Review

AMPK-Mediated Multi-Organ Protective Effects of GLP-1 Receptor Agonists

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Abstract: AMP-activated protein kinase (AMPK) is a key enzyme broadly involved in regulating cellular metabolism, often called an "energy sensor". Activated AMPK promotes ATP production and storage within cells, primarily by inhibiting ATP-consuming anabolic processes (such as protein, lipid, and ribosomal synthesis) and initiating ATP-producing catabolic pathways (such as fatty acid oxidation and glycolysis) to maintain energy homeostasis. AMPK regulates metabolic processes in various peripheral tissues, including glucose and lipid metabolism, cholesterol metabolism, and fatty acid and protein metabolism in pancreatic β-cells, the cardiovascular system, liver, kidneys, skeletal muscles, and the central nervous system. As an antidiabetic drug, the multi-organ protective effects of Glucagon-like peptide-1 receptor agonists (GLP-1RA) are increasingly being recognized. This paper reviews the mechanisms by which GLP-1RA confers organ protection via the AMPK signaling pathway.

Keywords: GLP-1; AMPK; multi-organ protection

1. Introduction

AMP-activated protein kinase (AMPK) is an enzyme closely related to energy metabolism. Abnormal AMPK activation or inhibition can lead to energy imbalance and subsequent cell damage. AMPK is a heterotrimer consisting of three subunits (α, β, γ), each with different isoforms encoded by distinct genes. Once the AMP/ATP ratio increases in the cytoplasm or other factors activate AMPK, it enhances glucose uptake and utilization, as well as fatty acid oxidation, to generate more energy. Simultaneously, it suppresses pathways such as gluconeogenesis, lipid synthesis, and glycogen synthesis to reduce energy consumption, thereby maintaining energy homeostasis within the cell [1]. Hence, AMPK is referred to as a "cellular energy regulator" [2–4]. Therefore, the AMPK signaling pathway plays an important role in various diseases, such as exercise-induced myocardial repair [5], myocardial ischemia-reperfusion injury [6], Parkinson's disease [7], sarcopenia [8], lung injury [9], kidney diseases [10], liver disease [11], etc.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone released in response to nutrients, particularly glucose. GLP-1 stimulates insulin secretion, inhibits β-cell apoptosis, and promotes β-cell proliferation and regeneration, thereby protecting pancreatic β-cells. It also suppresses glucagon secretion. Additionally, GLP-1 inhibits gastrointestinal motility, delays gastric emptying, and enhances glucose utilization. Due to these effects, GLP-1 has become an essential drug for the treatment of diabetes [12]. The commonly used GLP-1RAs include semaglutide, liraglutide, exenatide, dulaglutide and Tirzepatide, etc. [13]. Key clinical trials associated with these drugs, such as PIONEER [14], SUSTAIN [15], LEADER [16], DURATION [17], and the AWARD [18], have highlighted their therapeutic efficacy. The multi-organ protective effects of GLP-1RAs, including benefits in cardiovascular diseases [19–21], kidneys [22,23], heart failure [24,25], and reducing the onset of new diabetes [26], diabetes remission [27], have garnered increasing attention. Additionally, GLP-1RAs have shown promise as effective weight-loss agents [28–30]. Moreover, they are emerging as a research focus in fields like Alzheimer's disease [31] and fatty liver disease [32]. AMPK, which integrates nutritional and hormonal signals to respond to various metabolic stresses, such as fasting, exercise, and chronic nutrient excess from obesity [33], is closely linked with GLP-1RAs. Although there has been extensive research on the multi-organ protective effects of AMPK and

GLP-1, the connection between these two pathways has received relatively little attention. This paper reviews the regulatory mechanisms of GLP-1RAs in various organs through AMPK.

