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Cardiac Remodeling

Molecular Mechanisms

Springer

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This book is dedicated to my peers,
colleagues, teachers, students,
and friends who inspire and stimulate me
in lifelong search for knowledge that can be
applied to improve cardiovascular health
and benefit mankind;
And
to my family, who selflessly supported me in
my relentless pursuits of hidden truths:
Catherine Elizabeth (né Graham)
Bernadine Alexandra
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Sunil Keith (1973–1992)

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Preface

The concept of cardiac remodeling as a mechanism of heart disease leading to heart failure has evolved since the mid-1970s. The initial emphasis was on heart failure related to pressure and volume overload; this led to theories on adaptive and maladaptive structural and functional changes after life-threatening insults such as myocardial infarction and hypertensive heart disease. Later, the scope of cardiac remodeling expanded to pure and mixed pressure and volume overload states and a wide range of cardiomyopathies, inherited or acquired from infections or exposure to various therapeutic drugs with cardiotoxic pleiotropic effects and other cardiotoxic agents. Results of cardiovascular research at the bench and bedside levels and a host of population studies since the mid-1980s fueled the concept of adverse left ventricular remodeling during acute and subacute phases of myocardial infarction, with structural changes that have a negative impact on cardiac function. These studies have established that adverse cardiac remodeling is a major mechanism for progressive left ventricular enlargement, deterioration of ventricular function, increased suffering, and deaths from chronic heart failure. Concurrently over the last 4 decades, expanding knowledge of the basic molecular mechanisms and clinical implications of cardiac remodeling has identified several molecular pathways and potential targets, leading to drug discovery and development and improved therapies for major causes of adverse cardiac remodeling, such as myocardial infarction and hypertension. A major advance has been the appreciation that lifelong exposure to cardiovascular risk factors and cardiotoxic agents, beginning from the pediatric age through adulthood and old age, fuels the march to heart failure. This has opened up a new area of research into the biology of aging and its impact on cardiac remodeling.

Despite the advances, hearts continue to enlarge, and the heart failure burden continues to increase, especially after ST-segment-elevation myocardial infarction (STEMI). Many knowledge gaps exist. With the expanded spectrum of diseases that result in adverse cardiac remodeling, improved understanding of the underlying molecular mechanisms through research is crucial. During the last 20 years, attention focused on cellular and subcellular changes, including those at the molecular

and biochemical levels. There has been an explosion in knowledge of molecular and cellular mechanisms, importance of oxidative stress, metabolic pathways, extracellular and intracellular matrix remodeling, and the far-reaching effects of infarct and non-infarct zone fibrosis in the progression to heart failure. This has led to a profusion of original scientific and review papers dealing with several aspects of molecular mechanisms of adverse cardiac remodeling. There is therefore a need to synthesize these ideas into one book on molecular mechanisms of cardiac remodeling.

The main objective of this book has been to summarize the major research advances in molecular, biochemical, and translational aspects of cardiac remodeling over the last 2 to 3 decades under one cover and touch on future directions. The invited leaders and established investigators in the field have generously contributed 30 chapters on key topics relating to molecular mechanisms, with emphasis on selected biochemical and translational aspects of cardiac remodeling. The authors have succinctly summarized large volumes of data on these key topics and highlighted novel pathways and key molecules that need to be further explored and possibly targeted. They provide integrative reviews of the basic mechanisms and clinical correlates as well as critical assessments of publications on the key topics by the leading investigators in the field. The reference lists are fairly comprehensive and include key papers that are currently not easily accessed from Pubmed or other search engines. The book is carefully organized into two sections: Section A contains 15 chapters that focus mainly on molecular mechanisms in pressure and volume overload hypertrophy, with some overlap into brief ischemia–reperfusion injury; Section B contains 15 chapters that focus on molecular mechanisms after myocardial injury and infarction. The list of topics is by no means comprehensive but addresses some major areas needing attention. To our knowledge, there is no other book on this topic to date.

