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THE IMPACT OF APELIN LIGAND BINDING ON APJ RECEPTOR ON THE VARIOUS PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS OF METABOLISM and HOMEOSTASIS

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ABSTRACT

Apelin is identified as an endogenous ligand of the apelin receptor (APJ). APJ is a member of the G protein-coupled receptor family. The apelinergic system; apelin and its receptor APJ; are expressed in a wide variety of tissues including the heart, the kidneys and the lungs. Apelin is also synthesised and released by the adipocytes as an adipokine which has an important impact in obesity, glucose metabolism and energy homeostasis. Apelin and the APJ are also expressed in the hypothalamo- hypophysial system for regulation of fluid homeostasis and in the hypothalamo-hypophysial- adrenal axis for stress control. Their interaction may have relevant pathophysiologic effects in those tissues. In this review we have presented the structure, and regulation of apelin and its receptor. We have also explained the various roles played by apelin in human physiology, homeostasis and its probable involvement in the pathogenesis of high prevalent diseases such as hypertension, heart failure, Diabetes Mellitus Type 2, obesity, fluid imbalance, anxiety and depression. This involvement ranked it as a target for various therapeutic implications.

KEYWORDS: Apelin, APJ receptor (APJR), G Protein Coupled Receptors (GPCRs), Inotropic effect, vasodilator effect.

INTRODUCTION

History and discovery

The APJ receptor

In 1993, O'Dowd et al characterized a 700 base pair fragment by using polymerase chain reaction (PCR). A detailed analysis revealed a number of similarities with trans-membrane domains gene sequences of G protein-coupled membrane receptors (GPCRs). The codified protein had 380 amino acids and was named APJ[1]

High similarity between APJ receptor and Angiotensin II type 1 (AT-1) receptor was recognized as there is high resemblance in the tissue expression of both receptors, also 115 amino acid (AA) which form 30% of the total sequence and 86 AA which constitute 54% of the AA in the trans-membrane regions are similar in both receptors. However, apelin, an endogenous ligand of the APJ receptor, does not bind to AT-1 receptor, nor angiotensin II (Ang II) binds to APJ.[2] This receptor – the APJ (APJR or APLNR) – was kept "orphan" until 1998, when Tatemoto et al[3] identified a selective endogenous ligand, and named it Apelin or APLN. Earlier studies have demonstrated that the apelinergic system (Apelin and its receptor) are widely expressed all over the body. It is widely expressed in various organs such as the heart, lungs, kidneys, liver, adipose tissues, gastrointestinal tract, brain, adrenal glands, endothelium, and also the human plasma.[3]

Apelin was thought to be the only ligand for APJ until recently, a short secretory peptide was discovered by two research groups who worked independently. This peptide was called Elabela (ELA)10 by one group and Toddler11 by the other group. Through well-designed genetics studies using the zebrafish model system, both teams have demonstrated that ELA signaling is required for normal heart and vasculature development. ELA deficiency leads to severe defects in heart development and lymphogenesis. Remarkably, the ELA mutant phenotype is similar to the APJ mutants in zebrafish and therefore suggests that ELA and APJ are genetically in the same biological pathway. Definitely, ELA binds and activates APJ, establishing that ELA is the ligand of APJ required for normal cardiac development in zebrafish.[4]

Localization and physiological functions of the APJ

Apelin receptor mRNA is expressed at high levels in the lungs, heart, adipose tissue, kidney, spleen and in certain brain areas. At the cellular level, apelin signaling participates in cell relaxation (as with the smooth muscle cell) or contraction (as with the cardiomyocyte), migration and proliferation; at the physiological level, it

plays a role in the central and peripheral regulation of the cardiovascular system (actually, apelin is among the most potent molecules enhancing cardiac contractility), in the control of body fluid homeostasis (apelin inhibits vasopressin secretion), in drinking behaviour, food intake and, possibly, in the function of the gastrointestinal tract and the immune system.[5]

