NARRATIVE REVIEW

Time to broaden pharmacological treatment of cardiovascular disorders with physiological dimensions of Adropin

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Abstract

Adropin, an emerging substance hailed for its heart-protective potential, presents a promising avenue for combating cardiovascular ailments. The current narrative review was planned to underscore its link with metabolic syndrome and its role in preventing ischaemic heart disease, accentuating its multifaceted impact on metabolism and cardiac wellbeing. Mechanistically, it operates through diverse pathways, including modulation of endothelial nitric oxide synthase, anti-apoptotic properties, and regulation of pyruvate dehydrogenase phosphorylation to boost cellular energy production and mitochondrial function. Furthermore, its interactions with cellular receptors, signalling cascades and metabolic regulators unveil its prowess in mitigating cardiovascular risks and enhancing glycaemic control. To transition adropin from bench to bedside, rigorous human trials are imperative, encompassing dose optimisation, long-term safety assessments, and exploration of genetic influences. Inclusive research targetting diverse populations, especially high-risk cohorts, is advocated to unravel its full therapeutic potential. Interdisciplinary collaboration is pivotal for unravelling its mechanisms as a targetted therapy for cardiovascular disorders.

Keywords: Adropin, ENHO protein, Human protein, Rat protein, Myocardial ischemia, Coronary artery disease, Pyruvates, Pyruvic acid, Nitric oxide, Mitochondria, Apoptosis, Therapeutic, Risk factors, Collateral circulation, Homeostasis.

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Introduction

Metabolic syndrome (MS), a cluster of risk factors including high blood sugar, abdominal obesity, elevated blood pressure, and abnormal cholesterol levels, is a significant health concern.[1] According to the World Health Organisation, ischaemic heart disease (IHD) stands as the foremost global cause of mortality, contributing to 16% of total deaths, with a significant increase observed since 2000, reaching 8.9 million deaths in 2019.[2] In the Eastern Mediterranean Region (EMR), approximately 34% of non-communicable disease-related deaths are attributed to cardiovascular diseases (CVDs), and nearly 40% of adults in the region contend with high blood pressure.[2] CVDs, increasing from 25.3% in 1990 to 43.7% in 2019, ranked among the top-10 causes of years of life lost in Pakistan witnessed a notable rise in their contribution to total disability-adjusted life years (DALYs).[2]

The increasing incidence of cardio-metabolic diseases has led researchers to investigate it as a potential element in vascular health.[3] Adropin, a peptide hormone encoded by the Energy Homeostasis Associated gene ENHO (gene, has emerged as a focal point in recent research due to its diverse presence in bodily organs and its potential role in metabolic regulation and cardiovascular health.[4] Its pleiotropic effects across multiple organs[5], antioxidant properties and potential role in detecting MS in obese children[6] make it a promising subject for further exploration. The ongoing research, including its possible diagnostic utility and therapeutic implications, presents an evolving narrative in the field.[7] It has been extensively examined in the context of obesity[8], diet-induced obesity[9], type 2 diabetes mellitus (T2DM)[10], stress, homeostasis, heart disease, stroke, and aging.[11] Its overexpression demonstrates promising effects on dyslipidaemia and atherosclerosis, making it a critical element in vascular health.[12]

The current narrative review was planned to consolidate recent research about establishing adropin as a novel therapeutic target and diagnostic marker in cardio-metabolic diseases.

Structure of adropin

Adropin, a 76-amino acid peptide, possesses its active component within residues 34-76. Translated by the ENHO gene located on chromosome 9, this peptide plays a pivotal role in regulating metabolism and energy balance. While found in various body parts, such as the brain, heart, liver, pancreas and coronary artery, it

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predominantly resides in the brain[4], exhibiting a molecular weight of 4499.9Da.[13]

Cellular receptors and regulation

Researchers have identified potential receptors for adropin, including the orphan G protein-coupled receptor (GPCR) G-coupled protein receptor receptor 19 ((GPR19) and the cell adhesion protein Neuroblastoma [3], a gene involved in neurological development/ Contactin 6 (NB3/CNTN6), primarily situated in the nervous system.[14] The nuclear receptor, Liver X Receptor Alpha (LXRa) positively regulates its activity. Despite advancements, its precise impact on glucose metabolism in liver cells remains not fully understood.[7] With identified receptors in the nervous system, its potential impact on glucose metabolism in the liver remains an intriguing research avenue.

