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ROLE OF APELIN IN CARDIOVASCULAR DISEASE-MINI REVIEW

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ABSTRACT

Apelin is a novel bioactive peptide and the endogenous ligand for apelin receptor (APJ) it is an angiotensin-1-like receptor. Apelin and Apelin receptor (APJ) these are widely distributed in the body and mainly expressed in the heart ,lungs, kidney, adipose tissue, retina ,mammary gland , gastro intestinal tract. Several researches proved many research related to role of apelin in cardiovascular disease in human and animal model. Apelin is an novel drug target for cardiovascular disease and potential therapeutic implication for cardiovascular diseases. Targeting the apelin may bring the new therapeutic option for overcome all cardiovascular related problem in near future

Key Words: Apelin, angiotensin, cardiovascular disease, renin angiotensin aldosterone system

INTRODUCTION

Cardiovascular disease is classes of diseases or illness that mainly involves blood vessel which include veins, arteries and capillaries or the heart or the both. Etiology for the cardiovascular diseases is diverse but most common etiology is atherosclerosis and hypertension. [1,2]Most common risk factors that contribute cardiovascular diseases are, Hypertension, Radiation therapy-reported in the journal of American college of cardiology-scientist from karolinska institute, Sweden, Smoking, lack of sleep, hyperlipidemia, Partner with Diabetes mellitus, drinking too much of alcohol,stress,Chronic obstructive pulmonary disease, reduced lung function,age,sex,airpollution.In 2008 approximately 17.3, million people died from the cardiovascular diseases worldwide. Out of this 30% were registered as premature deaths and 7.3 million deaths are due to coronary heart disease.[1] Ant platelet drug-aspirin, Anti-coagulants-warfarin, heparin,Angiotensin converting enzyme inhibitors, beta blockers,Nitatrates-nitroglycerin, Calcium channel blockers,thrombolytics,blood cholesterol lowering agents.Non-invasive treatments-medications diet and exercise.

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Minimal invasive treatment-cardiac catheterization, valvuoplasty,endoluminal grafts, electrophysiological studies that is angioplasty and stenting,stent-grafting thrombolysis,embolization.[1] Surgical procedures-coronary artery bypass grafts (CABG), transmyocardial revascularization (TMR), artificial and tissue valve surgery, trial and ventricular septal defeat repair, pacemaker implants, ventricular aneurysm repair, aortic-aneurysm repair, ICD treatment.Newer treatment for heart disease-bone marrow cells transplant helps refractory anginaApelin helps heart function after bone marrow transplant.[3]

APELIN

Apelin is a novel bioactive peptide and the endogenous ligand for apelin receptor (APJ) it is an angiotensin-1-like receptor.[4] It is synthesized as the 77 amino acid prepopeptide which is then processed in to 70 c- terminal fragments and these are named based on their length of peptides namely apelin-36,apelin-19,apelin-17,apelin-13.[5] Apelin receptor (APJ) it is an G1 coupled transmembrane receptor.[6]Apelin and Apelin receptor (APJ) these are widely distributed in the body and mainly expressed in the heart ,lungs, kidney, adipose tissue, retina ,mammary gland , gastro intestinal tract.[7] Development in C-DNAanalysis has lead to the identification of the numerous G-protein -coupled receptor (GPCR) and to these G-protein- coupled receptor (GPCR) their natural ligands were not yet identified these are otherwise called “orphan receptors” and potential targets for drug discovery and a human gene has been identified which quietly resembles or homology to the gene coding to the angiotensin receptor and these

human gene which encoded to angiotensin receptor has been named as APJ, apelin receptor and thisapelin receptor (APJ) shares 40-50% identify with the angiotensin receptor1 in the hydrophobic transmembrane but it won't bind to the angiotensin -2.[8,9]

