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REVIEW

Brain stem adenosine receptors modulate centrally mediated hypotensive responses in conscious rats: A review

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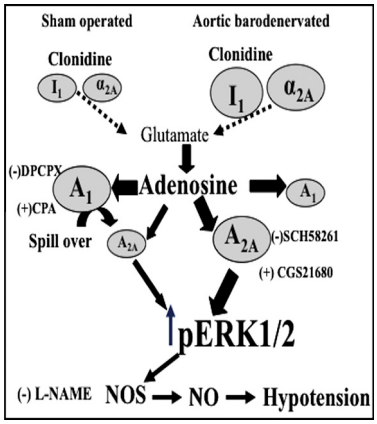
GRAPHICAL ABSTRACT



Abbreviations: A_{2A}, adenosine subtype A_{2A} receptor; A_1, adenosine subtype A_1 receptor; ABC, avidin biotin complex; ABD rat, aortic barodenervated rat; α_2 AR, alpha 2 adrenergic receptor; αMNE, alpha methyl norepinephrine; ATP, adenosine triphosphate; BP, blood pressure; cAMP, cyclic adenosine monophosphate; CGS21680, 2-[4-[(2-carboxyethyl)phenyl]ethylaminophenyl]ethylamino]-5′-*N*-ethylcarboxamidoadenosine. Selective A_{2A} receptor agonist; CNS, central nervous system; CPA, N^6-cyclopentyladenosine. Selective A_1 receptor agonist; DAG, diacylglycerol; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine. Selective A_1 receptor antagonist; I_1, imidazoline subtype 1 receptor; I.C., intracisternal; IP3, Inositol Triphosphate; I.V., intravenous; JNK, C-Jun N-terminal kinase; L-NAME, N^{ω}-nitro-L-arginine methyl ester hydrochloride. Non-selective nitric oxide synthase inhibitor; NOS, nitric oxide synthase; NO, nitric oxide; NTS, nucleus tractus solitarius; PC-PLC, phosphatidyl choline-selective phospholipase C; PC12 cells, pheochromocytoma cells; PD98059, selective extracellular signal regulated kinase inhibitor; ERK1/2, extracellular signal regulated kinase; PDE, phosphodiesterase; PKA, protein kinase A; RVLM, rostral ventrolateral medulla; SAPK, stress activated protein kinase; SCH58261, 5-amino-7-(2-phenylethyl)-2-(2-furyl)-pyrazolo[4,3-∈]-1,2,4-triazolo[1,5-c]pyrimidine. Selective adenosine A_{2A} antagonist; SHR, spontaneously hypertensive rat; SND, sympathetic neuronal discharge; SO, sham operated = conscious normotensive rats; 8-SPT, 8-(p-sulfophenyl)-theophylline. Non-selective adenosine receptor blocker; WKY, Wistar Kyoto rat.

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ABSTRACT

Adenosine is implicated in the modulation of cardiovascular responses either at the peripheral or at central level in experimental animals. However, there are no dedicated reviews on the involvement of adenosine in mediating the hypotensive response of centrally administered clonidine in general and specifically in aortically barodenervated rats (ABD). The conscious ABD rat model exhibits surgically induced baroreflex dysfunction and exaggerated hypotensive response, compared with conscious sham-operated (SO) rats. The current review focuses on, the role of adenosine receptors in blood pressure (BP) regulation and their possible crosstalk with other receptors e.g. imidazoline (I_1) and alpha (α_{2A}) adrenergic receptor (AR). The former receptor is a molecular target for clonidine, whose hypotensive effect is enhanced approx. 3-fold in conscious ABD rats. We also discussed how the balance between the brain stem adenosine A_1 and A_{2A} receptors is regulated by baroreceptors and how such balance influences the centrally mediated hypotensive responses. The use of the ABD rat model yielded insight into the downstream signaling cascades following clonidine-evoked hypotension in a surgical model of baroreflex dysfunction.

Noha Nassar is an Associate Professor of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University. She has 20 refereed scientific papers in addition to many poster and talks at international conventions. Her research findings have been published in top journals and have received fair citations. Dr. Nassar's research interests focus on signaling mechanisms and mediators implicated in neurodegenerative diseases as well as those involved in neural regulation of circulation. In addition to her contributions to research, Dr. Nassar has been active as a member of many scientific societies for the past 10 years including The American Society for Pharmacology and Experimental Therapeutics, and Society for Neuroscience and has served as a reviewer for a number of scientific journals.

Dr. **Abdel-Rahman** is Distinguished Professor of Pharmacology and Vice Chair of the Department of Pharmacology and Toxicology, Brody School of Medicine at East Carolina University, Greenville, NC, USA. He published over 120 refereed scientific papers in addition to 10 education-related articles. His research findings have been published in top journals in his discipline and cited hundreds of times in scientific literature. Dr. Abdel-Rahman research deals with neural control of circulation and neurobiology of hypertension. Two National Institutes of Health grants fund his research. In the first project his research team investigates the effect of ethanol on neuronal pathways that control blood pressure and cardiac reflexes. The second project deals with the neuroprotective and cardioprotective actions of estrogen and how concurrent alcohol use might compromise these beneficial physiological effects of estrogen. In addition to his contributions to research, Dr. Abdel-Rahman has been active as a member of many scientific societies for the past 30 years and has been named a Fellow of the American Heart Association. Dr. Abdel-Rahman also served as President of the East Carolina University Neuroscience Chapter in addition to his services as editor/associate editor and reviewer for a number of scientific journals. He has also served as a member of review boards (study sections) of the National Institutes of Health and the American Heart Association.

Introduction

The current review focuses on, the role of adenosine receptors in BP regulation and their possible crosstalk with other receptors e.g. imidazoline (I_1) and α_{2A} AR in a rat model of surgically-induced baroreflex dysfunction, the ABD rat. Furthermore, the current review delineates the role of the downstream adenosinergic-signaling pathway in mediating the centrally evoked hypotension elicited by clonidine and clonidine such as drugs. The review covers data generated in our laboratory and reported pertinent studies over the past 10 years, which covered the following: (i) imidazoline I_1-receptor and centrally mediated hypotension; (ii) clonidine and aortic barodenervation; (iii) clonidine and SHR rats; (iv) clonidine effects in the RVLM; (v) clonidine effects in the NTS; (vi) central adenosine receptor signaling; and (vii) central MAPK-NOS signaling.

The nucleus of the solitary tract (NTS)

The NTS mediates inhibitory actions of baroreceptors on sympathetic discharge and is considered the main site of termination of the baroreceptor afferent fibers via both the aortic depressor nerve and the glossopharyngeal (IX) from the carotid sinus [1–3]. Notably, lesions to the NTS abolish the baroreflex responses [3]. Several reports have shown important roles for activation of NTS glutamate [1,3] as well as adenosine receptors in BP regulation [1,2,4–7].

Rostral and caudal ventrolateral medulla

A large body of evidence supports the view that the RVLM is the major brain stem area that controls sympathetic drive by projecting directly to the spinal cord [1,8–10]. Neuronal activation in the RVLM causes an increase in arterial pressure mediated by an increase in peripheral resistance, cardiac output, and secretion of catecholamines [1]. Electrical and chemical stimulation of the RVLM produces immediate and marked increases in arterial pressure. The direct connection with the