Biological clock and systemic functions

Adropin's functions extend beyond metabolism, with a master control influence from the biological clock. It interconnects with central nervous system (CNS) activity, endothelial dysfunction, and CVDs.[15] Its involvement in synchronising glucose and fatty acid metabolism, dietary behaviour, and Uncoupling Protein 1(UCP1)-mediated energy balance adds complexity to its systemic roles.[16]

Regulation and therapeutic implications

Various factors, including gender, nutrient availability, physical activity and hormones, modulate adropin secretion. Notably, oestrogen receptor alpha (Erα) increases its production in response to excess dietary fats in females. This regulatory mechanism positions it as a potential therapeutic strategy for conditions like non-alcoholic fatty liver disease (NAFLD) in females.[17] Additionally, this approach may also have positive effects on heart and metabolic health.[18]

Correlation of adropin with cardiovascular risk factors

Adropin and gender: In the context of an obesogenic lifestyle, females with adequate adropin and nitrite levels exhibit a reduced risk of vascular insulin resistance, highlighting a potential gender-specific protective effect.[19]

Adropin and stress: Surprisingly, people with hyperphagia in chronic stress often experience weight-loss instead of weight-gain. One possible explanation for this weight-loss is an increase in the expression of ENHO gene. Specifically, it is believed to affect the process of differentiation, which is the transformation of immature cell lineage 3T3-L1 cells into mature adipocytes.[20]

Adropin and insulin: Adropin demonstrates a positive effect on insulin action, particularly in the liver. In conditions of obesity and insulin resistance, adropin improves hepatic insulin sensitivity, suggesting its potential as a therapeutic agent. Notably, adropin regulates glucagon receptor signalling, inhibiting the glucagon-induced cyclic adenosine monophosphate (cAMP)-protein kinase A pathway, which may limit hepatic glucose production. Higher adropin levels appear to attenuate the effect of glucagon on increasing hepatic glucose production.[21] It manages locally plus fine-tune the liver's response during fasting for maintaining energy.[22]

Adropin and metabolic risk factors: Lower adropin levels are associated with higher total cholesterol, glycated haemoglobin (HbA1c), fasting glucose levels, and insulin resistance, highlighting its potential role in metabolic dysfunction and the development of cardiovascular risk factors.[23]

Adropin and blood pressure regulation: Recent studies have reported a negative correlation between adropin levels and arterial blood pressure, suggesting a potential protective role of adropin in blood pressure regulation.[24]

Adropin and physical activity: In a study, two sessions of just descending stair walk 7 days a week for 12 weeks while raising its duration from 5 minutes to 60 minutes elevated adropin by 127%. The study also displayed its significant association with fasting glucose, Homeostasis Model Assessment (HOMA)-index, total cholesterol and high-density lipoprotein (HDL). Peculiarly, eccentric contractions work in conjunction with aerobic exercise to boost the blood's adropin concentration following exercise training.[25]

Adropin and inflammatory markers: There is growing evidence of a correlation between adropin levels and inflammatory markers. Its lower levels are often associated with higher levels of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6). It is thought to play a protective role against inflammation and oxidative stress (OS). For instance, studies have shown that in conditions like CVD and metabolic disorders, its altered levels often coincide with increased inflammation.[26]

Adropin and other indicators: In a comprehensive analysis of various risk factors, adropin levels were positively correlated with markers of renal and cardiac function (albumin, haemoglobin [Hb], serum creatinine, Kt/V which is a ratio used to assess the adequacy of dialysis by measuring the amount of waste cleared from

the blood, and ejection fraction [EF]) and inversely correlated with age, history of CVD and DM, inflammatory marker CRP, and indicators of cardiovascular structure (carotid artery plaque amount, carotid intima-media thickness (CIMT), left ventricular systolic thickness at diastole (LVSTd), and left ventricular posterior wall thickness).[26]

Mechanism of action

The various effects of adropin on heart disease are believed to occur through several mechanisms, with its impact on endothelial functions being the most prominent (Figure 1).

Mechanism after increase in endothelial nitric oxide synthase (eNOS)

One of the main ways adropin exerts its effects is by increasing the expression of eNOS, which is responsible for producing NO in the endothelial cells. When adropin is deficient, there is a decrease in the availability of NO in the endothelium. This deficiency is associated with endothelial dysfunction, a condition characterised by impaired NO production, and is known to be a predictor of coronary artery disease (CAD) development. It inhibits the clumping together of blood platelets, reduces excessive growth of smooth muscle cells in blood vessels, prevents the adhesion of leukocytes and monocytes to the endothelium, and inhibits the oxidation of low-density lipoprotein (LDL). These actions protect against the development of CVDs. In 102 patients with at least one primary epicardial artery blockage, the connection between adropin and collateral circulation of the heart has been investigated. Myocardial tissue exposed to ischaemia can get alternate blood flow via the coronary collateral circulation (CCC), which helps to maintain myocardial functions, and this alternate pathway depends on the interplay between NO and vascular endothelial growth factor (VEGF), which in turn relies on

