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Apelin and insulin resistance: another arrow for the quiver?

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Abstract

Apelin is a newly discovered peptide hormone which has recently been linked to insulin resistance and obesity. Collected data from both the clinical and basic research settings show that apelin (1) correlates with states of insulin resistance and obesity, (2) stimulates glucose utilization, (3) decreases insulin secretion, and (4) negatively regulates catecholamine-mediated lipolysis. These and other lines of evidence demonstrate that apelin may be a potentially viable candidate in the search for treatments for type 2 diabetes and the insulin resistance (metabolic syndrome). This review will summarize the literature to date on apelin's regulation of glucose and lipid metabolism and the signaling pathways

Introduction

Insulin resistance, defined as a decreased responsiveness to insulin, is a cardinal feature of type 2 diabetes mellitus (T2DM) and the metabolic syndrome. Given the prevalence of these conditions, restoration of insulin sensitivity has long been a focus of drug development over time. Sadly, despite the advancement of several effective medical therapies for insulin resistance, the successful deployment of these medications has been greatly outpaced by the staggering burden of morbidity and mortality inherent in the metabolic syndrome and T2DM worldwide. It is thus clear that the introduction of novel therapeutic modalities (i.e. arrows for the quiver) would be greatly welcomed by patients and caregivers.

In recent years, a number of adipocyte-derived regulatory hormones, termed adipokines, have become a focus of scientific inquiry. One of these adipokines, apelin, was initially discovered in 1998. In the 13 years since its identification, apelin has been found to exert a wide variety of biologically diverse actions in various organs. Additionally, consistent with its identity as an adipokine, it has become increasingly appreciated that apelin regulates insulin sensitivity. Despite a growing body of literature, however, research into apelin's function in insulin resistance and its underlying mechanisms remains relatively nascent. The goal of this review is thus to summarize the current literature and highlight gaps in our knowledge about apelin's relationship with insulin resistance.

Insulin resistance

Insulin resistance is a pathological condition in which a biological unit, be it a cell, tissue, organ, or organism, becomes less responsive to insulin. Insulin resistance is the pathophysiologic hallmark of T2DM, which accounts for about 90% to 95% of the estimated 26 million adult diabetics in the United States. Although T2DM is not particularly

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consequential in the short term, it is independently and strongly associated with an increased risk of heart disease, stroke, kidney failure, amputations, blindness, and mortality[1]. In addition to those with T2DM, insulin resistance also affects the estimated 79 million US adults with the so-called metabolic syndrome (Syndrome X)[2]. While the metabolic syndrome is felt to be a precursor to T2DM, it is also not without sequelae; for example, it is independently associated with cardiovascular mortality[3] and multiple types of cancer[4–7]. Insulin resistance is thus rapidly gaining in importance as a disease entity in the Western world. Unfortunately, while multiple treatment modalities have been developed, our current therapeutic armamentarium is inadequate to effectively manage the burden of the disease. A clear need for novel therapies therefore exists.

Apelin

Apelin is a recently discovered endogenous peptide hormone which has garnered significant investigative attention during the last decade. Apelin was first isolated from bovine stomach extracts[8] in a drug screen searching for endogenous ligands for a previously orphaned G protein coupled receptor named angiotensin-like receptor 1 (Agtrl1), or APJ (which itself was discovered in a search for isotypes of the vasopression receptor)[9]. APJ bears significant sequence homology to the type 1 angiotensin receptor[9], and is known to associate with the heterotrimeric G proteins G_i[10] and G_q[11]. At this time APJ is the only known receptor for apelin.

The human gene APLN is located on chromosome Xq25-26.1[12]. Its gene product is a 77-amino acid prepropeptide, that is subsequently cleaved post-translationally into several active forms, which are 36, 17, 13, and 12 residues in length[8]. Of these, the 36-amino acid isoform is the most widely expressed in different organs, including adipocytes, gastric mucosa, and endothelia of small arteries[13]. Nonetheless, the shorter isoforms (especially pyroglutamated apelin-13) are thought to induce a greater vasoactive response[13], though it has recently been suggested that apelin-36 possesses equal potency to pyr-apelin-13[14]. Though little is known about its metabolism *in vivo*, apelin is cleaved by the exopeptidase angiotensin converting enzyme 2 (ACE2)[15] under experimental conditions. While further efforts to characterize its pharmacodynamics have been hindered by lack of a robust, widely available diagnostic assay[16], apelin is believed to be rapidly cleared from the circulation with a half-life of no longer than 5 minutes[17].