Regulation of Activity and Mechanism of action

Binding of apelin peptides promotes a conformational change of the apelin receptor leading to activation of its associated G protein, where it induces GDP dissociation and GTP binding. As in the case of other GPCR, exposure of the receptor to apelin fragments results in a rapid internalisation of 50% of the receptors within 10 minutes.[6] The APJ is suggested to couple to a $G_{i/o}$ protein and upon stimulation based on the initial experiments showing that forskolin –stimulated cAMP production is suppressed by apelin-13.[3] This coupling which was supported by the inability of (pyr1) apelin -13 and apelin-36 to generate Ca^{++} mobilization or to release arachidonic acid metabolites into cells expressing the human APJ leads to the positive or negative regulation of various intracellular effectors. Intracellular cascades triggered by apelin include series of changes leading to inhibition of cyclic AMP formation, inhibition of adenylcyclase, increase of intracellular calcium and activation of extracellular signal-regulated kinases (ERKs), PI-3K and Akt.[6,7]

The APJ molecule exists in 9 states (or forms), there are 8 transitions between these states and it has 3 receptor functions: ALX40-4C: Antagonist, ApR-G2: Apelin13 Agonist and ApR-G2: Apelin36 Agonist[3]

Interactions with Ligands and Other Proteins

The gene encoding the endogenous ligand(s) corresponds to a signal peptide containing a preproprotein of 77 amino acids, the maturation of the proprotein could potentially generate several endogenous peptides of various sizes, such as apelin (42-77), named apelin 36, apelin (61-77), named apelin 17, or apelin (65-77), named apelin 13. Gel filtration chromatography of extracts from different tissues has clearly shown that there are two predominant apelin peptides corresponding to the (42-77) fragment and the (65-77) fragment.

Both fragments interact with a single class of high-affinity binding sites in tissues, suggesting the existence of only one apelin receptor. Mutational analysis has revealed that the N-terminal domain of the apelin receptor plays a critical role in ligand binding.[6]

Regulation of Concentration

Considerable variation in the amounts of apelin receptor mRNA is observed in various physiological situations. Marked increase in the number of receptor transcripts is observed during formation of the retinal vessels, this is followed by a decrease during the next steps of vessel maturation.

Acute and repeated stress leads to up-regulation of apelin receptor mRNA expression.

Also up-regulation of apelin receptors occurs at the transcriptional level as their expression can be turned on rapidly. Down-regulation of the receptor occurs by internalisation which is a process by which the cell surface receptors are taken up into the endocytic vesicles to the lysosome. The receptor will either be degraded or brought back to cell membrane where it is again able to interact with its ligand. This process leads to decreasing the number of receptors expressed on the cell surface.[8]

APELIN

DISCOVERY

The APJ receptor was kept orphan until 1998, when Tatemoto et al[3] isolated a 36-amino acids (A.A) peptide from bovine stomach extracts, and they named it apelin. The peptide induced extracellular acidification and inhibited cAMP formation in a cell line of Chinese hamster ovaries that expressed the APJ receptor. High homology was found between the different species in pre-proapelin protein sequence, namely in the 23 AA in terminal C. It was proved that the 65-77 C-terminal fragment of apelinergic peptides is key to bind to APJ receptor and to its biological activity, whereas N-terminal plays a key role in modulating ligand-receptor interaction.[3]

APELIN ISOFORMS

Apelin gene encodes a pre-proprotein of 77 amino acids, with a signal peptide in the N-terminal region. After translocation into the endoplasmic reticulum and cleavage of the signal peptide, the proprotein of 55 amino acids may generate several active fragments. The first studies on apelin identified different isoforms which are thought to exist *in vivo*:

