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Adropin: A crucial regulator of cardiovascular health and metabolic balance

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A B S T R A C T

Adropin, a peptide discovered in 2008, has gained recognition as a key regulator of cardiovascular health and metabolic balance. Initially identified for its roles in energy balance, lipid metabolism, and glucose regulation, adropin has also been found to improve cardiovascular health by enhancing endothelial function, modulating lipid profiles, and reducing oxidative stress. These protective mechanisms suggest that adropin may be able to help prevent conditions such as atherosclerosis, hypertension, and other cardiovascular diseases. Research has established connections between adropin and cardiovascular risk factors, such as obesity, insulin resistance, and dyslipidemia, positioning it as a valuable biomarker for evaluating cardiovascular disease risk. New studies highlight adropin's diagnostic and prognostic significance, showing that higher levels are linked to better cardiovascular outcomes, while lower levels are associated with a higher risk of cardiovascular diseases. This review aims to summarize current knowledge on adropin, emphasizing its significance as a promising focus in the intersection of cardiovascular health and metabolic health. By summarizing the latest research findings, this review aims to offer insights into the potential applications of adropin in both clinical practice and research, leading to a deeper understanding of its role in maintaining cardiovascular and metabolic health.

1. Introduction

Cardiovascular diseases (CVDs) are a major cause of death and morbidity globally which raises serious health concerns [1]. By the middle of the 20th century, cardiovascular disease became the leading factor of mortality and morbidity in developed countries [2]. By the end of the 20th century, cardiovascular diseases were one of the world's leading causes of premature mortality and a large portion of CVD-related deaths occurred in lower-income countries [3].

Several major risk factors that contribute to the development of CVDs are obesity, diabetes mellitus, smoking, dyslipidemia, high blood pressure, poor nutrition, and excessive alcohol consumption. These factors often act synergistically to increase the risk of CVDs and also they are modifiable through medication and lifestyle changes [4]. Thus, understanding and addressing cardiovascular risk factors are crucial for effective prevention and treatment strategies.Peptides are short chains of amino acids stabilized by disulfide bonds that are synthesized by both chemical and biological techniques. This flexibility allows for modifications in their sequence which will expand their potential applications [5–9]. Therapeutic peptides have already emerged as a potent tool in managing various diseases such as diabetes mellitus and its complications, and cancer, which shows their potential in treatment [10–12].

One important therapeutic peptide is adropin. It comprises 76 amino acids and was discovered in 2008 by Kumar et al. The discovery of this adropin made a significant breakthrough by playing a crucial role in regulating lipid and glucose metabolism and maintaining energy homeostasis [13].This review explores various aspects of adropin, highlighting its significance as a novel peptide hormone responsible for cardiovascular health and risk assessment. It aims to provide a comprehensive understanding of adropin as a potential therapeutic target and prognostic biomarker in cardiovascular medicine and metabolic dysfunction.

1.1. Literature search

To ensure a comprehensive literature search, databases including PubMed, Web of Science, Scopus, and Google Scholar were utilized. Boolean operators were employed with specific Medical Subject Headings (MeSH) terms and keywords such as "Adropin," "ENHO gene," "Energy homeostasis," "Metabolic regulation," and "Cardiovascular function."

Date of Search: April 04, 2024; **Number of Articles Found (Full Text available)**:194; **Adropin in Metabolic Disorders**: 121; **Adropin in Cardiovascular Health**: 28; Adropin in Neurological Conditions: 9;

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Adropin in Inflammatory Diseases: 30; Other articles related to Adropin: 6.

1.2. Adropin: discovery and expression

The term "Adropin" was created to show the hormone's connection with energy balance and its potential impact on metabolic processes. The name "Adropin" comes from the Latin words "aduro," meaning to set fire to, and "pinguis," meaning fat [13].

The ENHO gene encodes the peptide hormone adropin and is highly conserved across mammalian species. This conservation suggests that the gene plays a critical role in physiological processes, possibly related to energy balance and cardiovascular function. A comparative analysis of the ENHO gene across different species shows a high level of sequence similarity. In humans and mice, the ENHO gene shares approximately 80–90 % sequence identity, highlighting its conserved nature. This conservation extends to other important regions of the gene, such as the promoter and regulatory elements, which are essential for the gene's expression and function [13,14].

The C57BL/6J mice, also known as "Black 6″ mice, are a commonly used inbred strain in biomedical research. They were developed at The Jackson Laboratory and have been maintained as an inbred strain since 1921. Inbred strains like C57BL/6J are bred over many generations to ensure genetic uniformity, making them ideal for scientific research due to their consistent and reproducible genetic background. These mice are often used in studies related to metabolic diseases due to their susceptibility to obesity and type 2 diabetes when fed a high-fat diet. This includes research on the regulation of energy homeostasis and glucose metabolism. In 2008, Kumar et al. conducted an investigation that delineated the discovery of adropin and its pivotal role in metabolic regulation. The study elucidated the hypothalamic control over liver metabolism utilizing C57BL/6J mice deficient in the melanocortin-3 receptor (Mc3r −/−) and employed microarray analysis to interrogate liver gene expression profiles. This meticulous exploration led to the identification of a novel transcript responsible for encoding adropin, a peptide consisting of 76 amino acids crucially implicated in energy homeostasis and lipid metabolism [13]. Subsequent investigations, including those conducted by Kumar et al., unveiled a significant correlation between adropin levels and nutrient intake. Specifically, lean C57BL/6J mice subjected to a high-fat diet (HFD) exhibited heightened adropin expression in the liver compared to their counterparts on standard diets, whereas periods of fasting were associated with reduced adropin levels [14,15].

Moreover, extended inquiries involving diet-induced obesity (DIO) mice provided substantial evidence indicating a decline in Enho gene expression within the liver consequent to prolonged high-fat diet consumption. This finding supports the idea that impaired adropin function may contribute to metabolic disorders, including obesity [13].

In human studies, obese individuals were found to have significantly lower blood adropin levels compared to those with normal weight, highlighting adropin's role in metabolic regulation and its potential relevance in managing obesity-related conditions [14,15].

Adropin has been characterized as a peptide that can be both secreted and membrane-bound. Studies indicate its secretion by HEK293 cells and C57BL/6J mice [13]. Additionally, research highlights adropin secretion by brain tissue [15] and emphasizes the liver as a significant producer of adropin [16]. However, there are also reports suggesting adropin secretion by various tissues throughout the human body, demonstrating its widespread presence and potential multifunctionality [17]. The Enho gene, situated on chromosome 9 (9p13.3) between 34,521,043 and 34,522,990 base pairs, spans 1948 base pairs. It encodes adropin, a 76-amino acid peptide with two functional segments: adropin1−33 (amino acids 1–33) [Fig. 1] acts as a secretory signal peptide facilitating its secretion, while adropin34−76 is the biologically active region responsible for physiological effects [18,19].

Although the specific receptor for adropin's biological effects remains unidentified, Stein et al. demonstrated its action through the orphan G protein-coupled receptor (GPR19) in the brain, inhibiting water deprivation in rats [20]. While this sheds light on potential mechanisms, more research is needed to understand adropin's diverse activities [20]. Adropin has shown the ability to stimulate angiogenesis, proliferation, and migration of human umbilical vein endothelial cells (HUVECs) and coronary artery endothelial cells. There's also a proposal that adropin may act on vascular endothelial growth factor receptor-2 (VEGFR2) in endothelial cells, indicating a potential role in promoting vascular health and function [21]. These findings hold promise for therapeutic strategies targeting angiogenesis and endothelial cell activities, highlighting adropin's potential in enhancing vascular health.