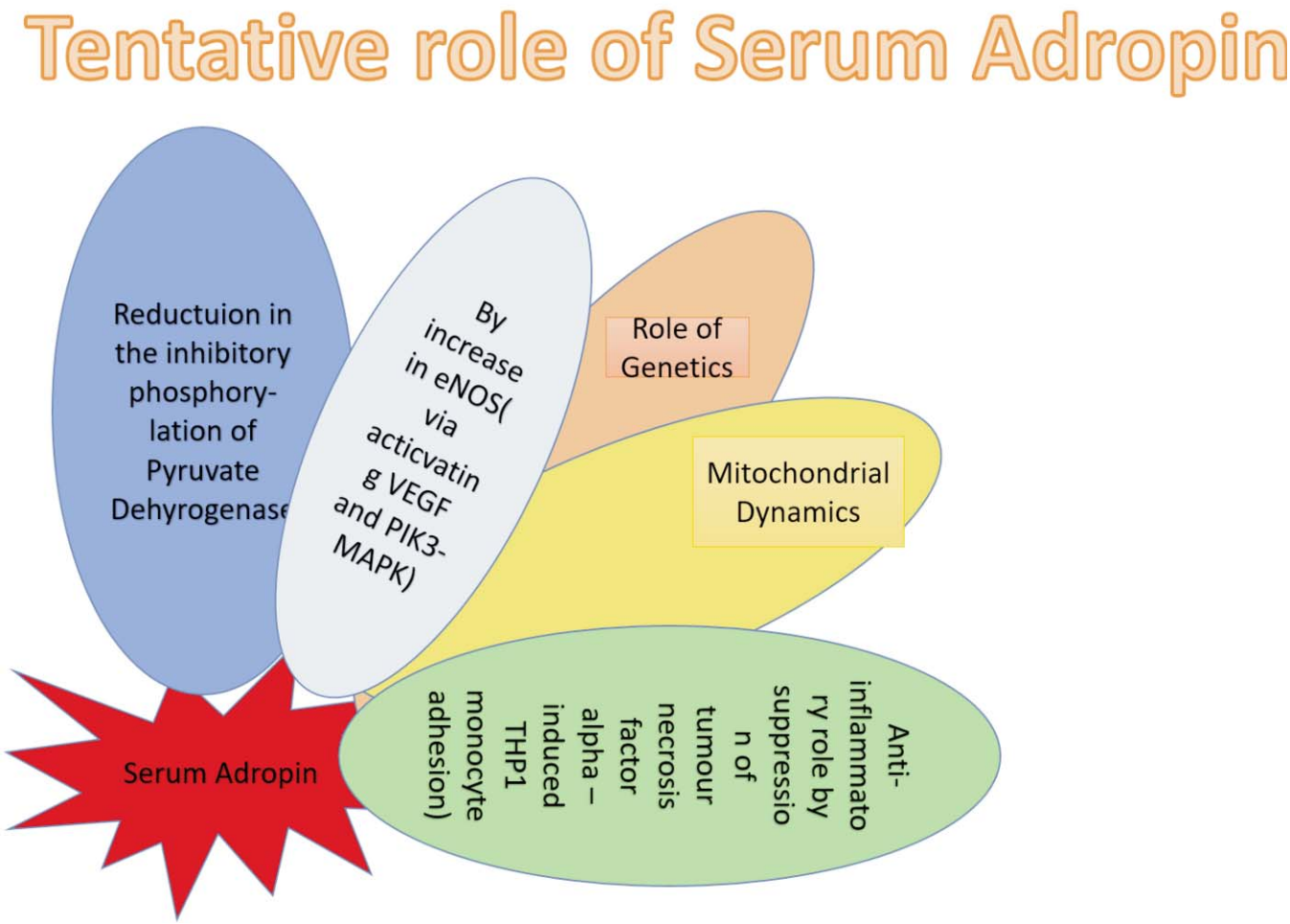

Figure-1: Tentative roles of serum adropin include reducing pyruvate dehydrogenase (PDH) inhibitory phosphorylation, enhancing eNOS activity via VEGF and PI3K pathways, improving mitochondrial dynamics, and providing anti-inflammatory and genetic regulation.

adropin. It increases VEGF receptor-2 (VEGFR-2), leading to an increase in the expression of eNOS messenger ribonucleic acid (mRNA) and eNOS protein. The activation of threonine kinase (Akt) and extracellular signal-regulated kinases (ERK), which are protein kinases involved in cellular signalling pathways, is responsible for mediating this effect. This up-regulation of eNOS is significant in the production of NO in endothelial cells, which contributes to the relaxation of blood vessels and improved blood flow. The activation of VEGFR-2 by adropin also has implications for the development of CCC. Coronary collaterals are alternative blood vessels that can develop to bypass blockages or narrowings in the coronary arteries. Their maturation is facilitated by VEGFR-2 activation, which can improve blood supply to the heart muscle. In the study, Rentrop scores and neutrophil-to-lymphocyte ratios (NLRs) were shown to be favourably linked with it (r: 0.17, p: 0.04).[27]Actually, it phosphorylates eNOS at a specific phosphorylation site on the protein eNOS, important in vascular function and nitric oxide production named Ser177. This phosphorylation event is mediated by the up-regulation of VEGFR-2, induced by adropin, which leads to the activation of downstream signalling pathways. One of them is the Akt pathway, specifically phosphorylating Akt at Ser473. The other one activated is the ERK1/2 pathway. These pathways play important roles in regulating cell survival, proliferation, and vasodilation. By phosphorylating eNOS at Ser1177, it enhances its activity, resulting in increased production of NO.24,[28] Studies have shown a progressive increase in adropin-induced vasodilation with advancing age, suggesting its potential as a therapeutic target for age-related endothelial dysfunction.[29] Additionally, it has been implicated in mitigating radiation-induced myocardial injury by reducing free radical damage, promoting angiogenesis, and inhibiting myocardial fibrosis and apoptosis through the activation of the Vascular Endothelial Growth Factor Receptor(VEFGR) Phosphoinositide 3-kinase (PI3K) and Protein Kinase B (Akt) pathway. The influences of exogenous adropin on the growth of scar tissue of myocardium, its mode of cell death, the density of its capillaries, free radical injury, and protein manifestation were seen after E0771(murine breast cancer cell line) cells were given to strain of laboratory mouse C57BL/6 mice and they underwent irradiation. This substantially reduced injury due to free radical, encouraged growth of new micro-vessels, and blocked myocardial fibrosis and apoptosis to treat Regional Integrated Myocardial Infarction (RIMI).[30] Moreover, it's up-regulation has been associated with improvements in central arterial stiffness, potentially through increased NO availability. It has been stated along with apelin as an up-regulating hormone, and their level was determined in 33 subjects who were enrolled in aerobic training for 8 weeks.[31] Similarly, high-intensity interval training (HIIT) has been shown to enhance its levels, along with NO production and flow-mediated dilation (FMD) in coronary arteries, suggesting its role in improving cardiovascular health and in reducing blood pressure. It was investigated in 66 T2DM patients at baseline and after12 weeks of HIIT or moderate-intensity continuous training (MICT). It was observed that peak oxygen consumption, adropin, nitric oxide metabolites (NOx), and FMD were all enhanced by HIIT. Moving one step forward, it was proposed that by increasing NO generation, it may contribute to a reduction in blood pressure to some extent.[32]

