CARDIOLOGY—IN-DEPTH LOOK: KINASES AS THERAPEUTIC TARGETS IN THE HEART

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1 KINASES AS PHARMACOLOGICAL TARGETS IN THE HEART—A NEW ERA IN MOLECULAR CARDIOVASCULAR THERAPEUTICS

Cardiovascular disease is the leading cause of morbidity and mortality in modern society, resulting in enormous health care costs. The spectrum of diseases encompasses a group of clinically heterogeneous ailments of the heart (e.g., ischemic heart disease or coronary artery disease, congestive heart failure, and cardiomyopathy) and of blood vessels (e.g., hypertension and atherosclerosis) with multifactorial origin, strongly influenced by race, gender, and environmental aspects. In recent years there has been extensive progress toward understanding the pathophysiology of cardiovascular disease, which has shown multiple cell signaling cascades. Anomalous activation of diverse neurohormonal systems (e.g., catecholamines, angiotensin II, endothelin-1, natriuretic peptides, cytokines, and growth factors), which are crucial for homeostasis under physiological conditions, play a role in the establishment and progression of cardiovascular disease. Furthermore, there is evidence that specific signaling pathways are involved in acute and chronic cardiovascular disease, and the molecules comprising these pathways are targets for future development of therapies. In fact, the efficacy of drugs such as angiotensin II and adrenergic receptor blockers provides confirmation that targeting these signaling pathways is valuable for the treatment of cardiovascular disease. Most of the signaling pathways consist of a cascade of protein kinases that transduce signals from a receptor on the cell membrane to the nucleus of the cell. This series of protein phosphorylation leads to specific cellular responses (e.g., gene expression, growth, and/or proliferation), and hypothetically it could be possible to modulate these events in order to achieve a desirable cellular effect. Since most of these signaling pathways and protein phosphorylation are mediated by these enzymes, changes in protein kinase activity by pharmacological agents could provide a therapeutic benefit in cardiovascular disease [1]. Even though there is an extensive selection of effective treatments that target cardiovascular disease (e.g., statins, β-blockers, antagonists of the renin–angiotensin system, calcium channel blockers, thrombolytic agents, and antiplatelet drugs), mortality associated to it remains high. Therefore, there is a need to develop new therapeutic agents that will positively impact quality of life and prolong survival.

Several protein kinases have been implicated in human cardiovascular disease by the successful use of G-protein-coupled receptor (GPCR) antagonists (e.g., protein kinase A and CaMKII mediate β-adrenergic receptor action) and in some cases by evidence of altered expression in diseased human heart tissue. In fact, the successful use of GPCR blockers have shown to reduce mortality from cardiovascular disease and suggests that a larger number of downstream kinases mediating the actions of these receptors are also

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing
Edited by Shayne C. Gad