[Signal Peptide (1–33 amino acids): The initial segment of the adropin protein, indicated in light blue, is the signal peptide. This segment (1–33 amino acids) directs the nascent protein to the secretory pathway. Secreted Peptide (34–76 amino acids): Shown in light blue, this region (34–76 amino acids) represents the mature adropin peptide that is secreted extracellularly]

During the initial discovery of adropin, researchers identified its expression in both the liver [13] and brain [22]. Subsequent studies have expanded our understanding of adropin's tissue distribution, revealing its presence in a wide range of tissues and cells [17]. Specifically, in the liver, adropin expression was observed in sinusoidal cells, while in the central nervous system (CNS), immunoreactivity of the peptide was detected in various areas including the vascular region, pia matter, neuroglial cells, Purkinje cells, granular layer, and neurons, as observed in rat models. These findings highlight the diverse distribution of adropin throughout different organs and cell types, providing valuable insights into its potential roles and functions beyond its initial discovery sites [18].

Immunohistochemical techniques were utilized to ascertain the expression of Adropin in key anatomical regions of the pancreas and

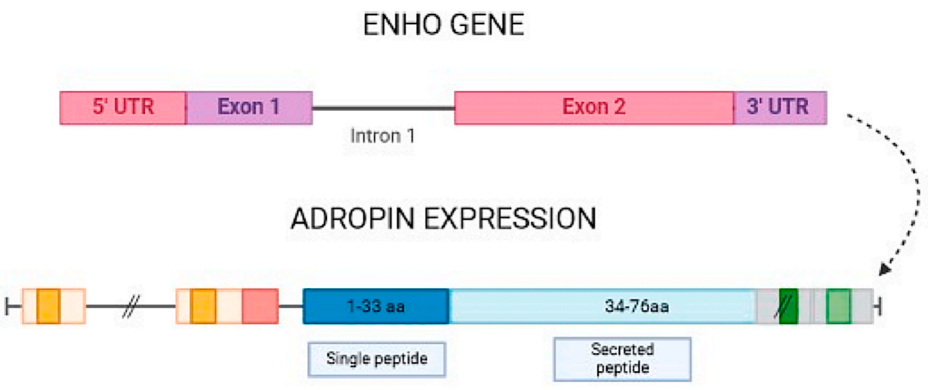

Fig. 1. Structure of the Enho gene and adropin expression.

kidneys. Specifically, the presence of Adropin was detected in acinar cells [18] and within the capillaries of the islets of Langerhans [23] in the pancreas. These findings underscore the potential roles of Adropin in pancreatic function and physiology. Similarly, immunoreactivity for Adropin was identified in the capillaries of renal glomeruli, as well as in the peritubular interstitial and peritubular regions [24] of the kidneys, suggesting its involvement in renal processes.

Within the circulatory system, Lovren et al. conducted investigations demonstrating the expression of Adropin in endothelial cells within cultured human umbilical vein and coronary artery endothelial cells (ECs) [21]. Their study proposed a vascular effect mediated by Adropin through endothelial cells, showcasing enhanced capillary-like tube formation, increased cell proliferation, and migration. Additionally, histological analysis revealed the localization of Adropin in the endocardium, myocardium, and epicardium of rat hearts [18]. Subsequent studies [25–27] have further supported the connection between endothelial function and Adropin, suggesting its probable presence and activity within endothelial cells. These cumulative findings highlight the potential of Adropin in influencing vascular function and contributing to overall cardiovascular health.

1.3. Laboratory evaluation of adropin

Blood samples are collected and processed to separate serum or plasma. Adropin levels are measured using ELISA kits, which use antibodies to detect and quantify proteins. Samples are added to adropin-specific antibody-coated wells, and a biotinylated detection antibody is then added. A substrate solution is added, and the color change is measured using a spectrophotometer. Known adropin concentrations are used to create a standard curve for quantification.

Limitations:

The antibodies used in ELISA may cross-react with other proteins, leading to false-positive or false-negative results. Variations in ELISA kit components can lead to inconsistencies in adropin measurements, affecting reliability and reproducibility. Additionally, sensitivity and specificity issues may affect accurate adropin detection. Single time point measurements may not reflect temporal changes in adropin levels. Sample handling, storage conditions, and serum or plasma components can introduce variability into the results.

2. Physiological functions of adropin

Adropin is predominantly considered a hepatokine due to its high expression in the liver, where its levels are regulated by dietary intake of carbohydrates and fats [19]. Although primarily sourced from the liver, adropin is also expressed in adipose tissue and muscle. Obesity and insulin resistance can influence adropin levels, particularly in adipose tissue [13].

Adropin is known to have various physiological processes in maintaining metabolic regulation, neurological function, and renal and pancreatic functions [28,29].

The following table summarizes major animal and human epidemiological studies on adropin, providing an overview of its role in various physiological and pathological conditions. These studies demonstrate the diverse effects of adropin on metabolic regulation, cardiovascular function, and overall energy homeostasis across different models (see Tables 1 and 2).

Table 1
The role of adropin in metabolic regulation: Insights from animal studies.

Study	Animal Model	Key Findings	Critical Comments
Thapa et al. (2019) [15]	Pre-diabetic obese mice	Adropin treatment improved cardiac glucose oxidation	Strong evidence for adropin's role in cardiovascular health; however, long-term effects and potential side effects need further investigation.
Stein et al. (2016) [20]	Mice (C57BL/6J)	Adropin regulates metabolic processes via circadian rhythms	An important link between circadian biology and metabolism; further studies are needed to elucidate detailed mechanisms.
Akcilar et al. (2016) [64]	Metabolic syndrome rats	Adropin administration ameliorated metabolic syndrome parameters	Promising results for metabolic syndrome treatment; however, species differences must be considered before translating to human treatments.
Gao et al. (2015) [19]	Diet-induced obese mice	Adropin improved glucose tolerance and substrate utilization	Highlights therapeutic potential for metabolic diseases; dose-response relationships and safety profile require more extensive study.
Butler et al. (2012) [99]	Obese and diabetic mice	Low adropin levels associated with metabolic syndrome; increased post-gastric bypass	Demonstrates therapeutic potential; study limited to specific obesity model, broader applicability needs confirmation.
Lovren et al. (2010) [21]	Mice (C57BL/6J)	Adropin improved endothelial function	The first study links adropin to vascular health; additional studies are needed to explore adropin's role in different cardiovascular conditions.
Kumar et al. (2008) [13]	Mice (C57BL/6J)	Identified adropin; linked to dietary macronutrient intake, energy homeostasis	Foundational study establishing adropin's role; however, mechanistic pathways were not fully explored.

2.1. Role of adropin in glucose homeostasis

Numerous investigations conducted in recent years have shed light on the crucial correlation between adropin levels and the intricate regulation of glucose metabolism. Adropin, a peptide hormone encoded by the Enho gene, exerts a significant regulatory influence on key aspects of glucose metabolism, including insulin sensitivity, glucose uptake, and utilization across various tissues [13,30]. These studies have provided compelling evidence suggesting that adropin plays a pivotal role in enhancing systemic glucose homeostasis, as evidenced by improved glucose tolerance and enhanced insulin sensitivity upon administration of adropin in experimental models.

The mechanisms through which adropin modulates glucose metabolism are indeed multifaceted, reflecting its complex and versatile nature in metabolic regulation. One of the primary pathways through which adropin exerts its effects is by enhancing insulin signaling pathways, thereby promoting glucose uptake in skeletal muscle and adipose tissue [31]. Moreover, adropin has been shown to inhibit hepatic glucose production, contributing to its overall impact on glucose homeostasis [Fig. 2].