From the bovine stomach endogenous ligand for apelin-36 was proposed mainly from the extracts of bovine stomach by monitoring extra cellular acidification rate changes in a Chinese hamster ovary cell line expressing the human APJ receptor.[8] Apelin receptor (APJ) was first cloned in the year 1993 by using the uman genomic human DNA using the degenerative oligonucleotide primers mainly it is an 377 amino acid and 7 transmembrane domain which is G1 coupled receptor in this the gene was localized in the long arm of chromosome 11 where as the natural ligand was synthesized by bovine stomach by tatemotoetal spanning 1726 base pairs of the genomic DNA with 3 exons.The apelin locus is highly integrated between the species which mainly synthesized as 77 amino acid and has been plays major role in cardiovascular function, central autonomic control and fluid homeostasis.[10] Apelin peptidesinvolves widely in the enzymatic reactions or cascades of Reninangiotensin aldosterone system (RAS) and it also act as antagonist or counter regulatory towards the action of angiotensin 2 supports the possible role of apelin in vascular reactivity maintenance in diabetes and also cardiovascular diseases, blood pressure maintenance. Any dysfunctioning or abnormalities in apelin- apelin receptor (APJ) signaling pathway contributes the decreased vasodilatation and increased vasoconstriction responses and also related to insulin resistance related disorders. Apelin peptides mainly exerts the endothelium dependant vasorelaxation by triggering the release of nitric oxide.[11]

Apelin also plays important role in the regulation of homeostasis both peripherally and centrally which was observed in th peripheral rat tissue,furtherly quantitative autoradiography shows that the presence of specific APJ binding sites in human and also rat myocardium with a comparable density to AT1.[12] Now recently discovered that the apelin exerts a strong positive inotropic effect on a molar basis (EC_{50} 33pmol/l) than any yet described.[13]
The apelin-apelin receptor (APJ)signaling pathway was recently identified as a potential important mediator in the pathophysiology of heart failure because the patient with heart failure shown with left ventricular levels of apelin and APJ and those are different with control or normal individuals.[14] In preclinical models, apelinsignaling pathways shows major effects on vascular tone, cardiac contractility and it also causes vasorelaxation in human mesenteric artery that is attenuated by the inhibition of nitric oxide but not prostacyclin.[15] Exogenous administration of apelin to the isolated rat myocardiocytes as well as in vivo administer to rats or miceis a potent activator of cardiac contractility.[16] Adipocytokine –apelin a promising strategy to solve ischemia/reperfusion injury which is an natural substance or structural analogue triggers signaling pathway associated with endogenous cardio protection and its beneficial effects attributed with mobilization of P13K-AKT and MEK1/2-ERK1/2 salvage kinases and inhibition of mitochondrial permeability transition pore(m-PTP),phosphorylation and activation of endothelial nitric oxide synthase (ENOS) are also implicated in myocardial protection afforded by apelin.[5]

Apelin-13 which was synthesized was most potent agonist at the cloned apelin receptor (APJ) receptor and also high levels of both prepoapelin and apelin receptor (APJ) was discovered from the rat myocardiocytes and suggest as vascular function in vivo.[8,9] Declined regulation of apelin receptor (APJ)-apelinsignaling pathway shows the pathology contributes to the heart failure the cardiovascular actions observed for apelin presents the future drug target for many cardiovascular related diseases includes for the treatment of hypertension and heart failure.Central apelin actions on ADH levels contribute the positive effects of apelin receptor agonist on blood pressure by acting on the respective neurons on hypothalamus. Apelin also cross the blood brain barrier by designing a small molecule non peptide mimetic of apelin action for penetration in to blood brain barrier. Angiotensin converting enzyme -2 (ACE 2) in the Reninangiotensin aldosterone system (RAS) functions as a carboy peptidase cleaving the C-terminal phenylalanine which contributes the action asendogenous vasodilator and cardio protective action same as that apelin which is an catalytic domain cleaves the C-terminal phenylalanine with high catalytic efficacy and potency.A novel discovery that the Angiotensin converting enzyme -2 (ACE 2) antagonist shows beneficial cardiovascular actions by blocking the breakdown of endogenous vasodilator apelin.[17] In obesity there is an increased apelin circulation and apelin is the most potent stimulator of cardiac contractility and also plays important role in cardiac remodeling.In contrast to angiotensin a potent vasopressor and anti diuretic hormone (ADH) and apelin both lowers the blood pressure by nitric oxide mechanism and also stimulates dieresis by inhibition of arginine vasopressin activity and release. A finished study on 38 patients of cardiac heart failure of ischemic etiology states that there is an decreased plasma apelin concentration.[18] By matrigel plug assay in the mouse and chick chorioallantoic membrane assay suggest the detailed evaluation of apelin receptor (APJ)-apelin expression patterns in embryogenesis and in the developing retinasuggests the autocrinesignaling pathway in cultured cells and shown to promote the migration and proliferation and blood vessels, growth promoting functions of apelin.[4] Apelin receptor system not only involved only in physiologically but also pathological retinal angiogenesis.[19] Apelin and orexins A&B are newly discovered neuropeptides synthesized in the brain and peripheral tissue these both play a major role in regulation of blood pressure. another action of apelin is to stimulate the neurons on the supra optic nucleus and thereby it cause stimulation of vasopressin not only this vasopressin stimulation it also stimulates the release the adrenocortico tropic hormone (ACTH),corticosterone.apelin also represents in the brain medulla,hypothalamus,paraventricullar and supra optic nuclei.[20] Low density of apelin receptors were found in