2. Alleviation of Pancreatic β-Cell Damage

GLP-1RAs have been shown to improve markers of insulin sensitivity and β-cell function, further supporting their clinical significance [34]. GLP-1RAs protect pancreatic β-cells by inhibiting apoptosis, promoting proliferation, and inducing regeneration. Studies have shown that liraglutide (100 nmol/L) significantly enhances β-cell (INS-1) survival under high glucose conditions (11.1 or 30 mmol/L), largely by activating the mammalian target of rapamycin (mTOR) and its downstream targets, including p70 ribosomal protein S6 kinase (P70S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (eIF4EBP1). This protective effect is diminished by the AMPK activator AICAR and the mTOR inhibitor rapamycin. Liraglutide also increases intracellular ATP levels and reduces glucolipotoxicity-induced apoptosis [35]. Additionally, liraglutide restores the circadian rhythm in β-cells by activating AMPK, improving β-cell dysfunction and glucose tolerance in type 1 diabetic mice [36]. However, excessive AMPK activation can have detrimental effects. Methylglyoxal (MG)-induced glucotoxicity causes β-cell apoptosis, mitochondrial dysfunction, and reduced ATP production, which lead to persistent AMPK activation. AMPK inhibitors can mitigate MG-induced damage, while GLP-1RAs reduce MG-induced apoptosis and mitochondrial dysfunction by limiting prolonged AMPK activation [37]. GLP-1 can also alleviate glucosamine-induced inhibition of glucose uptake in β-cells by inhibiting AMPK activation, thereby restoring the phosphorylation of P70S6K and 40S ribosomal protein S6 (S6RP) [38]. Furthermore, AMPK influences GLP-1R expression under different glucose conditions. Under low glucose (2.8 mmol/L), AMPK phosphorylation increases in β-cells, but as glucose levels rise, AMPK phosphorylation decreases. Moderate glucose (11.1 mmol/L) upregulates GLP-1R expression, while high glucose (22.2 mmol/L) suppresses it. AMPK inhibition increases GLP-1R expression under low glucose, but this effect diminishes in hyperglycemic db/db mice [39]. In addition, GLP-1 protects β-cells from cholesterol-induced toxicity by activating AMPK, which inhibits PARP-1 activity and reduces cholesterol-induced damage [40].

GLP-1RAs protect pancreatic β-cells through multiple mechanisms involving AMPK. While AMPK activation generally supports β-cell survival and function, prolonged activation can cause cell damage. Balancing AMPK signaling is critical for β-cell protection, particularly under stress conditions like glucotoxicity and cholesterol toxicity.

3. Gastrointestinal Function Improvement

GLP-1RAs have demonstrated significant effects in weight reduction, and they have become popular weight loss medications worldwide. This effect is closely linked to their impact on the gastrointestinal system, where they inhibit gastrointestinal motility and enhance the feeling of satiety [41]. GLP-1 is produced by the proglucagon gene. In pancreatic α-cells, the main expression product of the proglucagon gene is glucagon, while in the L-cells of the intestinal mucosa, prohormone convertase 1 (PC1) cleaves proglucagon into the carboxyl-terminal peptide sequence, which is GLP-1. A study showed that AMPK can limit the growth of L-cells, thereby inhibiting the secretion of GLP-1 [42]. One study investigated the role of autophagy in attenuating hepatic lipid accumulation after sleeve gastrectomy (SG). The results showed a significant increase in GLP-1 and autophagy in rats undergoing SG. In HepG2 cells, GLP-1 analog reduced lipid accumulation by activating autophagy by regulating the AMPK/mTOR signaling pathway [43]. One study showed that goat milk consumption improves glucose homeostasis and insulin sensitivity in STZ-induced diabetic rats, providing metabolic benefits by activating hepatic and skeletal muscle AMPK. Additionally, goat milk modulates gut microbiota, increasing the relative abundance of Lactobacillus and augmenting levels of propionic and butyric acids [44].

4. Central Nervous System (CNS) Regulation

In addition, GLP-1RAs have been widely studied for their effects on cognitive impairment. Numerous clinical studies are currently being conducted to explore the potential of GLP-1 to treat cognitive disorders, particularly Alzheimer's disease [45]. GLP-1R is widely distributed in brain tissues, and GLP-1RA can suppress appetite by influencing the feeding centers, thus assisting in glycemic control. Furthermore, the cognitive improvements from GLP-1RA are gradually gaining recognition. Studies show that the mTOR/p70S6K signaling pathway in the hypothalamus is closely related to feeding and energy metabolism balance. Hyperglycemia reduces hypothalamic AMPK expression, but GLP-1RA exendin-4 can restore this effect. Injection of exendin-4 activates AMPK and p70S6K in Zucker rats and lean rats [46]. Another study found that activation of GLP-1R in the hindbrain triggers an anorexic response, which can be inhibited by the AMPK stimulator AICAR. In hypothalamic GT1-7 cells,