1- Apelin-36 (apelin42-77)
2- Apelin-17 (apelin61-77)
3- Apelin-13 (apelin65-77)
4- Apelin-13 in its pyroglutaminated form [(Pyr1) apelin-13], which has N-terminal glutamate acids identical in both peptides. The N-terminal Pyr1 of (Pyr1) apelin-13 differs from the prepropeptide sequence as a result of post-translational modification.[2,4]

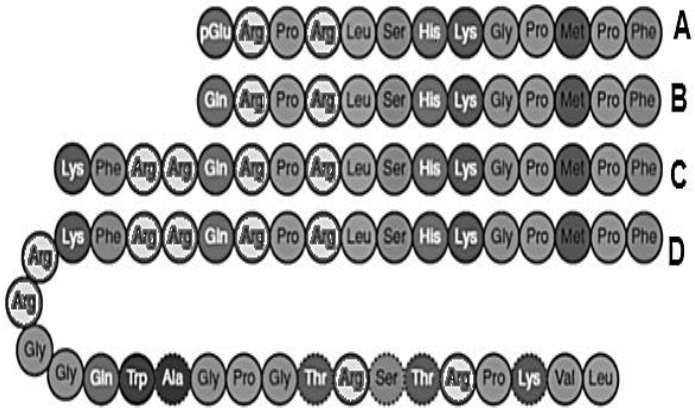

Figure.1 Amino acid sequences of (A) (Pyr[1]) apelin-13 (B) apelin-13 (C) apelin 17 (D) apelin 36

It is currently thought that Apelin-36 acts as a precursor, with limited biological activity; it undergoes proteolysis and post-translational changes to produce the more biologically active peptides, mainly (Pyr1) Apelin-13, in which the pyroglutamination preserves the biological function and prevents enzyme degradation.[2,4]

A possible APJ receptor antagonist is produced by substituting the C- terminal phenylalanine in apelin-13 with an alanine residue. The resulting peptide prevents the hypotensive action of apelin-13 in rats in a dose dependant manner.[2]

The distribution of the Apelinergic system

The early studies that characterized apelin tissue distribution were conducted in rats' tissues, and evidenced the presence of its pre-propeptide in a wide variety of tissues.[4,8,9&10] In humans, pre-proapelin mRNA is abundant in the CNS and in the placenta, as well as in moderate amounts in the kidneys, the lungs and the mammary glands.[9]

Apelin is biologically active in the cardiac tissues, the APJ receptor is found in the endothelial cells of small intramyocardial vessels, in coronary arteries, in endocardial endothelium cells, and in vascular smooth muscle cells. Surprisingly, APJ immunoreactivity follows a transversally striated pattern in cardiomyocytes, thus indicating the co-localization of receptor with the T-tubules. The proximity of the receptor and its ligand, together with the evidence for local vascular apelin synthesis, suggests an important role for APJ/apelin as a paracrine cardiovascular regulator system.[2]

Apelin is also present in the endothelial cells of the renal, pulmonary and adrenal vessels.[2] In endothelial cells, apelin is not found in Weibel-Palade bodies (which are vesicles resulting from induced endothelial peptide secretion) but it is localized to the secretory vesicles of the Golgi complex and the endoplasmic reticulum. This suggests that the synthesis of apelin occurs via the constitutive pathway.[2]

An enzyme immunoassay estimated the concentration of circulating apelin in humans to be between 3 and 4 ng/mL. This is a low concentration if compared to that of other circulating hormones. However, it is comparable to endothelium-derived vasoactive mediators, which suggests endothelial release of apelin.[11]

The enzyme carboxypeptidase Angiotensin Converting Enzyme 2 (ACE2) plays a role in apelin degradation through rapid cleavage of the C- terminal phenylalanine from the apelinergic peptides. This explained the marked importance of apelin in cardiovascular regulation since ACE2 is involved in the renin-angiotensin-aldosterone system, suggesting a therapeutic value in major cardiovascular pathologies.[2]

PHYSIOLOGICAL ACTIONS OF APELIN

Both apelin and APJ are widely distributed throughout the body, with apelin plasma concentrations much lower than tissue concentrations, suggesting that apelin works in an autocrine or paracrine manner.

