ventricular end-diastolic volume.

CARDIAC PERFORMANCE

The ventricular end-diastolic or "filling" pressure sometimes is used as a surrogate for the end-diastolic volume. In isolated heart and heart-lung preparations, the stroke volume varies directly with the end-diastolic fiber length (preload) and inversely with the arterial resistance (afterload), and as the heart fails—i.e., as its contractility declines—it delivers a progressively smaller stroke volume from a normal or even elevated end-diastolic volume. The relation between the ventricular end-diastolic pressure and the stroke work of the ventricle (the ventricular function curve) provides a useful definition of the level of contractility of the heart in the intact organism. An increase in contractility is accompanied by a shift of the ventricular function curve upward and to the left (greater stroke work at any level of ventricular end-diastolic pressure, or lower end-diastolic volume at any level of stroke work), whereas a shift downward and to the right characterizes depression of contractility (Fig. 265e-8).