Exendin-4 inhibits AMPK phosphorylation in a glucose-dependent manner and stimulates glycolysis. The glycolysis inhibitor 2-deoxyglucose (2-DG) reduces Exendin-4's effects. Intracerebroventricular injection of the AMPK agonist attenuates Exendin-4-induced anorexia, indicating that Exendin-4's inhibition of AMPK and feeding is dependent on central glucose metabolism [47]. Inhibition of AMPK is also linked to the activation of thermogenesis in brown fat by GLP-1R in the ventromedial nucleus of the hypothalamus and the browning of white adipose tissue [48]. Liraglutide is also associated with improved cognition through AMPK activation. Streptozotocin (STZ)-induced diabetic rats showed cognitive impairment and reduced phosphorylation of AMPK, AKT, ERK, and p70S6K, but liraglutide treatment improved phosphorylation levels, thereby enhancing cognitive function [49]. Liraglutide also prevents motor function decline and dopaminergic neuron loss in db/db mice through a mechanism involving the restoration of the impaired AMPK/PGC-1α signaling in the striatum, improving motor dysfunction and neuronal damage in type 2 diabetic mice [50]. For the treatment of status epilepticus (SE), the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin (ALO) increases GLP-1 levels by inhibiting DPP-4 activity. The results showed that ALO reduced seizure severity and associated hippocampal neurodegeneration while increasing γ-aminobutyric acid (GABA) levels, reducing glutamate spikes, and correcting glial fibrillary acidic protein (GFAP) changes. At the molecular level, ALO increased GLP-1 levels and activated its downstream AMPK/SIRT1/Nrf2 signaling pathway [51]. Depression is one of the most common complications in patients with diabetes. Puerarin effectively alleviated depression-like behaviors in high-fat diet mice by enhancing GLP-1R expression in the hippocampus, which subsequently activated the AMPK, CREB, and BDNF -TrkB signaling pathways to improve neuroplasticity [52].

GLP-1RAs influence multiple aspects of central nervous system function, including appetite regulation, energy metabolism, cognitive improvement, and neuroprotection. The AMPK pathway is central to these effects, particularly in linking glucose metabolism with feeding behavior and neuronal health. Through their modulation of AMPK, GLP-1RAs offer potential therapeutic benefits for conditions such as diabetes-related cognitive decline, motor dysfunction, seizures, and depression

5. Cardiovascular Protection

The role of **GLP-1RAs** in cardiovascular protection has become a major research focus in recent years. GLP-1RAs have become a recommended medication with cardiovascular benefits in diabetes guidelines, suggested as a first-line treatment for patients with cardiovascular risks [12]. Corresponding clinical trials have also demonstrated their cardiovascular protective effects [53]. In non-diabetic obese individuals, GLP-1RAs provide significant benefits, including reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke [54]. Studies show that hyperglycemia stimulates NADPH oxidase (NOX2) **i**n cardiomyocytes, increasing the production of reactive oxygen species (ROS). This activation of NOX2 is related to the enhanced activity of sodium-coupled glucose transporters (SGLT). In adult rat cardiomyocytes cultured in high-glucose conditions (21 mM), treatment with the AMPK activator A769662 inhibited ROS production. GLP-1RA reduces ROS production by activating AMPK-α2, which is predominantly expressed in the heart, with the maximum effect observed at 100 nmol/L. It was also observed that the anti-ROS effect of the AMPK activator is independent of glucose uptake or glycolysis. Additionally, the GLP-1/AMPK pathway inhibits PKC-β2 phosphorylation, reducing NOX2 activation [55]. Liraglutide treatment in diabetic rats reduced myocardial lipid deposition, inhibited PKC and NADPH oxidase activity, and improved myocardial metabolic function through AMPK activation, independent of its glucose-lowering effects [56]. In cardiomyocytes treated with high glucose, inflammatory response and oxidative stress are significantly elevated. Under the action of the GLP-1 receptor agonist liraglutide, the AMPK pathway is also activated, and GLP-1 receptor expression is increased, thereby mitigating high glucose-induced cardiomyocyte damage [57]. Phenylephrine (PE)-induced cardiac hypertrophy was used to simulate diabetic cardiomyopathy. Exendin-4 alleviates epinephrine-induced cardiac hypertrophy, and this protective effect can be counteracted by AMPK inhibitors, via the mTOR/p70S6K/4-EBP1 signaling pathway [58]. In hypertensive rats, liraglutide reduces cardiac hypertrophy by increasing GLP-1 receptor expression and AMPK phosphorylation, while reducing mTOR and p70S6K activity. These effects were blocked by the AMPK inhibitor Compound C or the mTOR activator MHY1485 [59]. GLP-1RAs also protect against ischemia-reperfusion injury. Liraglutide reduced myocardial infarction size and improved cardiac function in diabetic mice by increasing p-AMPK and the LC3 II/LC3 I ratio, while decreasing p-mTOR and p62 levels [60]. Liraglutide reduced myocardial infarction size and improved cardiac function in diabetic mice by increasing p-AMPK and the LC3 II/LC3 I ratio, while decreasing p-mTOR and p62 levels [61].