In short, one can clearly confirm production of NO and VEGF as its main mechanism. It is of ultimate importance to separate the threads of the key players in the development of collateral circulation, prevention of atherosclerosis, opening up of new anastomosis and lowering of hypertension. Cardiologists, endocrinologists, physical therapists, pharmacists, physiologists, as well as anatomy and biochemical experts should focus their research on a baseline assessment of CCC status and subsequent therapeutic intervention by adropin. Moreover, adropin34-76's large-scale preparation is fairly simple because it was made using a peptide synthesiser, a well-established method that is inexpensive and avoids the complex post-translational modifications that some other recombinant hepatokines need for their crucial function.[33]

Protection against apoptosis

A viable alternative treatment for cardiac disorders is stem cell therapy.[34] In vitro studies showed that adropin protected mesenchymal stem cells (MSCs) from apoptosis in a myocardial hostile microenvironment produced by hydrogen peroxide (H2O2). Additionally, adropin-induced anti-apoptotic effects were inhibited by reperfusion injury salvage kinase pathway (RISK) pathway inhibitors due to the reduction in the protein expression of Total Protein Kinase B(t-Akt), Total Extracellular Signal-Regulated Kinases 1 and 2(t-ERK1/2), B-Cell Lymphoma [2], a protein involved in regulating apoptosis (BCL-2), and B-Cell Lymphoma-Extra Large, another anti-apoptotic protein of the BCL-2 family(BCL-XL) (Figure 2). Peptide hormones have varying half-lives, ranging from 3 minutes to 30 minutes, and a study believed that it has a similarly short half-life of several minutes.[35] The study suggested that its solo booster after an ischaemic event may regulate the cardiac environment at the initial stage by suppressing inflammation. Adropin-pre-treated stem

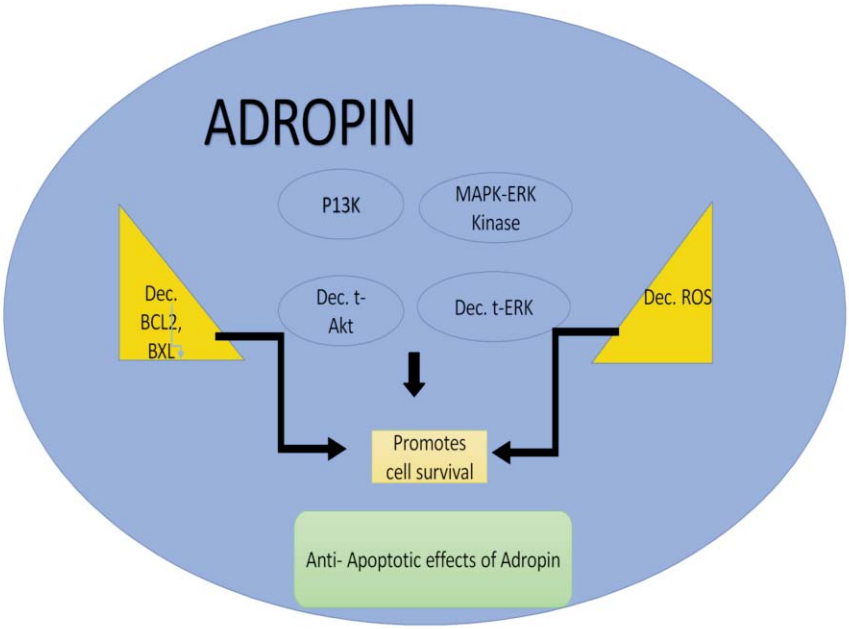

Figure-2: Schematic representation of the anti-apoptotic effect of adropin promoting cell survival by decreasing the activation of pro-apoptotic proteins (Bcl2, BXL), reducing reactive oxygen species (ROS), and influencing key signalling pathways, including PI3K and MAPK/ERK, which result in lower total Akt (t-Akt) and total ERK (t-ERK) levels.