In addition to direct effects on glucose metabolism, adropin's interaction with other metabolic regulators further amplifies its influence. For instance, adropin has been found to interact with adiponectin, a key adipokine involved in metabolic regulation, and AMP-activated protein kinase (AMPK), a master regulator of energy balance [32]. These interactions contribute to adropin's ability to modulate glucose metabolism and enhance overall metabolic health [Fig. 3].

AdipoR2 is one of the receptors for adiponectin, primarily expressed in the liver and muscle tissues. The binding of adiponectin to AdipoR2 activates downstream signaling pathways. Although adropin does not directly bind to AdipoR2, it is suggested to modulate the adiponectin

Table 2
The role of adropin in metabolic regulation: Insights from human studies.

Study/Year	Study Design	Population/Ethnicity	Major Findings	Method	Limitation
Soltani S et al., 2023 [14]	Meta-Analysis	**Sample size:** 2813 Multiple populations (Various Ethnicities)	**Lower adropin** levels associated with metabolic syndrome across studies	Various	Variability in methodologies across included studies; potential publication bias; heterogeneity in population and study design
Vural A et al., 2023 [107]	Cross-Sectional	Patients with Insufficient CCC and with sufficient CCC **Sample size:** Insufficient: 41, sufficient: 43 (Turkey)	The levels of serum adropin in patients with insufficient CCC were significantly lower compared to those with well-developed CCC.	ELISA	The study's small patient sample requires larger groups to confirm the link between adropin and CCC. The short follow-up period means unknown long-term effects of high adropin levels. Additionally, CCC development is multifactorial, and data on factors like physical activity, pre-infarction angina, and genetics were not collected.
Wei W et al., 2022 [36]	Cross-Sectional	Patients with and without carotid plaque. **Sample size:** Without carotid plaque: 223, With carotid plaque: 280 (China)	A linear association was observed between carotid atherosclerotic plaque and serum adropin levels in their study populations. Specifically, the higher the serum adropin level, the lower the incidence of carotid atherosclerotic plaque.	ELISA	The study's cross-sectional design limited the ability to determine the causality between serum adropin levels and carotid atherosclerosis. Additionally, being a single-center study with a small patient sample, the findings need confirmation through larger, prospective studies, including nondiabetic populations.
Muhammed AA et al., 2022 [108]	Case-Control study	Patients with normal weight and obese **Sample Size:** Case: 43, Control: 40 (Egypt)	Adropin levels were significantly lower in obese men compared to those with normal weight. Adropin had a significant negative correlation with TC, TG, and LDL-c levels, but showed a significant positive correlation with HDL-c levels.	ELISA	This study included participants with thyroid conditions and noted age-related variations in adiponectin, adropin, and testosterone levels. Future research should investigate adropin's impact on testosterone levels, potentially using rat injections or tissue cultures. These methods were unavailable for this study.
Xu Chen et al., 2020 [109]	Cross-Sectional	Patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and NASH (China) **Sample Size**: Total:109 15 normal histological controls, 26 NAFL patients, 21 NASH patients, and 47 control	The serum adropin level in NASH patients was significantly lower than in B-ultrasound normal controls, histological normal controls, and NAFL patients. There was no significant difference in adropin levels between the controls and the NAFL patients.	ELISA	The study's cross-sectional design cannot establish causation, so future prospective cohort studies are required to investigate the link between serum adropin and NAFLD progression. Additionally, the small sample size needs validation from larger, independent liver biopsy NAFLD populations.
Ghoshal et al., 2018 [89]	Case-Control	**Sample Size**: Cases: 120, Controls: 100. Adults with and without T2D (India)	**Significantly lower adropin** levels in Type 2 Diabetes (T2D) patients compared to controls	ELISA	Single time-point measurement; potential for cross-reactivity; limited generalizability due to regional specificity
Wu et al., 2014 [37]	Case-Control	**Sample Size**: Cases: 241, Controls: 151. Non-Diabetic and Diabetic patients (China)	Decreased serum adropin pro-moted coronary atherosclerosis in all patients including diabetic and non-diabetic patients.	ELISA	It is a cross-sectional study, and a small population and differing baseline characteristics, including various medications, may impact results. Despite the statistical adjustment, some bias may remain. Additionally, further investigation is needed to clarify the exact cross-talk mechanism.
Celik et al., 2013 [97]	Cross-Sectional	**Sample Size**: Cases: 86, Controls: 86. CSX group and Control Group (Turkey)	The levels of serum adropin were significantly lower in patients with CSX compared to healthy subjects.	ELISA	The study was limited by the small number of CSX patients. Further research on the effects of adropin-based therapies in these patients is needed through large, long-term follow-up studies after adropin administration.
Butler et al., 2012 [99]	Observational Cross-Sectional	**Sample Size**: 60 (total). Obese and Non-obese Adults (USA)	**Lower adropin levels** in obese individuals; levels increased post-gastric bypass surgery. Obesity and aging are linked to lower levels of adropin in humans.	ELISA	This study faced limitations such as single time-point measurement, potential for cross-reactivity, and kit variability.

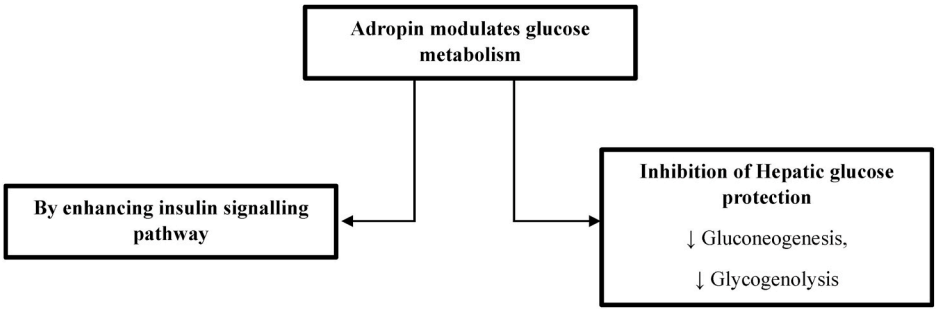

Fig. 2. Metabolic regulation of glucose by adropin.

