

Format for ANSWERING REVIEWERS

January 20, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 15990-review.doc).

Title: Autonomic and endocrine control of cardiovascular function

Author: Richard Gordan, Judith K Gwathmey, Lai-Hua Xie

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 15990

The manuscript has been improved according to the suggestions of reviewers:

Reviewed by 02639698

Well written description of the cardiac autonomic and endocrine regulation of the heart. The Authors should add a brief paragraph describing the technique clinically available to investigate these system (i.e. heart rate variability for the cardiac autonomic nervous system).

Response: Thank you for the suggestion. We have added a paragraph describing cardiovascular autonomic dysfunction and heart rate variability (page 14).

"It has been known that sympathetic stress/dominance occurs during heart failure or after myocardial infarction, and may trigger lethal arrhythmias. This sympathovagal imbalance is reflected by reduced heart rate variability (HRV). HRV is determined from electrocardiographic recordings (ECG) and has currently been used clinically as both a diagnostic as well as a prognostic factor for assessing cardiovascular autonomic dysfunction including cardiac autonomic neuropathy. Please refer a recent review article for specific HRV indicators and their interpretations {Metelka, 2014 #5039}."

Reviewed by 00504181

This is an excellent review of the autonomic and endocrine control of cardiovascular function. Perhaps the sections describing more 'basic' knowledge can be shortened.

Response: Based on the suggestion from the reviewer # 00396997, we would prefer to retain the "basic" knowledge for the ease of readers from various fields as well as serve as a foundation for transitioning to clinical information. We have provided three books in the reference list.

Trivial points 1) Typo: Introduction: 'across', instead of 'cross' 2) Typo: Page 8, 'cleft..' 3) Typo: Page 9: 'produces effects', instead of 'produces affects'

Response: All typos have been corrected. Thank you!

Reviewed by 00396997

This is a well-written comprehensive mini review regarding to the regulation of the cardiovascular system by autonomic nervous system and the endocrine system. The Authors have a great reputation in this field and this manuscript is indeed well organized. While this reviewer strongly believes that this review article gathers interests from the reader of the World Journal of cardiology, the manuscript could be improved through incorporation of the following several suggestions.

1. As emphasized also in the title of this review, the authors tried to summarize the knowledge of autonomic nervous system and the endocrine system in "cardiovascular system". However, this reviewer feels this review is a bit focusing on cardiac system (heart) rather than cardiovascular system (both heart and vessels). It is better to slightly add more information regarding to the vascular system to some chapters (e.g. 1.3).

Response: We have added the following statement in the revised version. (page12-13)

"1.3.5. Autonomic Regulation of Vascular function

In contrast to the heart, most vessels (arteries and veins) only receive sympathetic innervation, while capillaries receive no innervation. These sympathetic nerve fibers tonically release norepinephrine, which activates α_1 -adrenergic and β_2 -adrenergic receptors on blood vessels thereby providing basal vascular tone. Since there is greater α_1 -adrenergic than β_2 -adrenergic receptor distribution in the arteries, activation of sympathetic nerves causes vasoconstriction and increases the systemic vascular resistance primarily via α_1 receptor activation. On the other hand, modified sympathetic nerve endings in the adrenal medulla release circulating epinephrine, which also binds to α_1 and β_2 -adrenergic receptors in vessels. However, β -adrenergic receptors show greater affinities for epinephrine than for norepinephrine. Therefore, circulating epinephrine at low concentrations activates only β_1 -adrenergic (mainly in the heart) and β_2 -adrenergic (mainly in vessels) receptors, which increase cardiac output and cause vasodilation, respectively. It should be noted that vessels at different locations may react differently to sympathetic stimulation. For example, during the "fight or flight" response the sympathetic nervous system causes vasodilation in skeletal muscle but vasoconstriction in the skin."

2. I understand the authors summarized general and basic knowledge of cardiovascular system in the introduction section and therefore no references are provided in this section. It is better to provide some key and notable review articles or book chapters as references also in introduction for the ease of the readers from various filed.

Response: Three books have been added in section 1 title and the reference list {Boron, 2011 #5053;Gwathmey, 1993 #5055;Mann, 2014 #5056;Rhoadesand, 2009 #5057}.

Specific comments:

1. Page 6 and Table 1: I understand that beta 2-adrenergic receptors are mainly expressed in vascular smooth muscle, but please also emphasize in the text that there are some expression in the cardiomyocytes also.

Response: The following statement has been added (page 6)

"There are also some low expressions of β_2 receptors in cardiomyocytes."

2. Page 6 and Table 1: I understand that alpha 1-adrenergic receptors are expressed in mainly vascular smooth muscle, but please also emphasize in the text that there are some expression in the cardiomyocytes also.

Response: The following statement has been added (page 6)

“There are also some low expressions of α_1 receptors in cardiomyocytes.”