I- CARDOVASCULAR EFFECTS

The role for apelin and the APJ in the regulation of the cardiovascular system was suggested by the observation of widespread distribution of mRNA encoding both receptor and ligand in human and rat tissues particularly the heart and blood vessels where the levels of APJ mRNA expression were reported to be especially high.[9,10] The same is true for the receptor ligand apelin which is expressed at high levels in endothelial cells from human large conduit vessels. The discovery of apelin receptors in the human and rat heart and the media of human large conduit vessels using receptor autoradiography suggested a role for apelin /APJ in cardiovascular regulation. This concept is supported by the presence of substantial amounts of apelin in both rat endothelial cells and in endothelial cells throughout the human vasculature, including small resistance vessels

and large conduit arteries and veins.[9,10] Also it is supported by a previous study which proved an impaired heart contractility in apelin gene-deficient mice associated with aging and pressure overload[12]

Apelin displays several activities on the cardiovascular system as it is involved in fluid homeostasis, blood pressure control and cardiac contractility. It is a potent inotrope, vasodilator and diuretic with crucial cardioprotective effects against angiotensin and aldosterone insults.[2,9-20]

Recently, apelin was proved to be essential for cardiomyogenic differentiation of mesenchymal stem cells via activating extracellular signal-regulated kinase (ERK) 1/2 and 5[14]

Also a recent study showed that the Apelin /APJ system could be a novel promising therapy target for thrombotic diseases.[15]

A) Effects on the heart

Apelin has a positive inotropic effect *in vivo* in normal rat hearts also in failing rat hearts following myocardial infarction. Apelin may be used as an acute inotropic agent in patients with ischemic heart failure. Acute apelin administration in humans causes peripheral and coronary vasodilatation and increases cardiac output. APJ agonism represents a novel potential therapeutic target for patients with heart failure. Hemodynamic studies in mice have demonstrated that the administration of apelin reduces left ventricle preload and afterload. Apelin increases the cardiac output, with no evidence of hypertrophy.[16]

Used as an exogenous vasoactive agent, apelin showed a unique combination of inotropic and vasodilatory properties, this effect leads to a rise of cardiac output and to a decrease of systemic vascular resistance without significant arterial hypotension or tachycardia. This is an additional evidence about the importance of apelin and its receptor in the development of heart failure and the potential favorable effect of treatment with exogenous apelin in patients with systolic dysfunction.[17] A previous study showed that plasma apelin levels were decreased in human heart failure patients.[17] However, another study showed that plasma apelin levels increase during the early stages of heart failure before decreasing late in the disease, suggesting that the apelin–APJ system is engaged to support the failing heart in mild to moderate left ventricular dysfunction. This positive inotropic action on the failing myocardium was suggested by the authers to be due to a transient increase of Ca^{2+}.[18]

Mechanism of inotropic actions of apelin

Apelin does not work via adrenergic pathways, because both ß-And α adrenergic receptor antagonism, as well as inhibition of myocardial nitric oxide synthetase (NOS) and endothelin receptor antagonism, had no effect on the apelin-induced increase in cardiac contraction and the developed tension. While Inhibition of phospholipase C, protein kinase C, the sarcolemmal Na^+/H^+ exchanger, and the reverse mode sarcolemmal Na^+/Ca^+ exchanger all significantly suppress the effects of apelin. The inotropic effects of apelin may be caused by Na^+/H^+ exchanger-mediated intracellular alkalinization and sensitization of cardiac myofilaments to intracellular Ca^{++}, as well as to Na^+/H^+ exchanger-mediated accumulation of intracellular Na^+ that indirectly increases intracellular Ca^{++} via the reverse mode Na^+/Ca^+ exchanger.[19]