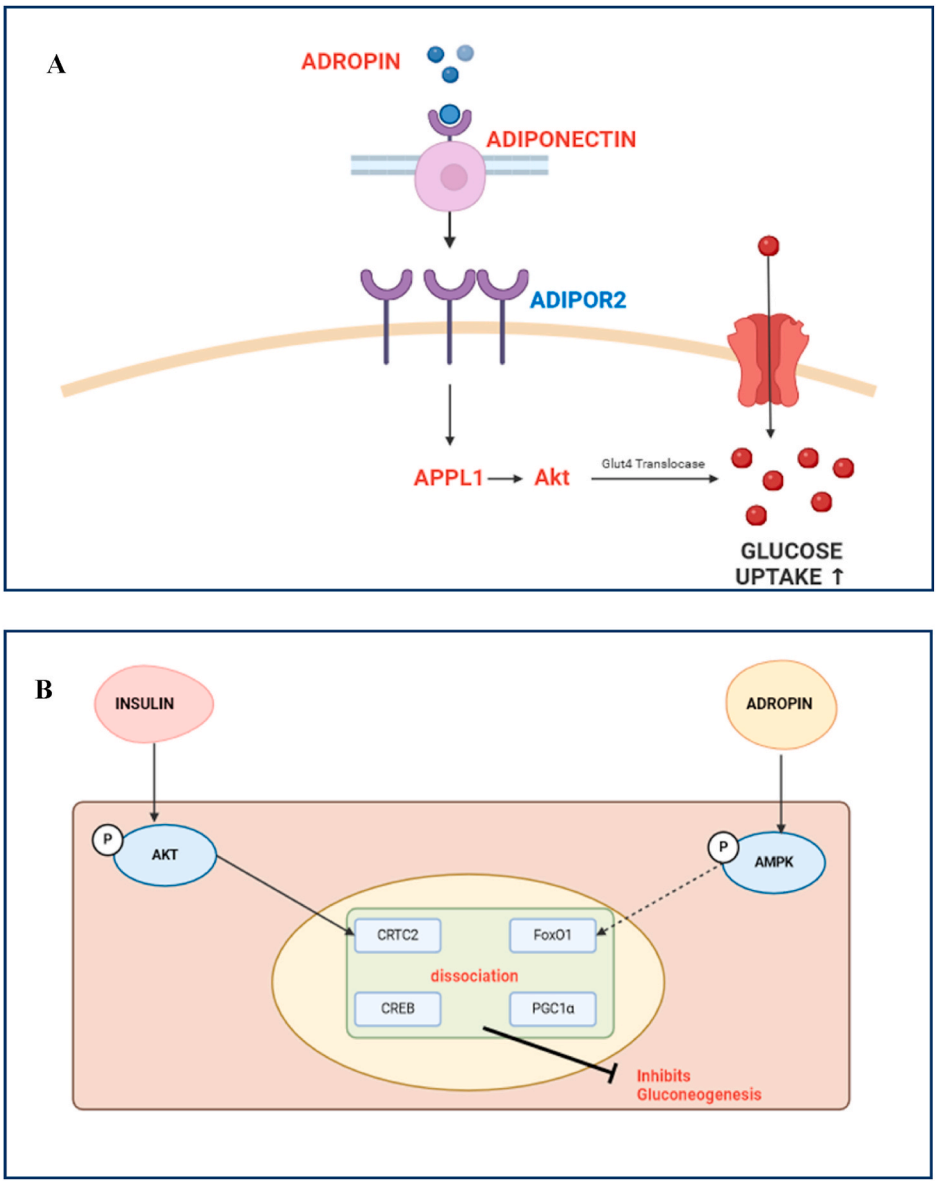

Fig. 3. Adropin interaction with metabolic regulators (A: Adropin interaction with adiponectin, b: Adropin interaction with AMP-activated protein kinase).

signaling pathway. The exact receptor for adropin has not been definitively identified, but it is believed to interact with membrane-bound proteins that can influence adiponectin signaling.

Furthermore, adropin expression is subject to regulation by various factors, further highlighting the complexity of its involvement in glucose metabolism. Studies have shown that nutrient status, metabolic disorders such as obesity and insulin resistance, as well as hormonal signaling pathways, can influence adropin levels [13,33]. For instance, alterations in adropin expression have been observed under conditions of fasting, high-fat diet intake, and hormonal imbalances, underscoring the dynamic regulation of adropin in response to metabolic cues.

During fasting, adropin levels decrease as part of a regulatory mechanism aimed at conserving energy and maintaining metabolic homeostasis [13]. High-fat diet intake significantly decreases adropin levels, potentially contributing to impaired metabolic functions and heightened susceptibility to metabolic disorders like obesity and insulin resistance, while hormonal imbalances in conditions such as metabolic syndrome and type 2 diabetes are associated with reduced adropin expression, underscoring its role in endocrine regulation and metabolic health [19].

2.2. *Role of adropin in lipid metabolism*

Adropin plays a pivotal role in modulating lipid synthesis pathways by inhibiting the activity of fatty acid synthase (FAS), a crucial enzyme involved in de novo lipogenesis [15]. This inhibition effectively reduces the conversion of excess carbohydrates into fatty acids and their storage as triglycerides, thereby decreasing lipid accumulation [13].

Furthermore, adropin promotes lipid oxidation by enhancing mitochondrial function [Fig. 4] [34]. Mitochondria, the cellular powerhouses responsible for energy generation, experience heightened functionality under the influence of adropin, leading to increased lipid oxidation and reduced lipid stores in tissues [35] (see Fig. 5).

Studies have shown that the administration of adropin results in reduced triglyceride levels [36,37]. Elevated triglyceride levels are associated with increased cardiovascular risk, making the reduction facilitated by adropin administration significant for improving overall lipid profiles and cardiovascular health. Moreover, adropin administration leads to an increase in high-density lipoprotein (HDL) cholesterol levels [36,37]. Higher HDL levels are beneficial as they are linked to a reduced risk of heart disease, further emphasizing the positive impact of

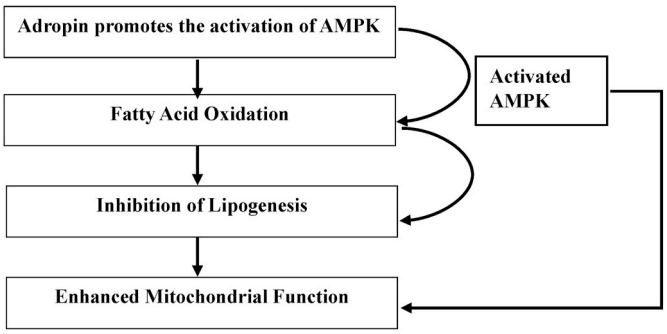

Fig. 4. Flowchart of adropin interaction with AMPK in Lipid homeostasis.

adropin on lipid metabolism and cardiovascular health.

In addition to its direct effects on lipid metabolism, adropin has been found to promote the activation of AMP-activated protein kinase (AMPK) [19]. AMPK is a key regulator of energy metabolism that helps maintain cellular energy balance. Activation of AMPK by adropin enhances lipid utilization by stimulating fatty acid oxidation while inhibiting lipogenesis, ultimately contributing to improved lipid metabolism.

Furthermore, adropin expression is influenced by nutrient status, with changes observed during fasting and high-fat diet intake [38]. This suggests that nutrient availability plays a role in regulating adropin expression, potentially linking adropin levels to different metabolic states. Additionally, hormonal regulation affects adropin expression, with key metabolic hormones such as insulin, leptin, and glucagon shown to modulate adropin levels [39,40]. This complex interplay between hormonal signaling and adropin expression underscores its importance in lipid metabolism regulation and metabolic homeostasis.

2.3. Role in energy homeostasis

Energy homeostasis is the intricate biological process that maintains a delicate equilibrium between energy intake, primarily from food consumption, and energy expenditure through various biosynthetic processes. This balance is crucial for sustaining overall metabolic health and stability over time [31].

The process of maintaining energy balance within the body involves many complex regulatory mechanisms that rely on interactions between different organs and physiological systems. The gastrointestinal tract (GI tract), pancreas, and liver are key players in this process, releasing hormones that communicate with specific parts of the central nervous system (CNS) to coordinate the intake, storage, and utilization of energy resources [41].

A comprehensive array of pivotal hormones are responsible for the intricate regulatory processes maintaining energy homeostasis. These hormones include ghrelin, gastric leptin, secretin, glucagon-like peptide 1 (produced within the gastric and intestinal regions), insulin, and glucagon (generated by the endocrine pancreas). Additionally, adipose tissue significantly contributes by releasing signals related to lipogenesis, storage, and lipolysis, thereby providing crucial input to the CNS for the regulation of energy balance [41]. - write it more academically like a medical research paper [41].