Endothelial cells play a crucial role in the formation of atherosclerosis and are thus commonly used as models for studying vascular injury. AMPK is closely related to endothelial function, maintaining normal endothelial cell

function by regulating metabolism and oxidative stress [62]. Liraglutide increases nitric oxide (NO) production and eNOS phosphorylation in human umbilical vein endothelial cells (HUVECs), while inhibiting NF-κB activation and reducing inflammatory markers such as MCP-1, VCAM1, ICAM1, and E-selectin. The inhibitory effect of liraglutide on NF-κB is attenuated by an AMPK inhibitor, and its phosphorylation of AMPK is independent of circulating AMP [63]. Other studies have also confirmed the link between the AMPK/eNOS signaling pathway. For example, exenatide has been shown to improve endothelial relaxation function in patients with type 2 diabetes and impaired glucose tolerance (IGT), and this mechanism is related to the activation of AMPK and the production of eNOS and NO in endothelial cells [64,65]. Palmitic acid (PA) activates the phosphorylation of JNK, as well as increases the expression of IKKα/β and IL-6 in HUVECs. These effects were improved by liraglutide. Additionally, liraglutide enhances the phosphorylation of eNOS and AMPK, and increases NO production [66]. Liraglutide increased NO production and eNOS phosphorylation in HUVECs, while inhibiting NF-κB activation and reducing inflammatory markers such as MCP-1, VCAM1, ICAM1, and E-selectin [67,68]. In endothelial cells, liraglutide reduces TNF-α and LPS-induced inflammation by decreasing adhesion molecule expression and increasing anti-inflammatory factors such as CaMKKβ, eNOS, CREB and AMPK. Knockdown of AMPK reduced these anti-inflammatory effects [69]. Liraglutide also mitigates high glucose-induced endothelial cell ROS damage by activating AMPK, which inhibits p47phox translocation and NAD(P)H oxidase activation [70]. The liraglutide treatment of the oxidized LDL-induced foam cell model was found to increase the superoxide dismutase (SOD) expression, decrease the ROS and malondialdehyde (MDA) levels, and activate AMPKα1, significantly reducing the phosphorylation of the sterol-regulatory element binding protein 1 (SREBP1) [71]. Muscle microvasculature regulates the exchange of insulin, nutrients, and oxygen. Insulin resistance reduces microvascular blood flow and capillary density. GLP-1 can expand blood volume and promote endothelial cell proliferation. In rats fed a high-fat diet, liraglutide improves microvascular insulin resistance and endothelial dysfunction, increases capillary density, and enhances insulin-mediated glucose utilization, which was linked to higher AMPK phosphorylation and increases VEGF expression [72]. Additionally, GLP-1 improves aortic endothelium-dependent relaxation in diabetic rats through the AMPK/NO pathway [73]. Vascular calcification (VC) is a complication of diabetes. In exendin-4 cultured in high glucose and β-glycerophosphate, exendin-4 restored mitochondrial function, increased mitophagosome-lysosome fusions, and reduced p62. Exendin-4 also increased AMPKα and ULK1 phosphorylation. However, AMPKα1 knockdown blocked ULK1 activation and the reduction of LC3B and p62, negating exendin-4's effects on VC in diabetic mice. Thus, Exendin-4 promotes mitophagy via the AMPK pathway, reducing mitophagy insufficiency and inhibiting osteogenic switching of VSMCs [74]. In HAECs, liraglutide rapidly increases extracellular Ca^{2+} influx via L-type calcium channels and activates AMPK, inhibiting the suppression of intercellular adhesion molecule-1 (ICAM-1) expression induced by advanced glycation end-products of bovine serum albumin (AGE-BSA) [75]. Many similar studies have also demonstrated the protective effects of GLP-1RAs on endothelial cells [76–78].

GLP-1RAs exert significant cardiovascular protective effects through AMPK activation. These effects include reducing oxidative stress, improving endothelial function, preventing cardiac hypertrophy, and mitigating ischemia-reperfusion injury. AMPK plays a central role in mediating these actions, highlighting its importance in both metabolic and cardiovascular health.