vascular smooth muscle identified by quantitative receptor autoradiography.[9] Cardiac diseases are independently associated with a deterioration of renal function and worsening of existing heart disease and adipose tissue which is considered as active endocrine gland now a days and substances produced by this tissue play a important pathological role in this diseases and apelin which is produced by adipocytes might be implicated on the cardio renal axis dysfunction.[21]

EVIDENCE FROM RESEARCH

ANIMAL STUDIES

Role of apelin and its receptor APJ have an important role in the angiogenesis modulation and this study conducted by the use of bovine ovary and apelin and apelinreceptor (APJ) hypothesized to be involved in the corpus lute a formation and regression during estrus cycle and m RNA expression and role of apelin in bovine ovary was identified by q-RT-PCR. In this it was observed as the mRNA expression of apelin and apelinreceptor in bovine ovary during corpus lute aluteal phase and pregnancy.[4]

Apelin had a vasoconstrictor role in human and the[$^{125}_{I}$]-(Pyr1)Apelin-13 binding sites were expressed in human cardiovascular tissue determined by using autoradiography and also in the coronary artery,arota and saphenous grafts and also apelin-apelinreceptors(APJ) are localized in molecular layer of the rat cerebellum, rat lung, rat heart and low levels in the rat kidney cortex. The results obtained from the binding experiments were analyzed by using the iterative, non-linear curve fitting programmers EBDA and LIGAND in the KELL package (Biosoft, Cambridge, U.K.).[8] The apelin augments or peptides shows contraction directly in failing rat cardiac muscle and also reported that the apelin, a ligand for apelin-angiotensin receptor-like 1 (APJ), has recently been shown to be a potent positive inotropic agent in normal hearts.[6] The Angiotensin converting enzyme-2 - ACE2-Ang-(1–7) Pathway in Cardiac Fibroblasts are noveltargets to treat Cardiac Remodeling and Heart Failure, and this pathway expressed in both rodents and humans and highly in the human heart, kidneys etc.[22] The increased cardiac Angiotensin converting enzyme-2 - ACE2 mRNA expression and activities in the infarct regionand the ischemic region surrounding a myocardial infarction (MI).[14] There is no change in Angiotensin converting enzyme-2 -ACE2 mRNA level at four weeks post-MI in rats.[23] The ontogeny of apelin, apelin receptor (APJ) in the gastrointestinaltract of rodent and its is an endogenous ligand expressed in the GIT of rodents and measuring the expression levelsby real time RT-PCR (polymerase chain reaction)and also characterize the abundance and cellular localization at an embryonic stage two postnatal stages.[7] The Angiotensin converting enzyme -2 (ACE 2) is a novel promising target for pulmonary hypertension.[24] The apelin plays an emerging role in medicine and biology and mainly involved in the regulation of cardiovascular function and fluid homeostasis and also represents as a substrates for angiotensin converting enzyme-2 (ACE2), a carboxypeptidaseand now recently described as a novel key enzymeforthe Renin–angiotensin–aldosterone system (RAS). And also apelin receptor(APJ) has further been reported to be a co receptor for the infection of CD4-positive cells with HIV in the central nervous system.[17] The genetics of heart failure by Genome wide association studies.[25]The effects of C-terminal fragment of adipokine apelin-12 (A12) its novel structural analoguesa putative agonist in in vivo model of ischemia/rin acute perfusion injury and myocardial infarction in rats.[23] The Apelin (APLN),the endogenous peptide ligand of the (APJ) apelinreceptor a novel regulator and play a important role in ischemic-perfusion injury and heart failure and also report that the loss of apelin exacerbates the ischemic-reperfusion injury by using the shame-operated mice and also reported that the apelin is an potential drug target.[5] The apelin regulates cardiovascular function as an endogenous ligand by experimentation on apelin and apelin receptor (APJ) null mice.[16]