Carbohydrates and fatty acids serve as primary substrates utilized in oxidative metabolism, crucial for maintaining energy balance throughout feeding and fasting cycles. Notably, the hormone peptide adropin has emerged as a significant regulator in controlling substrate oxidation preferences. Initially associated with glucose regulation and fat metabolism, adropin's role has expanded to encompass the modulation of carbohydrate metabolism and overall energy balance regulation [13].

Studies by Kumar et al. have shed light on the regulation of adropin expression in the liver. They found that adropin expression is influenced by hormonal signals from leptin and the melanocortin receptor. Loss of function in these receptors, as seen in obese leptin knockout animals (Lep^{ob}/Lep^{ob}) and melanocortin 3 receptor knockout mice ($Mc3r^{-/-}$), led to downregulation of adropin expression, highlighting its interconnectedness with energy regulation pathways [13,42,43].

Furthermore, nutritional status plays a crucial role in modulating adropin expression. For instance, a high-fat diet initially boosted adropin mRNA expression in lean mice but led to lower expression in diet-induced obesity (DIO) mice over time, indicating metabolic disturbances in chronic obese conditions [13].

Notably, adropin's impact extends beyond lipid metabolism to include carbohydrate metabolism and overall energy balance. Transgenic mice overexpressing adropin and fed a high-fat diet exhibited improved glucose homeostasis and delayed onset of obesity, contrasting with the typical effects of high-fat diets on metabolic health [44–46].

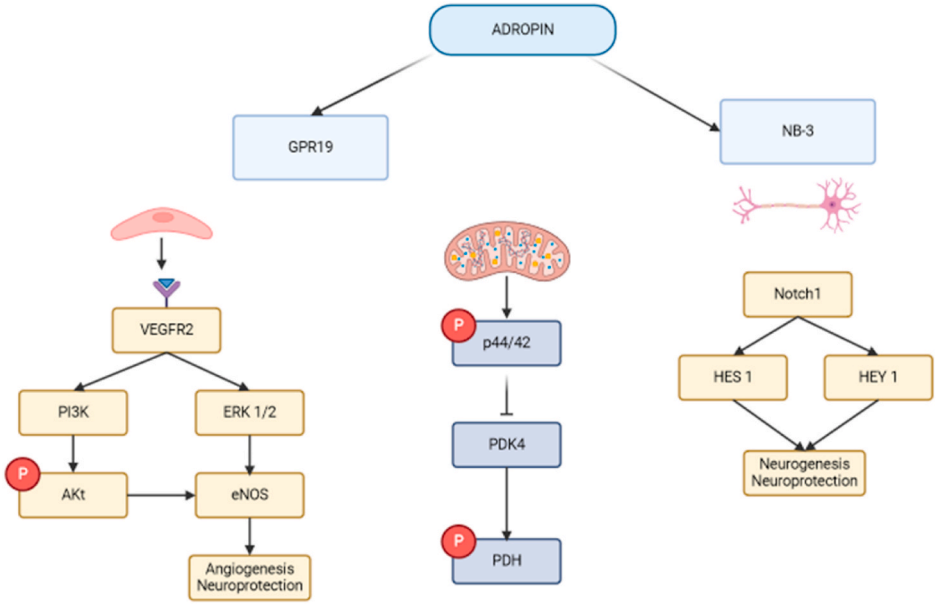

Fig. 5. Graphical Representation of the mechanism of Adropin in neurodegenerative diseases.

2.4. Neuroprotective role of adropin

The central nervous system (CNS) plays a crucial role in regulating various physiological processes, including energy homeostasis, cognitive function, mood regulation, and stress responses. Adropin receptors are expressed in key brain regions like the hypothalamus, hippocampus, and cortex, indicating their involvement in neural signaling and regulation [47].

Studies suggest that adropin has neuroprotective properties, as it can mitigate neuroinflammation, oxidative stress, and neuronal damage in preclinical models of neurodegenerative diseases such as Alzheimer's and Parkinson's disease [48].

Adropin interacts with GPR19, a G protein-coupled receptor, to initiate various physiological pathways crucial for cellular and systemic health. Through GPR19, adropin modulates signaling cascades such as VEGFR2, which plays a pivotal role in vascular endothelial growth and neuroprotection [49]. Activation of VEGFR2 promotes angiogenesis and supports neuroprotection, essential for maintaining vascular integrity and neurological function. Additionally, adropin influences the PI3K/Akt pathway, where PI3K activation triggers Akt signaling, promoting cell growth, survival, and angiogenesis. Adropin further activates the PI3K/Akt signaling pathway by phosphorylating Akt at Ser-473, promoting cell survival, growth, and proliferation. This pathway also influences downstream effectors like mTOR, crucial for processes such as angiogenesis and neuronal regeneration. Targeting this pathway, including Akt and mTOR, holds promise for therapeutic interventions in neurodegenerative and neuropsychiatric disorders, where Akt signaling defects are implicated [50,51].

In hypoxic conditions, adropin's effect on VEGFR2 contributes to angiogenesis and vascular remodeling, while VEGF activation via VEGFR2 plays a role in neurogenesis and neuroprotection, potentially benefiting vascular and neurological disorders [49].

Adropin interacts with NB-3 (Neuroblastoma Suppressor of Tumorigenicity 1), a receptor that plays a crucial role in adropin signaling pathways. Through NB-3, adropin influences Notch1 signaling, a pathway vital for cell differentiation and development. Upon activation, Notch1 signaling regulates the expression of transcription factors such as HES1 (Hairy and Enhancer of Split-1) and HEY1 (Hairy/Enhancer of Split Related with YRPW Motif Protein 1), which are essential for maintaining neural progenitor cells and promoting neuroprotection. This pathway supports neurogenesis by facilitating the formation of new neurons and contributes to neuroprotection by safeguarding neurons from damage, highlighting adropin's role in neural development and maintenance of neuronal health through NB-3-mediated signaling [52,53]. Through the p44/42 MAPK pathway, adropin regulates PDK4, which in turn affects PDH activity, crucial for mitochondrial energy metabolism.In animal models of Alzheimer's disease (AD), stimulation of the PI3K/Akt/Wnt/β-catenin pathway promotes neurogenesis and improves cognitive impairments [54]. Conversely, decreased phospho-Akt levels and increased FOXO3a levels in neuronal nuclei may lead to adipokine dyshomeostasis, oxidative stress, mitochondrial dysfunction, and neurodegeneration [55], highlighting Akt's crucial role in connecting insulin resistance, obesity, and AD pathogenesis.

In Parkinson's disease (PD), there's a selective loss of tyrosine hydroxylase dopaminergic neurons and reduced phosphorylated Akt at Ser-473 in the brain [56]. Glial cell line-derived neurotrophic factor (GDNF), a downstream target of phosphorylated Akt, exhibits neuroprotective effects against dopaminergic neurodegeneration [57].

Medications targeting the dopaminergic system via Akt activation or enhancing phosphorylated Akt levels have shown neuroprotective properties in PD [56–59]. Adropin, with its ability to activate Akt and target the dopaminergic system, holds promise as a potential treatment for PD.

2.5. Role of adropin in pancreatic function

The gastrointestinal tract (GI tract) and pancreas communicate hormonal signals to the central nervous system, which plays a crucial role in regulating energy balance and pancreatic function. Adropin, previously investigated for its involvement in lipid and carbohydrate metabolism, is now gaining attention for its role in pancreatic control. Its levels are influenced by dietary fat intake and fasting, and it is expressed in various tissues, including the GI tract and pancreas [60,61].