6. Improvement of Adipose Tissue Metabolism

GLP-1RAs have been proven to effectively reduce weight while also improving visceral fat [79]. Liraglutide significantly reduces weight gain in mice fed a high-fat, high-sugar diet, and is associated with a significant reduction in epididymal and inguinal fat pads. It also upregulates the expression of brown adipose tissue-specific markers in perigonadal fat and activates the AMPK-SIRT1-PGC1-α signaling pathway [80]. Central injection of liraglutide in mice stimulates thermogenesis in brown adipose tissue (BAT) and browning of adipocytes. pAMPK and its downstream target pACC levels in the hypothalamus were significantly reduced in liraglutide-treated mice. Central injection of the AMPK activator AICAR does not weaken the anorexic effect of liraglutide but prevents liraglutide-induced weight loss. Furthermore, by using an adenoviral vector encoding constitutively active AMPKα, overexpression of AMPKα in the ventromedial hypothalamus (VMH) completely blocks liraglutide-induced weight loss. Additionally, activation of AMPK in the VMH reduces liraglutide-induced UCP1 expression in BAT and WAT of rats [81].

GLP-1RAs effectively regulate glucose and lipid metabolism through the AMPK pathway, improving insulin sensitivity, reducing lipid accumulation, and promoting fat oxidation. These effects highlight the therapeutic potential of GLP-1RAs in managing metabolic disorders.

7. Improvement of Liver Metabolism

Nonalcoholic fatty liver disease (NAFLD) is a heterogeneous metabolic disease, and the "multiple-hit" theory for the development of NAFLD is widely accepted, including lipid accumulation in the liver, insulin resistance, oxidative stress, inflammation, genetic and environmental factors, etc. GLP-1RAs have been validated for the treatment of non-alcoholic fatty liver disease (NAFLD) and are used clinically to improve fatty liver in diabetic patients [82]. GLP-1 inhibits lipid accumulation in primary hepatocytes through the AMPK/ACC signaling pathway [83]. Dysregulated glucose and lipid metabolism in peripheral tissues is a major contributor to the metabolic disturbances seen in type 2 diabetes. In a study on the effect of GLP-1 on hepatitis C virus (HCV) replication, liraglutide activates AMPK and element-binding protein 2(TORC2), reducing gluconeogenesis by downregulating phosphoenolpyruvate carboxykinase (PEPCK) and G6pase RNA, key enzymes involved in this pathway [84]. In liver tissues, GLP-1 increases intracellular cAMP and phosphorylates AMPK, while targeted negative expression of AMPK reduces GLP-1-induced AMPK phosphorylation and its downstream lipogenesis effects [85]. The AMPK/mTOR signaling pathway is also involved in hepatic lipid accumulation [86]. Experimental and clinical studies show that liraglutide can improve NAFLD by increasing p-AMPK expression, significantly reducing the expression of gluconeogenic and lipogenic enzymes in the liver, and lowering lipid levels and distribution [87]. In liver-specific AMPK knockout models, liver damage is exacerbated in nonalcoholic steatohepatitis (NASH), demonstrating AMPK's protective role. AMPK phosphorylates the pro-apoptotic protein caspase-6, preventing its activation and subsequent hepatocyte apoptosis. When AMPK activity is reduced, caspase-6 is activated, leading to hepatocyte death via a positive feedback loop involving caspase-3, caspase-7, and the release of cytochrome c [88]. In the mouse model of NAFLD related to type 2 diabetes, liraglutide not only improved glucose metabolism but also reduced tissue damage in the liver. Transcriptomic analysis indicated that liraglutide regulated lipid metabolism-related signaling pathways, including AMPK and ACC. This mechanism was also verified in the HepG2 high-glucose cell model, where high glucose significantly decreased the levels of p-AMPK and p-ACC. Liraglutide treatment restores the levels of p-AMPK and p-ACC [89]. Similar studies found that in obese mice treated for four weeks with semaglutide, the mTOR pathway is attenuated, and insulin signaling and the AMPK pathway are enhanced, ameliorating liver gene expressions related to the metabolism of obese mice [90].

In conclusion, GLP-1RAs improve liver function by activating the AMPK signaling pathway, reducing lipid accumulation, and preventing hepatocyte apoptosis. These effects highlight the therapeutic potential of GLP-1RAs in treating metabolic liver diseases such as NAFLD and NASH.