In summary, this book provides a high-profile and valuable publication resource on molecular mechanisms of cardiac remodeling for both the present and future generations of researchers, teachers, students, and trainees. It should stimulate future translational research targeted towards discovery and development for preventing, limiting, and reversing bad remodeling over the next few decades, with the ultimate goal of preventing progression to systolic and/or diastolic heart failure. The chapters suggest potential novel strategies that should receive attention for translating basic research knowledge to application in patients at the bedside. We would like to thank all the authors for their excellent contributions. We would also like to express our deepest appreciation for the preparation and editorial help provided by Catherine E. Jugdutt, Eva Little, and Dr. Vijayan Elimban in assembling this book. Cordial thanks are also due to Ms. Portia Formento and Melanie Tucker, Springer, USA, for their continuous advice and understanding during the editorial process. We hope that the book will prove useful for scientists and clinicians, students and teachers, and the industry interested in drug and discovery research.

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Part I
Molecular Mechanisms of Remodeling in Pressure and Volume Overload Hypertrophy and Heart Failure

Chapter 1
β-Adrenergic Receptor Signaling in Heart Failure

Grace Jung Ah Lee, Lin Yan, Dorothy E. Vatner, and Stephen F. Vatner

Abstract Acute activation of the sympathetic system and resultant β-adrenergic receptor (β-AR) signaling are required to maintain homeostasis, providing inotropic support in times of need, as in "fight or flight" or response to any stress, such as cardiac dysfunction and heart failure. For most of the twentieth century, it was reasoned that sympathetic stimulation of β-ARs through administration of naturally occurring catecholamines or synthetic sympathomimetic amines could provide inotropic support and should be used in heart failure therapy. However, in heart failure, sympathetic drive to the heart is excessively increased, and chronic sympathetic stimulation is deleterious, since it increases $M\dot{V}O_2$, which cannot be met by appropriate increases in coronary blood flow, thereby creating subendocardial ischemia and intensifying the cardiac dysfunction. Furthermore, continued stimulation of the β-ARs also becomes problematic because it can activate multiple cellular processes including those involved in pathological remodeling seen in the development of cardiomyopathy. However, this reasoning took a diametrically opposite turn in the latter twentieth century when the adverse effects of chronic β-AR stimulation became apparent from experimental studies in transgenic mice with cardiac-specific overexpression of $G_{s\alpha}$ and β-ARs and also from clinical studies with poor outcomes for patients on chronic sympathomimetic amine therapy. At this time it was also found that internal compensatory physiological processes countering continued β-AR stimulation in the heart were cleverer than physicians. As a protective response, β-AR desensitize, which reduces the effectiveness of β-AR stimulation and the consequent increases in myocardial oxygen demands. Taken together, these factors were fundamental to the change in course from β-AR stimulation to β-AR blockade in the treatment of heart failure.

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1.1 Introduction

β-Adrenergic receptor (β-AR) signaling is central to all aspects of the pathophysiology of heart failure. The sympathetic nervous system including the neurohormones, epinephrine, and norepinephrine is rapidly called into action by any stress, such as cardiac dysfunction and heart failure. For most of the twentieth century, it was reasoned that sympathetic stimulation of β-ARs through administration of naturally occurring catecholamines or synthetic sympathomimetic amines could provide inotropic support and should be used in heart failure therapy. However, this reasoning took a diametrically opposite turn in the latter twentieth century when it was realized that patients with β-AR blocker therapy fared significantly better. The goal of this chapter is to document the scientific and clinical basis for the changing paradigm of the role of β-AR signaling in heart failure. To do this, the chapter has the following sections: Sect. 1.2 (The Discovery of β-ARs), Sect. 1.3 (Regulation of Cardiac Contractility by β-ARs), Sect. 1.4 (Targeting β-ARs in the Treatment of Heart Failure: Use of β-AR Inotropic Agonists), Sect. 1.5 (Adverse Effects of Chronic β-AR Stimulation in the Treatment of Heart Failure), Sect. 1.6 (Advent of β-AR Blockade Therapy), Sect. 1.7 (Mechanisms Mediating Salutary Effects of β-AR Blockade Therapy in Heart Failure), Sect. 1.8 (Future Directions), and Sect. 1.9 (Conclusions).