Studies examining adropin levels in diabetes have yielded conflicting results, with some studies reporting increases while others indicate reductions. Furthermore, the impact of adropin on insulin levels varies depending on the experimental conditions, highlighting the complex interplay in metabolic regulation [62].

Recent research has uncovered that adropin can modulate pancreatic exocrine processes, leading to a reduction in pancreatic juice output and enzyme activity in a dose-dependent manner. This effect is observed both under normal conditions and when stimulated with cholecystokinin (CCK-8). Adropin's mechanism of suppressing pancreatic exocrine function involves the duodenal CCK–vagal pathway, as evidenced by experiments involving vagal stimulation and the absence of responses following vagotomy and deafferentation [63].

Given that chronic inflammation is a significant contributor to pancreatic diseases like pancreatitis and pancreatic cancer, adropin's anti-inflammatory properties are of particular interest. Its potential to mitigate inflammation in the pancreas may contribute to a reduced risk of pancreatic disorders [64].

3. Mechanism of adropin in cardiovascular protection

3.1. Endothelial function and NO production

Adropin plays a crucial role in regulating arterial nitric oxide (NO) release by modulating the phosphorylation of endothelial nitric oxide synthase (eNOS) through the activation of VEGFR2 (vascular endothelial growth factor receptor 2) and its downstream signaling pathways, including Akt (protein kinase B) and ERK1/2 (extracellular signal-regulated kinase 1/2). When VEGFR2, Akt, or NOS (nitric oxide synthase) is inhibited, adropin-induced vasorelaxation is significantly reduced, indicating the importance of these pathways in mediating adropin's effects on vascular function [21,65–67].

Akt, a crucial factor in NO generation and endothelial function, is known to modulate eNOS phosphorylation. Studies have demonstrated that adropin may raise arterial adropin levels, VEGFR2 protein expression, and Akt phosphorylation, leading to higher eNOS activity and NO generation [68,69] (see Figure 6). Interestingly, although adropin and aerobic activity training (AT) has been found to increase vasodilatory function and decrease oxidative stress, the particular mechanisms behind these benefits are not entirely known.

Oxidative stress, which affects vascular NO bioavailability and leads to endothelial dysfunction, is known to rise with age. However, aerobic exercise training has been proven to attenuate age-related increases in oxidative stress indicators such as TBARS (thiobarbituric acid reactive substances) [70]. Adropin has been involved in exerting antioxidant properties, and its levels may be changed by aerobic exercise training [71].

In the setting of adropin-induced vasodilation, NOS inhibition dramatically diminishes this impact, showing the participation of the Akt-eNOS signaling pathway. However, adropin-induced vasodilation may potentially include additional mechanisms beyond NO production, which need more exploration for a thorough understanding [72].

3.2. Adropin and arterial stiffness

Arterial stiffness, a critical factor in cardiovascular health, is influenced by various factors such as collagen deposition, cross-linking, and

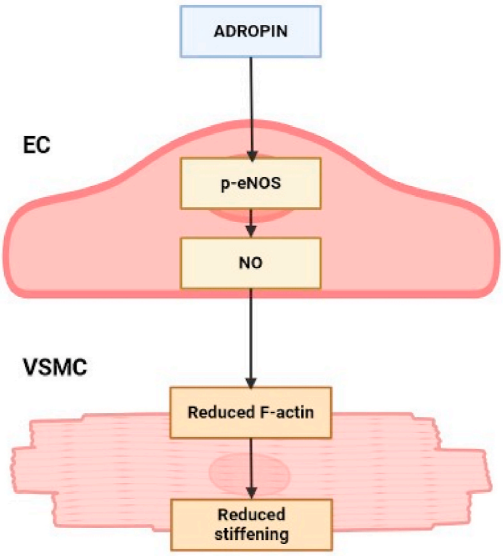

Fig. 6. Adropin-induced nitric oxide (NO) generation in endothelial cells (EC) enhances vascular smooth muscle cell (VSMC) actin depolymerization and decreased stiffness.

cytoskeletal actin polymerization. While collagen has long been recognized for its role in arterial stiffness, recent research emphasizes the importance of actin dynamics in cellular stiffness and its broader impact on arterial health. Adropin, a metabolic regulatory protein, emerges as a significant regulator of arterial stiffness through its effects on actin depolymerization and endothelial nitric oxide (NO) production [73].

Studies conducted on db/db mouse models and endothelial cells demonstrate that adropin administration leads to a notable reduction in F-actin stress fibers, indicating a destiffening effect at the cellular level [74]. This decrease in actin polymerization correlates with reduced cellular stiffness, as confirmed by atomic force microscopy (AFM) measurements. Critically, these destiffening effects of adropin rely on NO signaling, as they are reversed by inhibiting nitric oxide synthase (NOS) [75].

The mechanism behind adropin-induced actin depolymerization and cellular destiffening involves a series of events. Adropin's action on endothelial cells enhances NO production, subsequently triggering NO signaling in smooth muscle cells. This NO-mediated signaling pathway in smooth muscle cells leads to actin depolymerization and decreased cellular stiffness, ultimately contributing to the destiffening of the entire artery [76].

This process involves key players such as LIMK (LIM domain kinase), cofilin, and NO signaling pathways. Inhibiting LIMK prevents actin depolymerization induced by NO mimetics while stimulating actin polymerization counters the destiffening effects. These findings highlight the intricate interplay between NO signaling, actin dynamics, and cellular stiffness, with adropin serving as a pivotal regulator in this complex regulatory network [77].

3.3. Adropin and oxidative stress

Adropin exhibits significant antioxidative stress properties, which are crucial for maintaining cellular health and preventing various diseases. Research has demonstrated that adropin deficiency is associated with elevated oxidative stress, particularly linked to endothelial dysfunction in the brain of rats. This oxidative stress can lead to cellular damage and dysfunction [78].

One of the mechanisms through which adropin exerts its antioxidative effects is by activating ERK 1/2 (extracellular signal-regulated kinase 1/2) through VEGFR2 (vascular endothelial growth factor receptor 2). Activation of ERK 1/2, in turn, induces the nuclear factor erythroid 2-related factor 2 (Nrf2), a key regulator of cellular antioxidative responses. Nrf2 activation leads to the expression of antioxidant enzymes, ultimately protecting neurons and other cells from oxidative stress-induced damage [79] (see Figure 7). Inhibition of ERK 1/2, on the other hand, can impair DNA repair mechanisms, accelerate cell apoptosis, and contribute to neuronal loss [80].

Furthermore, adropin's antioxidative stress effect is linked to its immune-regulatory function. In conditions such as nonalcoholic steatohepatitis (NASH), adropin activates the Nrf2 signaling pathway, reducing reactive oxygen species (ROS) production from liver mitochondria. By protecting mitochondrial function, adropin helps alleviate oxidative stress and apoptosis, thereby safeguarding against liver injury and preventing the progression of NASH [81].

Excessive production of reactive oxygen species can also trigger inflammation. Studies have indicated that increased oxidative stress in fatty liver conditions can lead to the apoptosis of regulatory T cells (Tregs), resulting in reduced hepatic Treg numbers and diminished suppression of inflammatory responses. This process occurs due to elevated fatty acid metabolism, leading to heightened mitochondrial respiratory activity and excessive mitochondrial ROS production in the liver. The reduction in bcl-2 expression in Tregs due to oxidative stress selectively affects this subpopulation of T lymphocytes, contributing to inflammation [82–84].