Apelin has been demonstrated to have multiple unique effects in several organs and tissues, including the brain, heart, gut, and kidney (for review see 18). In contrast to APJ, which is expressed ubiquitously[19], apelin is secreted predominantly from endothelial cells[20]. This tissue distribution has led to the hypothesis that apelin exerts its actions in a paracrine fashion. More recently, both apelin[21, 22] and APJ[23] have also been found to be present in adipocytes. As such, an endocrine role for apelin (as an adipokine) has been proposed[24], though this contention awaits further clarification.

The association between apelin and insulin resistance: clinical evidence

Consistent with its putative role as an adipokine, apelin has been linked to states of insulin resistance in recent years. In clinical studies, compared to normal controls, plasma apelin concentration is increased in insulin resistant subjects[25], as well as in morbidly obese individuals with T2DM[26, 27]. When considered as a continuous variable, apelin also has been found to correlate positively with hemoglobin A1c (HbA1c)[28]. Notably, some recent reports have shown that plasma apelin levels are paradoxically decreased in newly diagnosed patients with T2DM[29, 30]. While it is difficult to reconcile these divergent findings, these data do suggest the possibility of alternative regulatory pathways for apelin production in the setting of insulin resistance.

At present, few genomic studies assessing for variants in the APLN and AGTRL1 genes have been published. To date, most recognized single nucleotide polymorphisms (SNPs) have been found to correlate with stroke[31], heart failure[32] and systemic hypertension[33–36]. That said, a recent study reported that male diabetics carrying the C allele of a SNP, rs2235306, in the APLN gene had a significantly increased fasting glucose level relative to those carrying the T allele[37]. However, this finding was not observed in females, and other measures of insulin sensitivity (e.g. 2 hour oral glucose tolerance test, fasting insulin, homeostatic model assessment-IR) showed no correlation, raising the possibility of a spurious result. Nevertheless, interest in identifying and assessing the significance of genetic variants in apelin and APJ related to insulin resistance remains high.

The association between apelin and insulin resistance: basic evidence

The clinical evidence demonstrating apelin's association with insulin resistance has also been borne out in the laboratory setting. Early research building on the observation that apelin and APJ were expressed in adipocytes reported that apelin secretion is regulated by insulin[21, 22], suggesting that apelin's correlation with insulin resistance was due to hyperinsulinemia. Lending further support to this possibility was the demonstration that apelin was downregulated in mice treated with the beta cell toxin streptozotocin[22]. Interestingly, glucose-stimulated pancreatic secretion of insulin is decreased in the presence of apelin, consistent with a negative feedback loop[38, 39].

Subsequent investigation has elucidated apelin's direct effect on glucose handling and insulin sensitivity. Direct injection of apelin in mice is sufficient to improve glucose handling as measured by a glucose tolerance test[40, 41]. Apelin has also been demonstrated to increase glucose uptake in isolated soleus muscle[41], cultured skeletal myotubes[42], and adipose tissue[43]. Mice with a generalized deficiency of apelin also have abnormal insulin tolerance and insulin suppression tests, are hyperinsulinemic, and have decreased adiponectin levels, suggesting a primary effect on insulin sensitivity[42]. Moreover, exogenous apelin administration results in reversal of these abnormalities. These data indicate that apelin directly increases insulin sensitivity and suggest that the elevations in circulating apelin observed in states of insulin resistance are compensatory.

Apelin and insulin signaling: mechanistic insights

The insights gained from exploring apelin's effects on insulin-glucose homeostasis have led to further investigation regarding the underlying mechanisms responsible for these effects. Thus far, G_i-, G_q- and AMPK-mediated pathways have been implicated in apelin's regulation of glucose uptake (Figure 1).

As discussed above, apelin binds to APJ, a G protein coupled receptor. Shortly after its discovery APJ was found to couple with the heterotrimeric G protein G_i[10]. Accordingly, it has been shown that pertussis toxin (a potent G_i inhibitor) inhibits apelin-stimulated glucose uptake and Akt phosphorylation[42], confirming that a G_i-mediated pathway participates in apelin's control of glucose uptake. While further signaling events downstream of G_i are not well characterized, it has long been appreciated that G_i is involved in the regulation of glucose uptake. For example, hepatocyte- and adipocyte-specific deletion of G_i results in insulin resistance[44], whereas hepatocyte-, adipocyte-, and myocyte-specific overexpression results in improved insulin sensitivity[45].