8. Protection of Kidney Function

The renal protective effects of GLP-1RAs have been confirmed by numerous clinical trials and have been included in guidelines as a first-line treatment for patients with diabetic nephropathy [16,91]. Studies show that treatment with GLP-1 receptor agonist exendin-4 significantly improves renal structure and function by reducing iron overload, oxidative stress, ACSL4-driven lipid peroxidation, and decreasing GPX4 expression and GSH levels in diabetic renal tubules. The AMPK signaling pathway is identified as a downstream target of exendin-4. AMPK activation triggers downstream signaling, activating fatty acid oxidation in mitochondria, inhibiting lipid synthesis and glycolysis, ultimately alleviating the accumulation of toxic lipids [92]. Exendin-4 inhibits high glucose-induced mesangial cell proliferation and fibrosis, by increasing AMPK phosphorylation and the MMP-2/TIMP-2 ratio [93]. In a diabetic nephropathy cell model, mesangial cells pretreated with AICAR, an AMPK signaling agonist, exhibit a significant increase in survival rate, reduced lactate concentration, and elevated activities of *Pfk*, *Sdh*, and *Pdh-e1* compared to the group treated with high sugar and high fat. These genes are associated with energy metabolism, suggesting that the AMPK signaling pathway plays a protective role in mesangial cells by regulating energy metabolism [94]. In studies involving weight-loss surgery, one-anastomosis gastric bypass (OAGB) in diabetic rats reversed weight gain, improved glucose tolerance, and restored kidney function by reducing glomerular hypertrophy, mesangial dilation, and collagen deposition. This improvement was associated with the activation of the Sirt1/AMPK/PGC1α pathway mediated by GLP-1 in diabetic nephropathy [95]. Similar pathways have also been identified in other studies [96]. However, another study found that liraglutide reduces the AMPK activation in the kidneys of high-fat and high-sugar diet-fed mice, and AMPK agonist bortezomib partially reversed the therapeutic effect of liraglutide on HDF-induced nephropathy in mice. The mechanism is related to the CaMKKβ/AMPK signaling pathway [97]. In mouse and proximal tubular acute kidney injury (AKI) models, it has been found that activation of AMPK prevents LPS-induced sepsis-related AKI, and this effect is mediated through the 3'-untranslational region of GLP-1R [98].

GLP-1RAs protect the kidneys by activating the AMPK signaling pathway, reducing oxidative stress, lipid peroxidation, and fibrosis. Despite some conflicting findings, these mechanisms highlight the therapeutic potential of the AMPK signaling pathway in the treatment of diabetic nephropathy and other kidney diseases with GLP-1RAs.

9. Regulation of Gonadal Function

The effects of GLP-1 RA on polycystic ovary syndrome (PCOS) remain unclear. In a study, female C57BL/6J mice were subcutaneously injected with dehydroepiandrosterone for 21 days to establish a PCOS model. After treatment with semaglutide, the mice experienced a reduction in body weight and an improvement in insulin resistance. Serum testosterone and IL-1β levels decreased significantly, while estradiol and progesterone levels increased. The relative expression of NF-κB phosphorylation and its upstream regulatory factor IκBα is upregulated in the ovaries of PCOS mice, whereas AMPK phosphorylation and SIRT1 expression are downregulated. Semaglutide improves pAMPK and SIRT1 expression while inhibiting pIκBα and NF-κB expression in a dose-dependent manner [99]. An interesting experiment explored the effects of GLP-1 on breast cancer cells. Exendin-4 and liraglutide activate AMPK in a cAMP-dependent manner. Blocking Ex4-induced activation of AMPK by inhibiting AMPK restores cell viability. Interestingly, Ex4 and liraglutide reduce the levels of glycolytic metabolites and decrease ATP production, suggesting that GLP-1RAs impair glycolysis. Notably, AMPK inhibition reverses the decline in ATP levels, underscoring the role of AMPK in this process [100].