3.4. Adropin and cardiac energy and metabolism

The study undertaken by Butler et al. and other investigations emphasized the possible involvement of adropin in regulating energy metabolism, especially in heart muscle. Cardiomyocytes, which are crucial for heart function, mostly depend on fatty acids for energy synthesis. However, adropin has been demonstrated to modify cardiac substrate metabolism and enhance cardiac efficiency, indicating its therapeutic significance in metabolic diseases affecting the heart [34].

Thapa et al. studied the effects of adropin on myocardial substrate metabolism in mice exposed to a high-fat diet. They showed that adropin therapy restored myocardial glucose oxidation by boosting pyruvate dehydrogenase (PDH) activity, a crucial enzyme involved in glucose use. This impact was linked to lower inhibitory lysine acetylation of PDH, accomplished by reducing the expression of the mitochondrial acetyltransferase GCN5L1. As a consequence, adropin enabled enhanced myocardial glucose consumption in diet-induced obese (DIO) mice in vivo [85].

In a comparable study by Altamimi et al., the impact of adropin on cardiac energy metabolism, insulin signaling, and cardiac efficiency was examined ex vivo. Adropin therapy was reported to increase ex vivo cardiac performance and efficiency, coupled by greater inhibition of fatty acid oxidation (FAO) by insulin. Additionally, adropin enhanced the activation of cardiac insulin signaling pathways via MAPK and FOXO1 signaling. This activation cascade, beginning by adropin binding to its probable receptor GPR19, led to lower levels of pyruvate dehydrogenase kinase 4 (PDK4) protein and enhanced PDH activity, eventually increasing glucose oxidation and consumption [86].

The combined results show that adropin plays a vital role in increasing myocardial glucose metabolism while suppressing fatty acid oxidation, a balance that is good for heart function and efficiency. By targeting critical enzymes and communication pathways involved in energy metabolism and insulin sensitivity, adropin shows potential as a therapeutic treatment for metabolic diseases affecting the heart, particularly in situations characterized by poor glucose utilization and increased fatty acid oxidation [87].

3.5. Adropin and circadian rhythm

Recent research indicates that adropin levels in human plasma exhibit a circadian rhythm, characterized by fluctuating levels

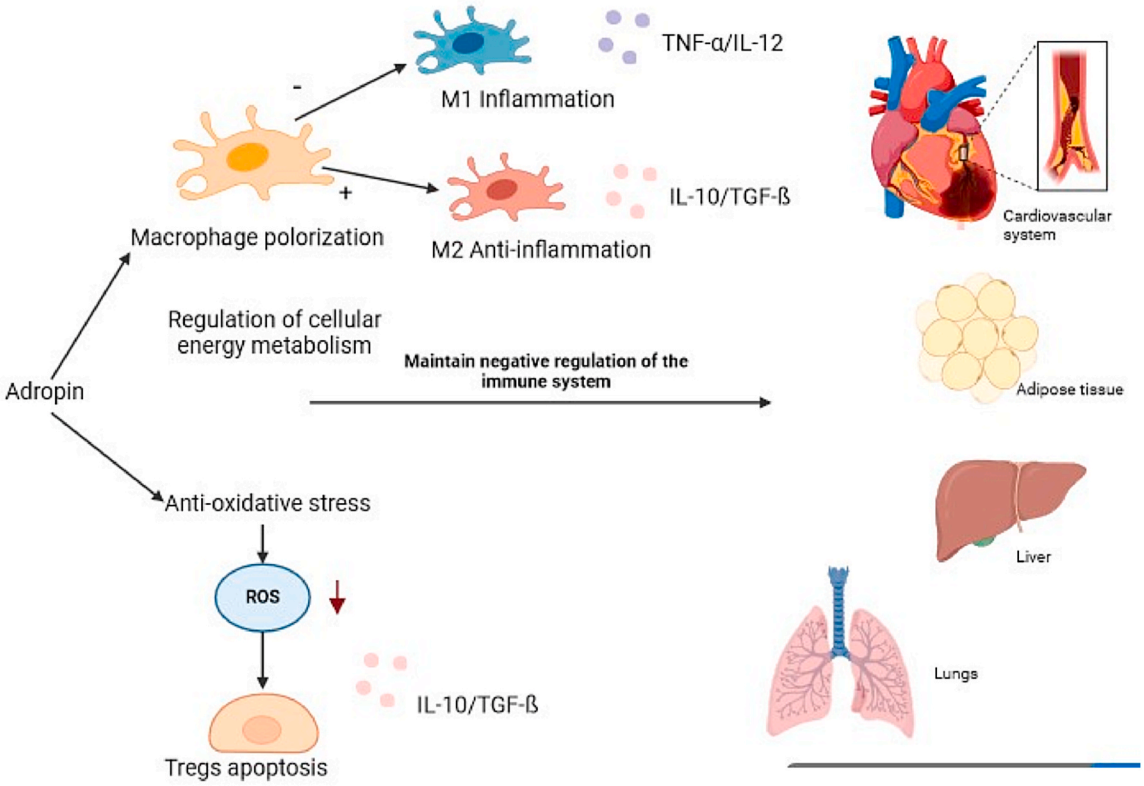

Fig. 7. Adropin serves an anti-inflammatory function in a range of tissues.

throughout the day in a predictable pattern. Specifically, a study by Banerjee S et al. (2020) observed higher adropin levels in the evening compared to the morning, suggesting a role in coordinating metabolic processes with the body's internal clock [88]. This diurnal variation implies that adropin may influence energy balance and nutrient utilization over the course of the day. Furthermore, adropin's interactions with other metabolic hormones and its impact on glucose and lipid metabolism underscore the significance of its circadian regulation [89].

3.6. Role of adropin in sexual development

Recent studies highlight adropin's involvement in sexual development and reproductive functions. It regulates gonadal function and hormone production, potentially impacting reproductive capabilities. Adropin levels show sexual dimorphism, varying between sexes and fluctuating across the estrous cycle in female rodents, suggesting a role in reproductive physiology. It also influences LH and FSH levels, crucial for menstrual cycle regulation and reproductive health. Additionally, adropin's role in energy balance implies it may indirectly influence puberty onset. This interplay between metabolic and reproductive systems underscores adropin's broader significance in sexual development and function, offering insights into potential therapeutic applications in fertility and metabolic disorders [90].

3.7. Role of adropin in fibrosis and systemic sclerosis

Adropin shows great potential for treating fibrosis and systemic sclerosis (SSc). This is due to its multifaceted effects on inflammation, regulation of fibrotic pathways, vascular health, and metabolic regulation. Firstly, adropin's proven anti-inflammatory properties are vital in reducing the chronic inflammation that leads to fibrosis in SSc. By affecting inflammatory pathways, adropin could potentially lessen the inflammatory response that contributes to the remodeling of fibrotic tissue [91].

Adropin regulates fibrotic pathways by influencing the expression of key fibrogenic cytokines and growth factors such as TGF-β. It also improves endothelial function and reduces vascular inflammation, which are critical in alleviating vascular abnormalities associated with SSc and impacting fibrosis progression.

When considering adropin's potential for therapy, increasing its levels or replicating its actions could have several benefits in SSc and other fibrotic diseases. These benefits include reducing inflammation, inhibiting fibrotic signaling pathways, improving endothelial function, and correcting metabolic abnormalities associated with fibrosis [92].

Recent research, including preclinical studies in animal models of fibrosis, supports these potential therapeutic effects. For example, in models of liver fibrosis, increasing adropin levels led to reduced collagen deposition and decreased expression of fibrotic markers. Although direct clinical evidence specific to SSc is limited, studies in humans have shown that adropin levels are altered in metabolic and cardiovascular diseases, which share common inflammatory and fibrotic pathways with SSc [93].