In addition to G_i, it is also believed that APJ couples to G_q. Consistent with this, apelin has been demonstrated to increase accumulation of inositide triphosphate (IP_3)[46]. Additionally, inhibition of G_q-dependent entities, such as phospholipase C, protein kinase C, and the sarcolemmal Na^+/H^+ and Na^+/Ca^{2+} exchangers, has been demonstrated to block apelin-

mediated contraction in isolated hearts[11]. Finally, three-dimensional modeling of APJ using a hidden Markov algorithm predicts a strong likelihood of coupling to G_q[47]. Taken together, these data strongly suggest that apelin activates G_q via its interaction with APJ. Whether apelin-mediated glucose uptake is dependent on G_q, however, remains undetermined.

Apelin's effects on glucose uptake have also been shown to involve the energy sensing enzyme AMP-activated protein kinase (AMPK), which is well known to mediate the metabolic response to intracellular ATP depletion (for review see 48). Apelin is known to activate AMPK, and inhibition of AMPK activity, be it pharmacologic, genetic, or molecular, results in the abrogation of apelin-induced glucose uptake[41, 42]. The signaling events connecting APJ with AMPK have yet to be fully elucidated, though the likelihood of a G_i-mediated mechanism is lessened by the well established G_s/cAMP/PKA-mediated activation of AMPK[49, 50]. Interestingly, a signaling cascade involving phospholipase C, IP_3, and Ca^{2+} release (a classic G_q response) was recently implicated in adiponectin-mediated AMPK activation[51]. Also, as with signaling proximal to AMPK, the distal pathways germane to apelin/APJ are not well understood. However, inactivation of AMPK has been shown to inhibit apelin-mediated Akt phosphorylation[41, 42], suggesting the involvement of the latter.

An area of controversy concerns the relationship between apelin/APJ and canonical insulin signal transduction. It is clear that apelin stimulates several components of the insulin pathway, including phosphoinositol 3-kinase (PI3K)[52] and Akt[41, 42]. However, it is less certain whether apelin potentiates insulin-mediated glucose uptake. It has been shown that apelin increases insulin-stimulated glucose uptake in soleus muscles and white adipose tissue[41]. The authors of this paper postulated that apelin's effects were mediated by AMPK in a pathway also involving endothelial nitric oxide synthase (eNOS). Work in our laboratory, however, has not verified a similar effect in cultured skeletal myotubes[42]. While a definitive explanation for these discrepant results has not been advanced, the former study was conducted in the *ex vivo* setting, whereas our research was conducted *in vitro*. It is therefore possible that in *ex vivo* circumstances apelin may secondarily influence a process external to the target cell (e.g. eNOS activity) to produce the observed effects on insulin-mediated glucose uptake (and ultimately, insulin sensitivity).

While the APJ-AMPK-eNOS pathway represents the best-studied putative explanation for apelin's effects on insulin sensitivity, other possibilities exist. For example, apelin has been shown to inhibit NF-κB expression by triggering an interaction between APJ and the type I angiotensin receptor[53]. NF-κB downregulation would, in turn, be expected to inhibit TNF-α-mediated insulin resistance. Further support for this mechanism comes from a recent report demonstrating an apelin-mediated improvement in insulin-mediated glucose uptake in cultured adipocytes[54]. Apelin has also been noted to reduce the production of inflammatory mediators other than NF-κB, including reactive oxygen species[55], interleukin-6, and monocyte chemoattractant protein-1 (MCP1)[56]. Ultimately, it is likely that apelin's salutary effects on insulin sensitivity occur via multiple pathways. Full elucidation of these pathways, as well as their significance relative to each other, awaits further research.

The effect of apelin on adiposity and fatty acid handling

Given its relationship with insulin resistance, it should come as no surprise that apelin is also associated with states of obesity. In clinical studies, compared to normal controls, plasma apelin concentration is increased in morbidly obese patients[57], and a reduction of body weight results in a coincident decline in apelin expression[58]. Apelin also correlates positively with body mass index (BMI)[57]. In animal studies, apelin supplementation decreased white adipose tissue mass and body adiposity in obese mice fed with a high-fat

diet[40]. Additionally, apelin null mice were found to have increased abdominal adiposity and epididymal fat weight; these changes were reversed with apelin infusion via osmotic pumps[46].