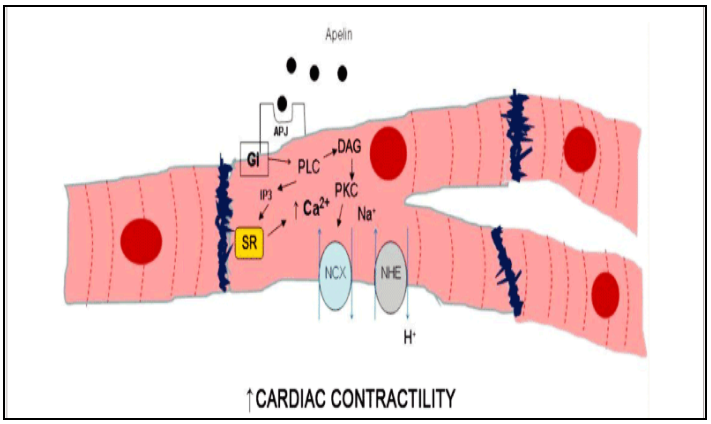

Figure 2. Binding of Apelin to the APJ receptors leads to an increase in the intracellular calcium and is the basis of the positive inotropic effect of apelin.[2] DAG- Diacylglycerol, Gi-inhibitory G protein, IP3- Inositol Triphosphate, NCX- Na^+/Ca^{2+} Exchanger, NHE- Na^+/ H^+ Exchanger, PKC- Protein Kinase C, PLC- Phospholipase C, SR- Sarcoplasmic Reticulum.

Other actions of Apelin on the Heart

1. Endogenous apelin-APJ signaling plays a role in maintaining basal cardiac function in adult mice with a more importantl role during conditions of stress. In addition, an autocrine pathway seems to exist in myocardial cells, the antagonism of which reduces cellular contraction without change in calcium transient.[20]

Apelin therapy in rats with isoprenalin-induced lesions promotes the restoration of cardiac function, and is also cardioprotective against lipid peroxidation.[21]
Apelin may also be involved in the pathophysiology of cardiovascular diseases secondary to chronic renal failure; this may have a potentioal therapeutic value as a treatment approach for uremic cardiomyopathy.[2]

2. Apelin levels are reduced in patients with isolated atrial fibrillation, so the serum concentration of that peptide may be used as a risk index for this arrhythmia before the development of any clinical manifestations.[2,22]
3. Apelin may be used as a diagnostic marker to distinguish the dyspnea from pulmonary causes from that of cardiovascular cause.[23]
4. Centrally, ICV injection of the active form of apelin (apelin 13) in rats leads to a dose dependant increase in the arterial blood pressure and heart rate. Pre-treatment with angiotentin II type 1 receptor (AT 1) antagonist did not alter the apelin induced increase in blood pressure. However the peripheral effects of apelin are relatively weaker if compared to its central effects.[24] However, pre-treatment of cardiac fibroblasts with Apelin-13 (1–100 nmol/l) inhibited angiotensin II-mediated cardiac fibrosis, collagen production and activation of connective tissue growth factor (CTGF) and transforming growth factor (TGF)-β.[25]

B) Effects on the blood vessels

1- Vasodilator effect

Apelin causes endothelium-dependent vasodilatation by triggering the release of vasodilators, such as nitric oxide (NO), from endothelial cells[2,16,24&30] Apelin mediates phosphorylation and activation of endothelial nitric oxide synthase (eNOS) in isolated wild-type mouse endothelial cells, causing NO release from endothelial cells. NO, in turn, activates soluble guanylate cyclase in vascular smooth muscle cells, resulting in increased levels of cyclic guanosin monophosphate (cGMP) which mediate dilation of vascular smooth muscle cells. On the other hand, apelin induced activation of eNOS was not observed in endothelial cells from apelin receptor-deficient mice, proofing that apelin acts on APJ. Thus, in the absence of a functional endothelium, apelin may directly activate APJ on vascular smooth muscle to cause vasoconstriction[16] (Fig. 3).