1.2 The Discovery of β-ARs

Although the concept of β-ARs mediating the signaling from the sympathetic nervous system to regulate cardiac function is axiomatic today, this was not always the case. Throughout much of the twentieth century, it was erroneously believed that adrenergic signaling was primarily mediated by two classes of neurotransmitters, sympathin E (excitatory) and sympathin I (inhibitory), classified according to their physiological response [1, 2]. This was due, in part, to the use of natural adrenalin, which contained variable mixtures of epinephrine and norepinephrine with quite different agonistic activities, resulting in obscured conclusions that masked their distinct effects. In retrospect, the fallacy of their results is clear. Not only do epinephrine and norepinephrine have different effects, e.g., norepinephrine has α-vasoconstrictor activity as well as β-vasodilator and inotropic activity, whereas epinephrine does not have much α-activity, but both elicit reflex effects in vivo with the most prominent mediated by the arterial baroreflex, which modulates the direct actions of the catecholamines on arterial pressure, heart rate, and peripheral vascular resistance.

In 1906, Dale first introduced the concept of receptors in connection with the sympathetic nervous system [3]. In his studies, he observed the actions of ergot alkaloid antagonists on the effects of epinephrine and proposed there are two distinct receptor types. One type, in which epinephrine mediated excitatory responses, was antagonized by ergot alkaloids, whereas in the second type, ergots had no effect on the inhibitory effects of epinephrine. Then in 1948, a major step was taken by Ahlquist, who challenged this idea of sympathins by characterizing two AR types, α and β, based on the rank order of catecholamine potencies rather than the nature of their physiological response (contraction vs. relaxation) [2].

However, the idea of ARs existing as physical entities received much skepticism [4, 5]. Even Ahlquist noted in his later paper that ARs are hypothetical structures that hold momentary value until the exact mechanism of adrenergic signaling is deciphered [6]. However, his seminal studies persevered and in 1967, Lands et al. extended his classification scheme by introducing two β-AR subtypes, β_1 and β_2, based on their affinities for epinephrine and norepinephrine [7]. Whereas β_1-ARs in cardiac and adipose tissue have approximately equal affinity for epinephrine and norepinephrine, β_2-ARs relax bronchial and vascular smooth muscle and have greater affinity for epinephrine than for norepinephrine. Then in 1972, Carlsson et al. provided pharmacological evidence that both β_1- and β_2-ARs are present and functional in the feline heart and that β_1-AR is the predominant subtype in both the atria and the ventricles [8].

From these findings, Lefkowitz developed highly specific radioligand-binding assays that allowed selective labeling of β-ARs, which was responsible for the most significant progress in the field in the latter half of the twentieth century [9]. Using this method, he and his colleagues physically identified cardiac β-ARs for the first time in the canine heart in 1975 [9]. Moreover, the radioligand-binding technique made possible the quantification of the relative proportions of β_1- and β_2-ARs and in 1983, it was reported that human left ventricle (LV) consists of 86% β_1-AR and 14% β_2-AR [10], thus confirming and extending the work of Carlsson. In addition, the interactions of β-ARs with various agonists and antagonists were explored based on the concept that the radioligand competes for the binding site with an agonist. In 1980, it was discovered that binding of an agonist and antagonist was affected by GTP [11], and taking into account that adenylyl cyclase systems require GTP for activation [12], the ternary complex model, consisting of the adrenergic receptor coupling to GTP-binding G protein to activate adenylyl cyclase (AC), was proposed [13].

The advances in molecular biology techniques that shortly followed led to the successful cloning of the β_2-AR, the very first G protein-coupled receptor to be cloned [14]. Then by the 1990s, six α-AR subtypes (α_{1A}, α_{1B}, α_{1C} and α_{2A}, α_{2B}, α_{2C}) [15, 16] and three β-AR subtypes (β_1, β_2, β_3) [17–19] were firmly established. Moreover, insights on the physiological actions of various AR subtypes were made possible through generation of transgenic mice models with targeted disruption of ARs [20–23]. Today, we now understand that α-ARs have positive inotropic activity