10. Improvement of Muscle Metabolism

Clinical studies have suggested that combining GLP-1 with exercise can effectively reduce weight while maintaining lean body mass [101]. In a mouse exercise model, acute exercise and short-term endurance training significantly increase GLP-1 secretion in mice. Overexpression of GLP-1 in skeletal muscle enhances endurance and promotes glycogen synthesis, glucose uptake, Type I muscle fiber formation, and mitochondrial biogenesis. In vitro experiments showed that the GLP-1 receptor agonist exendin-4 significantly promotes glucose uptake, Type I fiber formation, and mitochondrial respiration. Knockdown of AMPK reverses the effects induced by GLP-1RA activation in vitro [102]. Studies show that liraglutide increases cAMP levels in myotubes, activates GLUT4 translocation, and promotes the phosphorylation of AMPK, AS160, and TBC1D1. Using AMPK siRNA and Compound C can significantly reduce GLUT4 translocation [103]. Exendin-4 enhances 2DG uptake in rat L6 skeletal muscle cells by increasing AMPK-α Thr172 phosphorylation, independent of IRS1, AKT, ERK1/2, or JNK1/2 pathways. Inhibition or knockdown of AMPK attenuates this effect, indicating that AMPK plays a key role in Exendin-4-mediated glucose uptake [104]. In ob/ob mice, 4 weeks of exenatide treatment improves lipid metabolism by activating AMPK, increasing the expression of FATP1, CPT-1, and UCP1, and reducing lipogenic enzymes such as SREBP-1 and FAS. It also enhances insulin signaling and reduces lipid accumulation in palmitate-treated C2C12 myoblasts [105]. In high-fat diet-induced obese mice, exendin-4 treatment reduces body weight, fasting glucose, and lipid levels, improves fat oxidation, and inhibits fat synthesis by upregulating AMPK and insulin signaling pathways [106]. Metabolic syndrome is associated with vitamin D3 deficiency. One study aimed to examine the efficacy of vitamin D3 in inhibiting MetS-induced myopathy and to determine whether the beneficial effects of vitamin D3 are mediated by the inhibition of DPP-4. Vitamin D3 alleviates MetS-induced metabolic dysfunction and reduces intramuscular glycogen and lipid accumulation. Furthermore, vitamin D3 increases serum GLP-1 levels, muscular AMPK activity, and GLUT-4 content. This suggests that GLP-1 partially ameriolates the MetS-induced metabolic changes and myopathy [107].

11. GLP-1RAs and Spinal Cord Injury via AMPK

Liraglutide promotes motor function recovery after spinal cord contusion, reduces necrosis, and preserves motor neurons. Liraglutide upregulates the levels of p-AMPK/AMPK, FOXO3, and p-FOXO3 (phospho-ser253). It also activates autophagy, enhancing the expression of autophagy markers LC3B-II/LC3B-I and Beclin-1 while reducing p62 levels. These effects are partially reversed by the AMPK inhibitor Compound C [108]. In an experimental autoimmune encephalomyelitis (EAE) model of mice, liraglutide administration improves disease scores, delays disease onset, and alleviates pathological demyelination and inflammation in the lumbar spinal cord. In EAE mice, phosphorylated AMPK expression was significantly decreased, along with protein levels of p62, Beclin1, and LC3, which were reduced by 37–50%. Liraglutide treatment partially restores these protein levels [109].

12. GLP-1RAs in Psoriasis Treatment via AMPK

GLP-1RAs have been demonstrated to effectively treat psoriasis by improving the Psoriasis Area and Severity Index (PASI) in patients [110]. In a study where inflammation is induced in keratinocytes using lipopolysaccharide (LPS), liraglutide was found to significantly reduce the viability of HaCat cells and inhibit macrophage migration towards these cells. LPS treatment increases the phosphorylation of IKKα/β, S176/S180, NF-κB p65, JAK2, STAT3, and SOCS3, as well as the intracellular levels of TNF-α and IL-6 in HaCat cells. Liraglutide reverses these effects and increases AMPK phosphorylation. The effect of liraglutide in inhibiting p-NF-κB p65 and p-STAT3 was hindered by the AMPK inhibitor Compound C, suggesting that the potential therapeutic effect of GLP-1RA on psoriasis is related to the AMPK signaling pathway [111].

13. Conclusions and Perspectives

GLP-1RAs confers protection against various systemic diseases by activating the AMPK signaling pathway. As a key regulator of cellular energy metabolism, AMPK plays a central role in modulating glucose metabolism, lipid oxidation, inflammation, and autophagy. By activating AMPK, GLP-1RAs reduce oxidative stress and lipid peroxidation in cardiovascular, liver, and kidney metabolic disorders and improve diabetes and its associated complications by regulating metabolic pathways and preventing cell apoptosis. The role of the AMPK pathway in diseases such as polycystic ovary syndrome (PCOS), spinal cord injury, muscle metabolism, neurological disorders, and psoriasis further broadens the clinical applications of GLP-1Ras (Table 1).