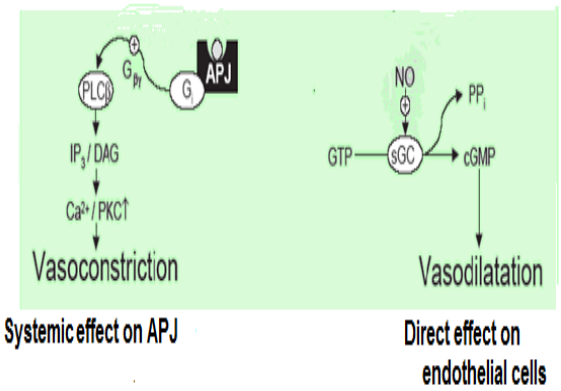

Figure: 3. Suggested mechanism of action on blood vessles by systemic or endothelial apelin. cAMP: cyclic adenosine monophosphate, cGMP: cyclic guanosine monophosphate, Cit: citrulline, DAG: diacylglycerol, GTP: guanosine triphosphate, IP3: inositole 3,4,5 trisphosphate, NO: nitric oxide, PKC: protein kinase C, PLC: phospholipase C, PPi: pyrophosphate, rER: rough endoplasmic reticulum, sGC: soluble guanylate cyclase, uTFa: unidentified transcription factor (active), uTFi, unidentified transcription factor (inactive).

However, another study on blood pressure showed conclusive evidence that apelin-induced cardiovascular actions are mediated by APJ has been proved by the decrease in mean arterial blood pressure (MABP) after an intravenous infusion of apelin-13 into wild-type mice, while the infusion of the peptide into APJ-deficient knockout mice did not result in alterations of cardiovascular parameters. Hypotensive actions observed in wild-type mice were completely abolished by pretreatment with nitric oxide synthase inhibitor, in agreement with the previous findings suggesting the presence of an endothelium-dependent mechanism that mediates hypotensive apelin actions in rats.The 2 different apelin isoforms, apelin-36 and (Pyr^1) apelin-13, caused a rapid onset of vasodilation.[16] Apelin-36 exhibits a much slower dissociation from the APJ receptor than (Pyr^1) apelin-13 and causes prolonged biological activity, however the shorter apelin peptides (apelin 13) have more potent depressor activity in rats.[16]

2- Vasoconstrictor effect

In humans, however, the only functional study of cardiovascular apelin actions reported potent vasoconstrictor actions of apelin in endothelium denuded isolated saphenous vein. The observed vasoconstriction most likely represents an immediate effect on vascular smooth muscle in the absence of functional endothelium.[26]

3- Angiogenesis

Apelin is a powerful stimulator of blood vessel growth and endothelial cell proliferation. This angiogenic activity is a result of apelin action on the proliferation and migration of the endothelial cells.[2,9] Hypoxia-induced apelin expression regulates endothelial cell

proliferation and regenerative angiogenesis. Apelin activates inside the cell transduction cascades (ERKs, Akt and p70S6 kinase phosphorylation, which lead to the proliferation of endothelial cells and the formation of new blood vessels.[2,9,27]

Apelin and APJ are expressed during formation of retinal vessels and knockout of apelin gene is associated with a delay in the development of the retinal vasculature. Apelin is required for the normal vascular pattern of the frog embryo. In addition, a variety of in vivo and in vitro assays demonstrate that apelin is a powerful stimulator of blood vessel growth and endothelial cell proliferation.[27]