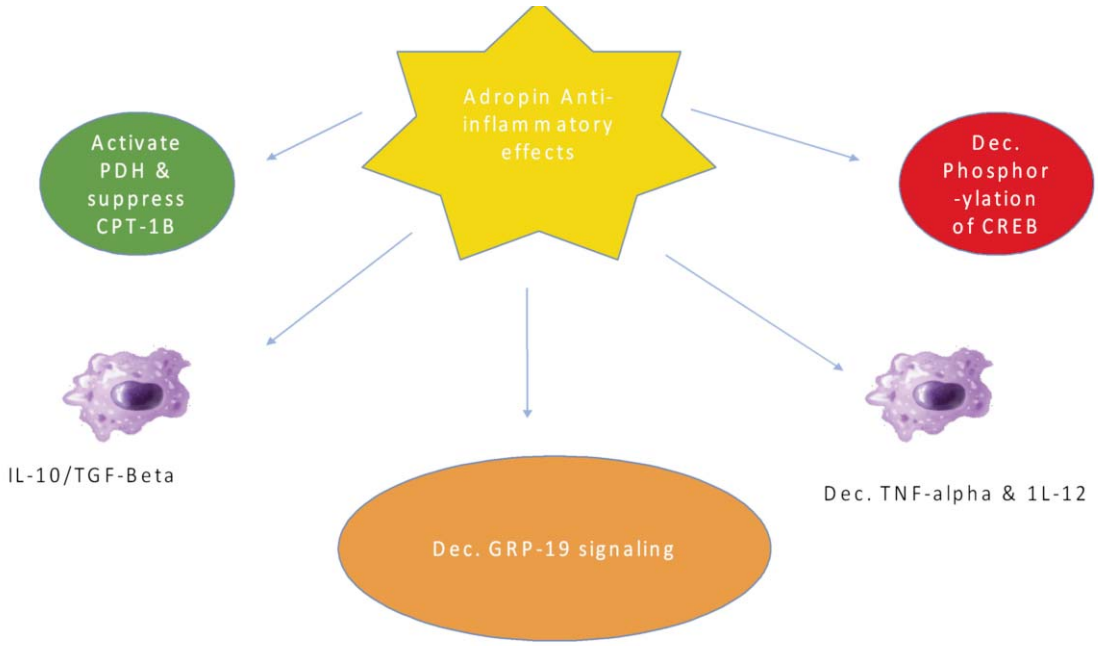

Figure-3: Adropin's anti-apoptotic effects involve promoting cell survival by decreasing ROS, reducing t-Akt and t-ERK levels through PI3K and MAPK/ERK pathways, and down regulating pro-apoptotic proteins Bcl2 and BXL.

cells are also believed to have a stronger ability to survive in the injured tissue. They defend the endothelium via the RISK pathway. The study altered the cardiac milieu in vivo, and it was combined with the transplantation of MSCs to create a dual adropin-based therapy. These combined protective actions may enhance ventricular remodelling and cardiac performance.[35]

More research is necessary to see whether this translates to humans. Today, mice, rats, rabbits, pigs and monkeys are the animals most frequently utilised to create

myocardial infarction (MI) models. The approach for simulating MI that is most frequently utilised is coronary artery ligation. Better clinical applicability can be achieved through real-time monitoring and assessment of the modelling procedure using an electrocardiogram, pathology, and serum enzymology. The use of cardiac tissue engineering and associated biomaterials is a favourite trend in MI healing.[36]

Anti-inflammatory role

Several studies have found a connection between serum adropin levels and various disorders characterised by chronic low-grade inflammation, including diabetes, atherosclerosis, polycystic ovary syndrome, and obstructive sleep apnoea. It is believed that the presence of inflammation, particularly pro-inflammatory cytokines, like tumour necrosis factor-alpha (TNF-α), may lead to a reduction in its levels (Figure 3).[37] When it is deficient, it leads to damage in the blood vessels due to activation of neutrophils and release of a protein called Myeloperoxidase (MPO). Peroxisome proliferator-activated receptor gamma (PPARG) has been as a core gene involved in this process.[38]