Looking forward, the mechanisms of the AMPK pathway remain central to research on GLP-1RAs. Based on the therapeutic benefits of GLP-1RAs in cardiovascular, renal, obesity, and fatty liver conditions, AMPK and its related pathways may also represent a potential therapeutic target. In-depth analysis of the molecular mechanisms regulating AMPK, including its tissue-specific roles and upstream and downstream signaling pathways, will help elucidate its broad applications in disease prevention and treatment. This includes investigating the relationship between GLP-1 through the AMPK signaling pathway and inflammation and fibrosis, the synergistic effects of GLP-1RAs and AMPK in multi-system diseases, and the development of new GLP-1RAs and AMPK-targeting drugs. By further unraveling the mechanisms of AMPK, GLP-1RAs hold promise for providing more comprehensive and effective treatment strategies for metabolic and other systemic diseases.

Table 1. Relationship Between GLP-1 and AMPK in Various Organs.

Organ	Disease Model	Clinical Effect of GLP-1RAs	AMPK Role	Mechanism	Signaling Molecules	Experimental Type
Pancreas	β-cell injury	Promotes insulin secretion, improves β-cell function	Activation	Activation Increase ATP levels, inhibit apoptosis, promote regeneration	mTOR, P70S6K, eIF4EBP1, mTORC1, PKA, PARP-1	Mice, pancreatic β-cells
Cardiovascular System	Cardiac hypertrophy, myocardial ischemia, diabetic cardiomyopathy, endothelial injury	Reduces cardiovascular mortality risk, including fatal and fatal shock, myocardial infarction, and risk of heart failure hospitalization	Activation	Reduce oxidative stress, increase eNOS activity	eNOS, NOX2, PKC-β2, SOD, NF-kappaB/IKKa/β, NADPH, p47phox	Rat, mice, adult rat cardiomyocytes, human umbilical vein endothelial cells
Liver	Fatty liver, diabetes-related liver injury	Reduced liver fat, decreased inflammation	Activation	Increase autophagy, reduce lipid deposition, decrease inflammation, inhibit lipid synthesis	ACC, SREBP-1, CPT-1, FAS, PEPCK, G6pase	Mice, primary hepatocytes
Kidney	Diabetic nephropathy, Acute kidney injury	Reduces composite renal risk, decreases new onset of persistent macroalbuminuria	Activation/Inhibition	Reduce oxidative stress and fibrosis, improve energy metabolism	Sirt1, ACSL4, GPX4, PGC1α, MMP-2, TIMP-2	Rat, mice, mesangial cell, tubular cell
Central Nervous System	Feeding, thermogenesis, epilepsy, cognitive impairment	Suppresses appetite center, Improved cognitive function, reduced neuronal damage	Activation	Improve cognitive function, inhibit neuronal apoptosis, regulate energy metabolism	AKT, ERK, P70S6K, CREB, BDNF, TrkB	Rat, mice

Table 1. *Cont.*

Organ	Disease Model	Clinical Effect of GLP-1RAs	AMPK Role	Mechanism	Signaling Molecules	Experimental Type
Adipose Tissue	White and brown adipose tissue	Increased energy expenditure, reduced adiposity	Activation	Promote lipolysis, induce browning of white adipose tissue, increase energy expenditure	UCP1, PGC1α, SIRT1, ACC, pACC	Rat, mice
Skeletal Muscle	Insulin resistance, exercise endurance	Improved insulin sensitivity, Reduces risk of sarcopenia	Activation	Promote glucose uptake, increase mitochondrial biogenesis, enhance muscle endurance	GLUT4, AS160, TBC1D1, TORC2, FATP1	Mice, skeletal muscle cells
Gastrointestinal	Bariatric surgery, insulin resistance	Inhibits gastrointestinal emptying, enhanced GLP-1 levels	Activation	Increase GLP-1 levels, improve gut microbiota	ULK1, mTOR, PC1	Rat, L-cells of the intestinal
Ovary	Polycystic ovary syndrome	Inhibits gastrointestinal emptying, enhanced GLP-1 levels |	Activation	Reduce inflammation, restore hormone levels	IκBα, NF-κB, SIRT1	Mice
Spinal Cord	Spinal injury, myelitis	Enhanced neuroprotection, reduced inflammation	Activation	Increase autophagy, reduce inflammation, promote neuroprotection	LC3B, Beclin-1, FOXO3, p62	Mice
Skin	Psoriasis	Treats psoriasis, Reduced skin inflammation	Activation	Reduce inflammation	NF-κB p65, JAK2, STAT3, SOCS3	HaCat cells

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