II- THE EFFECTS ON HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

The apelinergic system has a widespread expression in the central nervous system (CNS) including the paraventricular nucleus, supraoptic nucleus and median eminence, and isolated cells of the anterior lobe of the pituitary[2,9&28] This pattern of expression in hypothalamic nuclei known to contain corticotrophin-releasing factor (CRF) and vasopressin (ADH) and to coordinate endocrine responses to stress, has generated interest in a role for apelin in the modulation of stress, perhaps via the regulation of hormone release from the pituitary. Emerging data confirm that the *in vivo* effects of apelin on hypothalamic–pituitary–adrenal neuroendocrine function appear to be mediated through both CRF- and ADH-dependent mechanisms. Apelin administration increases ACTH and cortisone serum levels while decreasing prolactin, FSH, and LH levels within 30 minutes after infusion.[28]

Fluid Homeostasis

Neurons of supraopticus and paraventricular nuclei play a considerable role in the physiological regulation of fluid homeostasis. Apart from the production of oxytocin, these neurons also produce vasopressin (ADH). Axonal transport translocates ADH to the posterior pituitary, where it is released in response to osmotic stimuli sensed by hypothalamic neurons to regulate water and sodium uptake in the kidney as well as vascular tone. Immunocytochemistry detected apelin-LI in the neurons expressing ADH mRNA, suggesting a role for apelin/APJ in the regulation of fluid homeostasis. Functional evidence supporting this concept is provided by a study showing that both apelin-13 and apelin- 17 induced a decrease in circulating plasma ADH levels and water intake after ICV administration. Intraperitoneal administration in rats resulted in an increase in water consumption over the first 60 min postinjection, these different effects may be explained by the different route of apelin administration.[29]

However, another study showed an increased water intake observed after the ICV administration of apelin-13 in rats. This may be clarified by differences in the time frame of observations.[30]

Apelin and arginine-vasopressin (AVP) show antagonistic effect in the regulation of body fluid and osmotic homeostasis, in a recent study it was found that in pateints with polyurea polydepsia syndrome, normal plasma apelin to copeptin ratio indicates a normal water homeostasis while in patients with central or nephrogenic diabetes Insipidus the increasd or decreased apelin to copeptin ratio, respectively, reflects a disturbed osmotic and body fluid homeostasis.[32]

III- ENDOCRINAL EFFECTS, DIABETES AND OBESITY

1- Apelin is one of the adipokines released from adipocytes. These adipokines (including leptin, adiponectin, resistin and others) are described to be regulated during the onset of obesity or diabetes.[33] Adipokines are also involved in physiological regulations (as fat development, energy storage, metabolism, eating behavior and food intake) or in the development of obesity-associated disorders (as type 2 diabetes and cardiovascular dysfunctions). Due to the large mass of adipose tissue during obesity, the quantitative importance of these adipokines in the control of biological functions is of major interest.[33] Apelin controls food intake and a positive correlation exists between plasma apelin levels and the body mass index as it is known for leptin.[34]

2- A strong relationship exists between adipocyte-secreted apelin and insulin. Both adipocyte apelin mRNA levels and plasma apelin concentration are increased in various mouse models of obesity associated with hyperinsulinemia[32] Accordingly, adipocytes of insulin-deficient mice (streptozotocin-treated) had lower apelin mRNA levels. Physiological variations of insulin by exposing mice to fasting/ refeeding sequence were followed by a dramatic reduction of adipocyte apelin mRNA level during fasting while refeeding restores apelin expression to that found in fed animals.[35]

The metabolic responses due to ICV administration of apelin- 13 are diminished in diet induced obese rats fed on high fat diet. High-fat diet induced an up-regulation of the expression of the APJ receptor, while ICV of apelin induced a down-regulation of the receptor, but only in the diet induced obese animals on the high-fat diet. So there is a diminished CNS response to apelin with obesity.[31]

3- However, intraperitoneal administration of apelin in normal and obese mice reduced body adiposity without affecting food intake, reduced insulin, leptin and triglycerides level, increased adiponectin levels, increased the expression of uncoupling proteins (UCP), and reduced respiratory quotient.[33]