Mitochondrial dynamics

Reduction in the inhibitory phosphorylation of pyruvate dehydrogenase (PDH): The choice of the myocardium's metabolic substrates can be altered by the functional state of pyruvate dehydrogenase kinase[4] (PDK4), which in succession influences myocardial energy metabolism. Adropin's pharmacological effects on energy metabolism and PDK4 in cardiomyocytes suggest that it might be a potential therapy option for cardiac illness linked to decreased insulin sensitivity. It reduced PDK4 and activated PDH in the muscle of these animals via inhibiting Carnitine Palmitoyltransferase 1B (CPT-1B), a crucial enzyme in the oxidation of fatty acids.[39] Additionally, it was revealed that in contrast to failing hearts, which exhibit a generalised weakening of mitochondrial oxidative phosphorylation and a greater reliance on glycolysis, the heart in diabetes is more dependent on fatty acid oxidation for energy generation and exhibits deregulation of glucose absorption and insulin signalling[40]. In the study, fasting mice were given adropin that had improved cardiac performance and efficiency, while having insulin had an increased inhibitory effect on cardiac fatty acid oxidation. Both the in vivo and ex vivo dealing procedures resulted in a decrease in the amount of PDH, which is the primary enzyme for glucose oxidation. Nevertheless, the concentration of PDH kinase [4], responsible for regulating PDH, as well as the inhibitory phosphorylation of insulin-signalling proteins called c-Jun N-terminal Kinase JNK (p-T183/Y185) and Insulin Receptor Substrate 1(IRS-1) (p-S307) were also reduced. These findings suggested that the acute mechanism of receptor and/or post-translational modifications played a role in this decrease.[40]

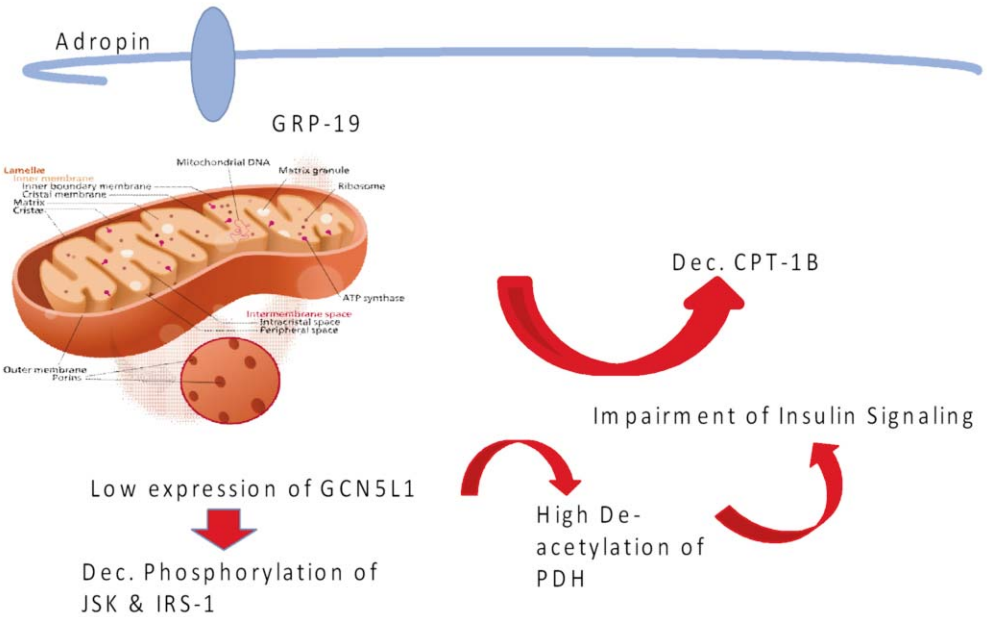

Figure-4: Adropin, GRP-19, GCN5L1 (General Control of Amino Acid Synthesis 5-Like 1), JSK (Jun N-terminal kinase), IRS-1 (Insulin Receptor Substrate 1), CPT-1B (Carnitine Palmitoyltransferase 1B), and PDH (Pyruvate Dehydrogenase) are key proteins and enzymes involved in insulin signaling, fatty acid oxidation, and energy metabolism.