Notably, obesity is associated with increased circulating free fatty acids (FFAs), and in turn, insulin resistance[2]. In fact, it is believed that increased FFAs, in part, underlie the pathogenesis of insulin resistance. For example, increases in circulating FFAs invariably result in diminished insulin sensitivity[59–61]. Furthermore, pharmacologically lowering FFAs is known to increase insulin sensitivity[62]. While the mechanism for this phenomenon has not been definitively established, it is believed that the link involves intracellular lipid accumulation, subsequent inactivation of glycolysis and glucose uptake, and buildup of toxic metabolites, including diacylglycerol and ceramide[63].

Consistent with this framework, apelin null mice have an increased concentration of plasma FFAs[46]. Moreover, administration of apelin decreases circulating FFAs. In exploring possible etiologies for these findings, potential mechanisms can broadly be classified into two groups: (1) those that decrease FA entry into the circulation (i.e. “supply”), and (2) those that increase FA utilization (i.e. “demand”).

On the supply side, many research groups have looked into caloric intake. Unfortunately, apelin’s impact on this parameter is controversial, as investigators have separately reported an increase[64], a decrease[65], or no change[28, 40] in food intake in various settings. The reasons these discrepant results may lie in the animal model chosen, the method of administration, and the chronicity of administration, all of which were different between the studies. Apelin’s effects on lipolysis (the catecholamine-mediated hydrolysis of triglycerides to FFAs in adipocytes) have also been investigated. In isolated murine adipocytes, as well as in cultured 3T3L1 cells, apelin has been shown to inhibit isoproterenol-induced FFA release in an AMPK, G_i, and G_q-dependent fashion[46]. In this study, apelin’s actions were found to be associated with a reduction in stimulatory phosphorylation of the triglyceride hydrolase hormone sensitive lipase (HSL) at the Ser-563 residue, as well as an increase in inhibitory phosphorylation of HSL at Ser-565. Notably, a more recent study has reported no apelin-mediated changes in lipolysis in human adipose explants[43]. These seemingly contradictory results may reflect differences in organism choice (human vs. mouse) and assay methodology.

On the demand side, apelin has been shown to increase body temperature and UCP3 expression in brown fat[40]. Apelin is also known to increase mitochondrial respiratory enzyme activity, expression of respiratory chain components, and protein content, suggesting an increase in mitochondrial biogenesis[66]. While the latter findings are of great interest given the importance of mitochondria to fatty acid and glucose metabolism, it remains to be seen whether apelin affects more significant assessments of mitochondrial function, such as oxygen consumption and membrane potential. Moreover, apelin’s effects on mitochondrial substrate utilization (i.e. fatty acid and glucose oxidation, glycolysis) have not been evaluated.

Conclusion

In recent years, there has been a growing appreciation of apelin’s involvement in the pathogenesis of insulin resistance. Apelin secretion is regulated by insulin, and clinical studies have demonstrated elevated plasma apelin concentrations in individuals with insulin resistance. Moreover, direct administration of apelin has been shown to increase insulin sensitivity, peripheral glucose uptake, and adiponectin levels, as well as decrease adiposity, hyperinsulinemia, and free fatty acid levels. While a human study evaluating apelin’s effects on insulin sensitivity has not been completed, the available evidence nevertheless suggests

that apelin ameliorates insulin resistance, positioning apelin/APJ signaling as a possible pharmaceutical target for the treatment of T2DM and the metabolic syndrome. Despite this early promise, however, unresolved issues remain regarding apelin and its association with insulin sensitivity. The intracellular mechanisms governing apelin-induced glucose uptake, and its relationship with the classic insulin signaling cascade, have yet to be fully characterized. Moreover, apelin's regulation of fatty acid homeostasis, as well as its significance relative to insulin sensitivity, needs to be further clarified. Nevertheless, targeting apelin/APJ signaling may represent a potentially novel avenue in designing therapies for insulin resistance.

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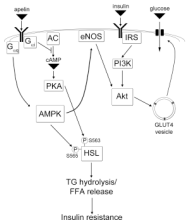

Figure 1.

Putative signaling mechanisms for apelin's regulation of insulin sensitivity. Apelin directly enhances glucose uptake via a pathway involving AMPK and eNOS. Apelin also inhibits lipolysis via phosphorylative regulation of HSL, indirectly increasing insulin sensitivity by reducing FFA release to the circulation. Abbreviations: AC (adenylate cyclase), AMPK (AMP-mediated protein kinase), eNOS (endothelial nitric oxide synthase), FFA (free fatty acid), HSL (hormone sensitive lipase), IRS (insulin receptor substrate), PI3K (phosphoinositide 3-kinase).