4- Apelin is necessary for the maintenance of insulin sensitivity. Acute intravenous injection of apelin has a powerful glucose-lowering effect associated with enhanced glucose utilization in skeletal muscles and

adipose tissues.[37] These effects on glucose uptake and AKt phosphorylation may be mediated by a G_i and AMPK- activated protein kinase dependant pathway. Apelin restored glucose tolerance and increased glucose utilization in obese insulin resistant mice. So, apelin could represent a promising target in the management of insulin resistance.[37]

5- A significant positive correlation exists between apelin and TNFα expression in adipose tissue from lean or obese subjects. As obesity and insulin resistance are associated with chronically elevated levels of both insulin and TNFα, the relationship between TNFα production and apelin adipocyte expression suggests a synergistic role between them in the onset of obesity-associated disorders such as chronic adipose inflammation and subsequently insulin resistance[38]

6- Apelin may also play a relevant role in regulating cardiovascular function in diabetes condition: diabetic mice treated with apelin reported increased vasodilating response to acetylcholine through PI3K/Akt/eNOS pathway.[39]

7- Islet apelin expression is negatively regulated by glucocorticoids, and upregulated in T2D animals. The presence of apelin receptors in islets suggests a role for apelin as a paracrine or autocrine messenger within the islets[40]

OTHER FUNCTIONS OF APELIN

The hepatic effects of apelin

The endogenous apelin system is also involved in the pathogenesis of the hepatic remodeling, cardiovascular and renal complications occurring in advanced liver disease. Apelin was highly expressed by hepatic stellate cells, whereas apelin receptor was over-expressed in the hepatic parenchyma of animals with cirrhosis. Rats with cirrhosis treated with the apelin receptor antagonist showed diminished hepatic fibrosis and vessel density, improved cardiovascular performance, and renal function and lost ascites. Human patients with cirrhosis also showed a marked increase in apelin levels. The selective hepatic activation of the apelin system, together with the drop in fibrosis and neoangiogenesis and the improvement in cardiovascular and excretory function resulting from apelin receptor blockade, points to the hepatic apelin system as a novel therapeutic target in liver disease.[41]

Apelin suppresses apoptosis of human osteoblasts.

Apelin stimulates the proliferation of osteoblasts and inhibits apoptosis. This action is mediated via the APJ/PI-3 kinase/Akt signaling pathway. Also apelin protects against the apoptosis induced by the glucocorticoid dexamethasone. In the future, it may be used as a therapeutic support for some bone diseases.[42]

Apelin/APJ and human immunodeficiency virus

The APJ receptor is a co-receptor for the entry of HIV in host's cells. Apelin was shown to inhibit the infection of CD4+ and APJ+ cells, with efficacy being higher in heavier isoforms. It was found that apelin-36 is more efficient in blocking HIV infection in APJ-positive cells, while shorter isoforms seem to be more powerful in their cardiovascular action.[2]

Antidepressant effect

The localization of APJ in limbic structures suggests a potential role for apelin in emotional processes. It was proved that apelin-13 exerts antidepressant-like and recognition memory improving activities through activating PI3K and ERK1/2 signaling pathways in stressed rats.[43]

Apelin and preeclampsia

Recently, apelin has been suggested as a novel therapeutic target in preeclampsia due to the reno-protective effects of **(Pyr1)-Apelin-13.**[44,45]

CONCLOSION

The distribution of the apelin peptides and receptor are widespread in the central nervous system and periphery, with reported roles in the hypothalamic-pituitary- adrenal axis, blood pressure regulation and as one of the most potent positive inotropic substances yet identified.

Apelin has been also involved in the regulation of fluid homeostasis, vessel formation and cell proliferation. It also contributes in glucose homeostasis, insulin secretion, food intake and body adiposity. Apelin has an emerging role in HIV, liver and bone pathology. However, Future work is still needed to clarify these actions. The identification of the major naturally occurring ligands for the APJ receptor as well as their pharmacological characterization will facilitate the development of specific receptor agonists and antagonists.

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