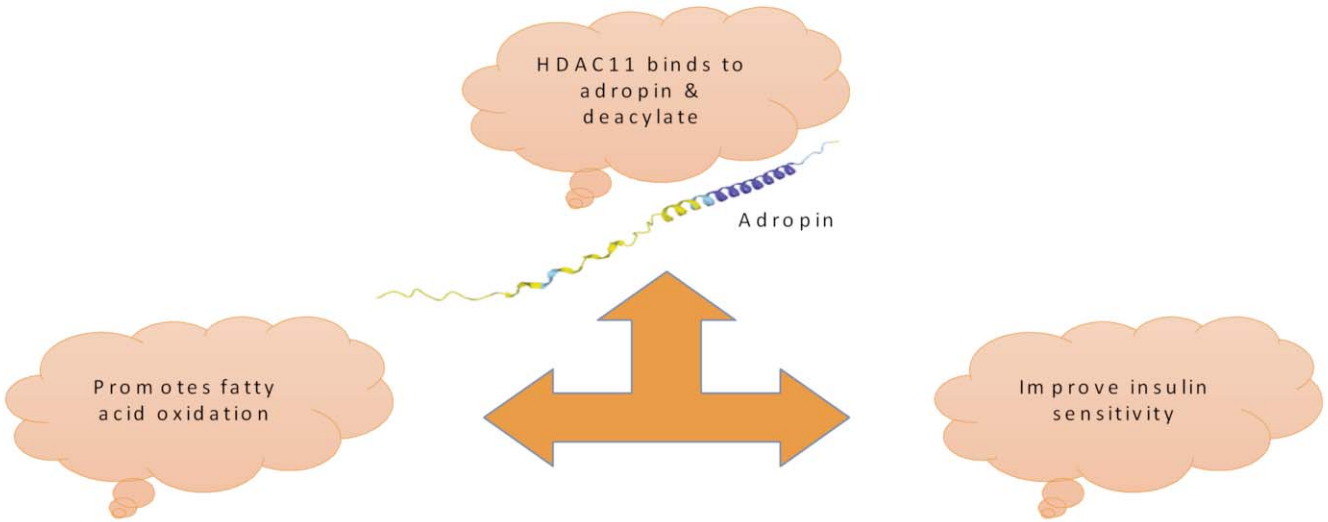

Figure-5: HDAC11 (Histone Deacetylase 11) binds to adropin, facilitating its deacetylation. This interaction enhances adropin's role in promoting fatty acid oxidation and improving insulin sensitivity, which are key factors in metabolic regulation.

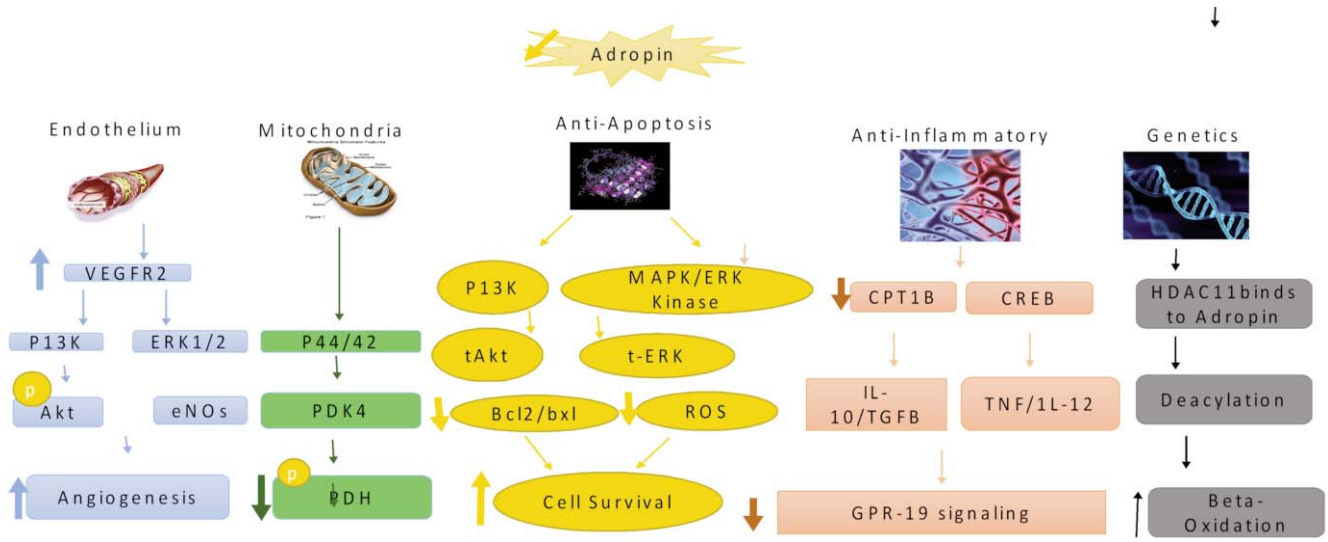

Figure-6: Summary of all mechanisms of adropin.

VEGFR2 (Vascular Endothelial Growth Factor Receptor 2); PI3K (Phosphoinositide 3-Kinase); ERK1/2 (Extracellular Signal-Regulated Kinase 1/2); PDK4 (Pyruvate Dehydrogenase Kinase 4); Akt (Protein Kinase B); eNOS (Endothelial Nitric Oxide Synthase); PDH (Pyruvate Dehydrogenase); MAPK (Mitogen-Activated Protein Kinase); t-Akt (Phosphorylated Thr-308 Akt); t-ERK (Phosphorylated Thr-202/Tyr-204 ERK); Bcl2/BXL (B-cell lymphoma 2/BCL-XL proteins); ROS (Reactive Oxygen Species); CPT-1B (Carnitine Palmitoyltransferase 1B); CREB (cAMP Response Element-Binding Protein); IL-10 (Interleukin 10); TGFB (Transforming Growth Factor Beta); TNF (Tumor Necrosis Factor); IL-12 (Interleukin 12); HDAC11 (Histone Deacetylase 11); GPR-9 (G Protein-Coupled Receptor 9).

