*Forum Minireview***New Aspects for the Treatment of Cardiac Diseases Based on the Diversity of Functional Controls on Cardiac Muscles:****Novel Approaches for the Diagnosis and Treatment of Cardiac Diseases**Takeshi Suzuki^{1,*} and Hikaru Tanaka²¹Faculty of Pharmacy, Division of Basic Biological Sciences, Keio University, Tokyo 105-8512, Japan²Department of Pharmacology, Toho University Faculty of Pharmaceutical Sciences, Chiba 274-8510, Japan

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The rise in the number of patients with cardiac diseases in the coming aging society would increase the needs for accurate diagnosis and therapeutics for cardiac diseases. The function of the heart is supported by excitation and contraction of the myocardium, which are complex processes involving generation of the action potential, Ca^{2+} mobilization, and the activation of the contractile proteins. These are supported by myocardial energy metabolism and are under neurohumoral control. Under pathological conditions, alterations occur in the proteins involved in myocardial contraction and also in the neurohumoral status. Many biomarkers have been demonstrated to be useful for the diagnosis of cardiac diseases. Under the atrial fibrillation condition, changes in interleukin-6 (1, 2), C-reactive protein (CRP) (2), atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP) (3) were reported. Under the ventricular tachycardia and premature contraction, changes in BNP and CRP are also reported (4, 5). Under the heart failure condition, changes in both facilitating markers (e.g., rennin – angiotensin – aldosterone system, sympathetic nervous system) and protective markers (e.g., ANP, BNP) are reported (6, 7). These may be either the result of the pathological changes forming a vicious cycle or rather a reflection of some compensatory mechanism against the pathological changes.

Concerning pharmacological treatment of cardiac disorders, new types of therapeutic agents such as antibodies and nucleic acids are now under development in addition to the standard drugs consisting of low molecular weight compounds. Furthermore, in the near future, molecular biology and regenerative techniques would enable manipulation of the functional proteins

and replacement of the damaged myocardium with regenerated myocardium. Under such circumstances, an understanding of the optimum balance of function in the heart, as well as information on the individual elements, is important for the development of an effective therapeutic strategy. The following reviews summarized below provide a basis for such comprehensive understanding of the heart.

In “**Diversity in the excitation–contraction mechanisms of the heart**”, Hikaru Tanaka (Toho University Faculty of Pharmaceutical Sciences) et al. (8) presented an overview of myocardial diversity among species, developmental stage, and the region of the heart. Diversity in the ion channels results in diversity in action potential waveform and excitability of the myocardium. The Ca^{2+} release from the sarcoplasmic reticulum, which is the major determinant of myocardial contractile function, is largely affected by the action potential waveform through the activity of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger. Myocardial contraction is dependent on the energy metabolism and is under neurohumoral regulation. A precise and comprehensive understanding of each type of myocardium including various pathological models is essential for the clarification of the general principle of myocardial regulation and the development of novel therapeutic agents.

In “**Acute effects of female hormones on cardiac ion channels and cardiac repolarization**”, Junko Kurokawa (Medical Research Institute, Tokyo Medical and Dental University) et al. (9) introduced their recent results showing that physiological levels of ovarian steroids, estradiol and progesterone, have reverse effects on myocardial repolarization, which may create cyclic variation of cardiac repolarization in women. Estradiol prolongs while progesterone shortens action potential duration and QT interval through direct effects on cardiac ion channels, a regulatory mechanism distinct

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from the well-characterized transcriptional regulation by steroid hormones. These findings may explain dynamic changes of arrhythmia risk in women during the menstrual cycle and around the delivery, and they can be a clue to avoid the potentially lethal arrhythmia in long-QT syndromes.

In **"Mitochondrial ion channels and cardioprotection"**, Hirofumi Nishida (Chiba University Graduate School of Medicine) et al. (10) summarized their recent findings on mitochondrial ATP-sensitive K^+ channels and Ca^{2+} -activated K^+ channels. Mitochondrial K^+ influx through these channels occurs independently of each other and confers cardioprotection in a similar manner. Adenosine and bradykinin stimulate the opening of the mitochondrial ATP-sensitive K^+ channels through activation of protein kinase C while adrenomedullin stimulates the opening of mitochondrial Ca^{2+} -activated K^+ channels through activation of protein kinase C. These endogenous substances have cardioprotective effects such as reduction of infarction size after ischemia–reperfusion injury. Thus, protection of the mitochondria through mitochondrial potassium channels appears to be a promising strategy for cardioprotection.

In **"The regulatory mechanisms of cardiac innervation and their critical roles in cardiac performance"**, Masaki Ieda and Keiichi Fukuda (Keio University School of Medicine) (11) presented their recent findings on the molecular mechanisms underlying the normal development of cardiac innervation and demonstrated the importance of innervation in the maintenance of normal cardiac function. Endothelin-1 plays a critical role in the development of cardiac innervation through upregulation of nerve growth factor, a neural chemo-attractant essential for the survival and differentiation of peripheral sensory and sympathetic neurons. The expression pattern of *Sema3a*, a neural chemorepellent, was found to be a major determinant of the epicardial-to-endocardial gradient of sympathetic innervation. Perturbation of *Sema3a* expression leads to disruption of the sympathetic innervation pattern and abnormal excitability of the ventricle.

In **"Effects of targeted disruption of the type 5 adenylyl cyclase gene"**, Satoshi Okumura (Yokohama City University Graduate School of Medicine) et al. (12) presented their recent findings obtained with type 5 adenylyl cyclase knockout mouse. The results obtained suggested that among the adenylyl cyclase isoforms present in the heart, type 5 is potentially important in the autonomic regulation and Ca^{2+} -mediated regulation of the heart. Type 5 adenylyl cyclase also appears to be involved in the induction of myocardial damage in response to pressure overload and catecholamine stress. Thus, concerning the pharmacological treatment of heart failure, selective suppression of type 5 adenylyl cyclase activity may have an advantage over the current β -

adrenoceptor blockade, which suppresses the entire β -adrenergic signaling pathway.

Observations shown in the above articles would indicate to us several novel approaches for the accurate diagnosis and therapeutics for cardiac diseases.

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