Apelin receptor (APJ) is an putative agonist for angiotensin type -1 receptor andin the diabetic mice apelin modulates the aortic vascular tone by nitric oxide synthase phosphorylation pathway.[11] The endogenous ligand reduces cardiac load and improves cardiac contractility invivoand they carried out histology and immune histo chemistry to assess cardiac hypertrophy and to localize apelin and apelin receptor (APJ) in the adult and embryonic mouse heart and role of apelinin cardiac function remains unclear.[10] There was no alteration in receptor density, on the medial smooth muscle forurotensin-II and apelin with CAD and reported the GPCR in atherosclerosis and comparing the vasoconstrictors with the de-orphanized receptor that is apelin and urotensin-2.[8,9] The novel endogenous ligand regulates the cardiac contractility in isolated per fused rat hearts, infusion of apelin (0.01 to 10 nmol/L) induced a dose-dependent positive inotropic effect (EC50: 33.1_1.5 pmol/L).[12] The animal and human studies suggest that it may play a role in the pathogenesis of heart failure by modulating the harmful effects of angiotensin II.[26]The in vivo inotropic effects of apelin in normal and failing heart by usingnative and ischemic cardiomyopathic rat hearts using a novel combination of a perivascular flow probe and a conductance catheter.[14]

HUMAN STUDIES

The apelin levels are evaluated apelin might have a significant marker andassociated with cardiovascular mortality, hospitalization, renal function, and cardiovascular risk factors in type 2 diabetic patients with mild to moderate chronic kidney disease (CKD) in this study 150 patients were taken and evaluateddiabetes patients the apelin levels associated with cardiac mortality mainly in the type-2 during a 87-month period from January 2005 to December 2011.[21] The apelin is reduced in patients who arewith heart failure and up regulated following favourable left ventricular remodeling and apelin also play a major role in thepathogenesis of heart failure mainlyby modulating the harmful effects of angiotensin II and apelinacts as a putative agonist for angiotensin 2.apelin inducesthe phosphorylation of the myosin light chainsand in human saphenous veins and thereby it causes Vasoconstriction in the absence of a functional endothelium.[26]

Apelin act as an acute inotropic agent in patients with ischemic heart failure and also reported that theapelin expresses in the cells of human coronary artery endothelial cells and human coronary artery smooth muscle cells, and apelin receptor (APJ) for apelinis located in vascular smooth muscle cells at very low density in both diseased and nondiseased human epicardial coronary arteries.[14] Apelin act as potent endogenous inotrope in human dysfunction. by performing the transcriptional profiling using a spotted cDNA microarray with 12 814 unique clones on paired samples of left ventricle obtained before and after placement of a left ventricular assist device in 11 patients and reported that the increased levels of apelin was seen in patients with left ventricular dysfunction and reported the apelin as a novel drug target in cardiovascular diseases.[16] Theapelin receptors in the vascular smooth muscle cells at very low density in human epicardial NCA and CAD identified by using Quantitative receptor autoradiographyand shows greater vasoconstriction and proliferation of smooth muscle in disease.[8,9] The effects of acute apelin administration in healthy volunteers and patients with heart failure on the peripheral, cardiac, and systemic hemodynamic variables. and study shows the Eighteen patients with class II to III chronic heart failure and 6 patients undergoing diagnostic coronary angiography, and 26 healthy volunteers participated in a series of randomized, double-blind, placebo-controlled studies and the Intracoronary bolus of apelin-36 administration reduces the left ventricular pressure and end-systolic left ventricular pressures increases thecoronary blood and Systemic infusions of (Pyr^{1})apelin-13 (30 to 300 nmol/min)lowers the mean atrial pressure and peripheral resistance and increase cardiac index in healthy controls but increased heart rate only in control subjects.[15]

The plasma apelin levels were measured in 202 congestive heart failure patientsand observed the low plasma apelin levels in congestive heart failure (CHF) patients and also concluded that the apelin-apelin receptor (APJ)signaling pathway play a major role in pathophysiological process of CHFmainly by regulating blood pressure by nitric oxide dependant mechanism and also impliespotential therapeutic applications in cardiovascular diseases.[18] The apelin deficiency cause decreased vascular sprouting, impaired sprouting of human endothelial progenitor cells, and compromised in vivo myocardial angiogenesis and mainly by using the human explanted hearts and loss of apelin may exacerbates the myocardial infarction (MI) and ischemic/reperfusion injury and novel potential therapeutic target for cardiovascular diseases.[5]

FUTURE PERSPECTIVES

Apelin is a novel drug target for cardiovascular disease and potential therapeutic implication for cardiovascular diseases. Targeting the apelin may bring the new therapeutic option for overcome all cardiovascular related problem in near future

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