4. Association of adropin with cardiovascular risk factors

4.1. Hypertension

The study conducted by Gu et al. revealed a significant decrease in plasma adropin levels among individuals with hypertension compared to healthy controls. Moreover, a clear negative correlation was observed between declining adropin levels and elevated blood pressure in hypertensive individuals, suggesting a potential link between adropin and blood pressure regulation [94].

Several studies have demonstrated that adropin has protective effects on endothelial function in various conditions, including obstructive sleep apnea, cardiac syndrome X, and type 2 diabetes [95–97]. One of the mechanisms through which adropin exerts its protective actions on endothelial health is by upregulating endothelial nitric oxide synthase

(eNOS), leading to increased production of nitric oxide (NO). This increase in NO production promotes vasodilation and contributes to improved vascular function.

The vasodilatory effect of nitric oxide is a well-known mechanism involved in blood pressure regulation. Besides, paracrine and neuroendocrine factors play crucial roles in modulating blood pressure by influencing metabolic balance, energy utilization, and endothelial health. Among these factors, adropin has emerged as a multifaceted regulator, impacting insulin sensitivity, endothelial function, and the nervous system, particularly in hypertension (HT).

Recent investigations have highlighted the relationship between adropin and endothelin-1 (ET-1) in individuals with HT [94]. ET-1 is recognized for its vasoconstrictive properties and its role in endothelial dysfunction, contributing to elevated systolic blood pressure. The inverse correlation between plasma adropin levels and ET-1 levels suggests a potential regulatory role of adropin in endothelial function and blood pressure control.

Moreover, adropin's ability to enhance endothelial function has been consistently demonstrated in various studies [95]. This indicates that adropin may influence blood pressure regulation by positively impacting endothelial health, thereby counteracting the vasoconstrictive effects associated with elevated ET-1 levels in HT. These findings underscore the intricate interplay among different regulatory factors in blood pressure modulation, with adropin emerging as a promising target for further investigation in HT management.

4.2. Obesity

Several research have studied the association between adropin levels and obesity, giving information on its physiological activities and consequences in metabolic diseases [98].

One of the important discoveries in studies associating adropin to obesity is its negative connection with body mass index (BMI) and adiposity. Multiple investigations have consistently revealed reduced circulating adropin levels in obese persons compared to lean counterparts. This inverse connection shows that adropin may have a regulatory function in adipose tissue metabolism and energy balance [28].

Adropin's influence on adipose tissue goes beyond its relationship with BMI. It has been hypothesized that adropin may alter adipocyte development, lipid metabolism, and insulin sensitivity. Experimental investigations in animal models have indicated that adropin administration may attenuate diet-induced obesity and increase insulin sensitivity, indicating a possible treatment pathway for obesity-related metabolic diseases [98].

Furthermore, adropin has been linked in the control of lipid metabolism. It is believed that adropin may limit lipogenesis while boosting fatty acid oxidation in adipocytes and other organs. These actions lead to a shift towards a more favorable lipid profile and enhanced metabolic health.

The mechanisms behind adropin's activities in obesity are currently under research. It is suspected that adropin may exert its effects via multiple signaling pathways, including AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma (PPARγ), and sirtuin 1 (SIRT1). These pathways are important in energy balance, glucose metabolism, and lipid control, illustrating the diverse nature of adropin's physiological roles [95,99].

4.3. Diabetes mellitus

Several research have studied the association between adropin and diabetes, offering insight on its physiological roles and possible treatment implications.

One of the important discoveries in studies associating adropin to diabetes is its connection with insulin sensitivity. Multiple studies have found reduced circulating adropin levels in persons with type 2 diabetes mellitus (T2DM) compared to healthy controls. This inverse connection shows that adropin may have a function in altering insulin sensitivity and glucose metabolism [100].

Experimental research in animal models have offered insights into the processes behind adropin's impact on diabetes. Adropin treatment has been demonstrated to increase insulin sensitivity, glucose tolerance, and decrease hyperglycemia in diabetic mice. These effects are hypothesized to be mediated via several signaling pathways, including AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma (PPARγ), which are implicated in glucose absorption, insulin signaling, and energy metabolism [101].

Furthermore, adropin has been linked to the control of pancreatic function and beta-cell health. Beta cells are important for insulin synthesis, and their malfunction leads to the development and progression of diabetes. Studies reveal that adropin may protect beta cells from oxidative damage, apoptosis, and inflammation, hence maintaining their function and boosting insulin production [102].

In addition to its direct effects on insulin sensitivity and pancreatic function, adropin may indirectly alter lipid metabolism and cardiovascular health, which are strongly connected to diabetic problems. Some research has shown that adropin treatment may improve lipid profiles, minimize atherosclerosis, and protect against cardiovascular problems in diabetic animal models [64].

5. Adropin as biomarker for cardiovascular disease

Adropin's diagnostic and predictive value as a serum biomarker has been primarily elucidated by studies examining its correlation with heart-related conditions, including heart failure (HF), coronary artery disease (CAD), acute myocardial infarction (AMI), and Cardiac Syndrome X (CSX) [97,103].

Numerous investigations conducted in different populations, including studies from Turkey and China, have consistently shown significant differences in plasma adropin levels between patients with heart disease and healthy individuals. Low adropin levels have been identified as an independent predictor of heart disease across various studies, emphasizing the potential importance of adropin in cardiovascular health assessment [104–106].

In the context of heart failure, investigations have shown a link between adropin levels and heart failure severity. Individuals with more severe stages of heart failure had higher plasma adropin levels than those with less severe forms of the disease, suggesting that adropin may be used as a biomarker to determine the severity of heart failure [103,105].

Similar results have been frequently seen in patients with diseases such stable angina pectoris (SAP), angina pectoris (AMI), CSX, and stable coronary artery disease (SCAD) when compared to controls. Reduced adropin levels have been associated to an increased risk or severity of disease, and have been proposed as a predictive biomarker for these disorders [106].

Furthermore, Studies have investigated the relationship between adropin and the severity of coronary atherosclerosis using scoring systems like Gensini, Friesinger, and SYNTAX. The findings indicate that lower levels of adropin in the bloodstream are inversely correlated with higher severity scores, suggesting that adropin could potentially predict the progression of coronary atherosclerosis independently [37]. Moreover, adropin has shown predictive value in specific post-surgical complications, such as Saphenous Vein Graft Disease (SVGD) following coronary artery bypass grafting (CABG). Lower serum adropin levels were associated with an increased risk of SVGD, highlighting its potential as a prognostic marker in post-operative cardiac care [103].

6. Conclusion

Adropin is a crucial factor in maintaining cardiovascular health and regulating metabolism. It has a cardiovascular protective role and influences metabolic homeostasis, making it a promising target for

treating cardiovascular diseases and metabolic disorders. Further exploration of mechanisms of action of adropin, therapeutic potential, and it's clinical applications will advance our knowledge of human physiology and help in developing targeted interventions to improve health outcomes.

CRediT authorship contribution statement

S. Rooban: Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **K.A. Arul Senghor:** Writing – review & editing, Validation, Supervision, Formal analysis. **V.M. Vinodhini:** Writing – review & editing, Validation, Supervision, Formal analysis. **J. S. Kumar:** Writing – review & editing, Validation, Formal analysis.

Declaration of competing interest

During the preparation of this work, the author(s) used Quillbot in order to improve writing language. After using quillbot, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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