Adropin regulates PDH activity through a pathway involving GPR19 and the Mitogen-Activated Protein Kinase (MAPK/ERK1/2) pathway. In fact, its activation of GPR19 leads to the activation of MAPK, which in turn phosphorylates certain molecules involved in cellular signalling. This phosphorylation event ultimately leads to the down-regulation of PDK4 (Figure 4). By inhibiting PDK4, it allows PDH to function without inhibition, promoting the utilisation of glucose as an energy source in cardiac cells.[41]

Mitochondrial bioenergetics

The heart's mitochondrial energy supply is crucial. The heart uses a lot of high-energy phosphates, and about 8% of the body's entire adenosine triphosphate supply. In the mitochondria, oxidative phosphorylation is used to renew adenosine triphosphate. The term mitochondrial dynamics refers to the synchronised successions of fission

and fusion that occur within the extremely dynamic organelles of mitochondria. Optical atrophy protein 1 and dynamin-related mitofusins (mitofusin-1 and mitofusin-2) are the main mammalian cell. Besides, mitochondrial fission is mediated by the mitochondrial fission 1 protein and the dynamin-related protein 1 (DRP1).[42] Regarding diabetic cardiomyopathy in mice, Adrenergic Receptor (ADR) could reduce myocardium fibrosis and enhance diastolic function. The study showed adropin administration decreased the manifestation of the mitochondrial acetyltransferase enzyme named General Control of Amino Acid Synthesis 5-Like 1(GCN5L1), restoring glucose oxidation in vivo. Although the mechanism underlying this action is still not fully understood, the reduction in GCN5L1 abundance changed the acetylation and the use of fuel metabolism enzymes to support glucose depletion. All this implies that adropin regulates mitochondrial bioenergetics output in cardiac cells by acting as a potential cellular receptor for GPR19.[43]

Role of genetics

Target genes are regulated by Long Non-Coding RNAs (LncRNAs) at different epigenetic levels. It was found that histone deacetylase 11-antisense RNA 1 (HDAC11-AS1) performs a shielding effect in the progress of circulatory illnesses despite the paucity of studies on the function of lncRNAs. Adropin is found to have an influence on the potential mechanism by inducing Lipoprotein Lipase (LPL) expressions.[44] In the study, the researchers investigated its critical function in increasing LPL's triglyceride (TG) hydrolysis, which is arbitrated through the AMPK pathway. It also inhibits the adhesion of monocytes and endothelial cells plus the proliferation of smooth muscle, which suggests that it is tangled in plasma lipid metabolism, and it diminishes the plaque formation in vessels. HDACs are essential for the epigenetic control of target gene expression, which includes genes involved in lipid metabolism. HDAC11-AS1 decreased histone deacetylation of adropin (Figure 5), while dramatically increasing it after HDAC11 treatment in Human Aortic Vascular Smooth Muscle Cells (HA-VSMCs). This demonstrated that HDAC11 limited adropin expression by causing its histone to become deacetylated. LncRNAs have been linked to the development of CVDs, making them possible new biomarkers for coronary heart disease and myocardial infacrion.[44] Another study found that inhibiting HDAC11 improved the preclusion of TNF-induced pyroptosis in human umbilical vein endothelial cells (HUVECs), suggesting that atherosclerosis may be prevented by down-regulating HDAC11-related signalling pathways.[45] The only HDAC11 inhibitors that have been reported to have been used in animal trials are FT895[46], romidepsin and quisinostat.[47] Its genetic role is influenced by STAT3(Signal Transducer and Activator of Transcription 3) activation, which raises circulating adropin and encourages ENHO illustrations in the hepatocytes of diabetic rats. A potential curative aim for the treatment of diabetes problems brought on by adropin may be STAT3.[48, 49]

In conclusion, it highlights the multifaceted regulatory roles of lncRNAs and the significance of adropin in lipid metabolism and cardiovascular health. The findings suggest that targeting HDAC11-AS1 and modulating its expression may hold therapeutic potential for managing circulatory illnesses, including atherosclerosis and diabetes-related complications.

Pharmacological research on adropin

The enzyme-linked immunosorbent assay (ELISA) remains the gold standard for measuring adropin levels. This method is known for its sensitivity and specificity, allowing for accurate detection of low concentrations of adropin in biological samples, such as blood plasma or serum.

Results of pharmacological research on adropin is still emerging, but there are some promising directions, including the following:

Adropin mimetic: Development of synthetic peptides that mimic adropin's function, potentially offering therapeutic benefits for metabolic and cardiovascular diseases.

Gene therapy: Strategies to enhance endogenous adropin production through gene therapy techniques.

Small molecules: Identification of small molecules that can modulate adropin signalling pathways.

Combination Therapies: Using adropin-based treatments in conjunction with other therapies to enhance overall health benefits.

This article has highlighted the potential of these innovations, although they are largely in pre-clinical stages and require further research to establish efficacy and safety.

On the basis of all the adropin mechanisms (Figure 6), it is clear that the time is right to expand research on adropin therapeutic potential in cardiac disorders.

Conclusion

To transition adropin from bench to bedside, rigorous human trials are imperative, encompassing dose

optimisation, long-term safety assessments, and exploration of genetic influences. Inclusive research targeting diverse populations, especially high-risk cohorts, is recommended to unravel its full therapeutic potential. Interdisciplinary collaboration is pivotal for unravelling its mechanisms as a targeted therapy for CVDs.

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AUTHORS' CONTRIBUTIONS:

SA: Concept, data search, picture formatting, final approval and agreement to be accountable for all aspects of the work.