

Effects of AMPK Stimulation on the Pathogenesis and Progression of Parkinson's Disease

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ABSTRACT: AMP-activated protein kinase (AMPK) is a master regulator present in all mammalian cells. Recently, studies have shown that AMPK stimulation may prevent Parkinson's disease pathogenesis and progression in animal and cell models, but the relationship between AMPK and Parkinson's disease is unclear. In this study, I will explore how AMPK stimulation affects Parkinson's disease. I will discuss the mechanisms of four AMPK-stimulating drugs, metformin, acadesine, resveratrol, and trehalose in detail. Based on reviewed papers, there appears to be a strong connection between AMPK and Parkinson's disease. I connect drug treatments to the decline of Parkinson's disease symptoms by focusing on the upstream and downstream pathways of AMPK. Changes in AMPK level are shown to affect both Parkinson's disease pathogenesis and progression through autophagy, neuroinflammation, mitochondrial quality control, and protein aggregation pathways. I attempt to solidify the mechanism of drug action as well as the connections between AMPK and PD. In the future, AMPK-stimulating drugs might be used as an effective treatment for Parkinson's disease.

KEYWORDS: Molecular Biology; Parkinson's disease; AMP-activated protein kinase (AMPK); autophagy; protein aggregation; molecular biology; neurogenetics.

■ Introduction

Introduction to Parkinson's disease:

Among all the age related diseases, Parkinson's disease (PD) catches the attention as the second most common neurodegenerative disease in the world, and a disease that currently has no cure.¹ As the global population ages, PD becomes more prominent since the risk of PD increases five to ten times when a person goes from 60 to 90 years old.² Clinically, PD is associated with motor problems such as tremors, rigidity, and slow movement, but PD symptoms may vary between patients. Driven by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the subsequent lack of the neurotransmitter dopamine, PD is sometimes accompanied by other non-motor disabilities like depression, rapid eye movement sleep behavior disorder, and constipation.² PD is usually diagnosed after neurological symptom onset, but neuroimaging modalities like MRI, PET, and SPECT can be used to diagnose PD during the early stages.³

Treatments such as levodopa, deep brain stimulation, and some dopamine agonists are available to alleviate some PD symptoms. Still, they are not able to prevent the disease or slow down disease progression.¹ Other developing cell and gene therapies, such as stem cell replacement, seek to regenerate lost dopaminergic neurons. Still, they must first overcome the problems of the host's immune response and the possibility of developing cancer.

Pathogenesis of Parkinson's disease:

A major obstacle to developing PD treatments is the heterogeneity of the disease: PD can be split into subtypes with different causes and progression processes so that treatments

may affect specific subtypes of PD differently. Broadly, PD can be grouped into familial and sporadic subtypes, with body-first and brain-first disease progression in sporadic cases. Familial PD is caused by the inheritance of mutated genes and accounts for 5% to 10% of all PD cases.² Identifying the causative disease genes enables biological researchers to clarify disease mechanisms and has led to the development of predictive genetic testing.

In familial cases, the pathogenesis and pathology differ not only by causative gene but also by mutation site. The inheritance of genetic risk factors greatly increases the likelihood of developing PD, and several disease genes have been identified.⁵ Mutations of PTEN-induced kinase 1 gene (*PINK1*) or parkin RBR ubiquitin protein ligase (*PRKN*), the gene coding for Parkinson's, lead to impaired mitophagy (autophagy of mitochondria), which causes the accumulation of dysfunctional mitochondria, leading to an arrest of mitochondria motility along the axon and neuronal death.^{2, 6, 7} Certain mutations of leucine-rich repeat kinase 2 (*LRRK2*) increase kinase activity and decrease autophagy, which increase dopaminergic neuron susceptibility to other insults. Mutations in synuclein alpha (*SNCA*), the gene that codes for alpha-synuclein (α Syn), result in misfolded α Syn. Aggregates of misfolded α Syn protein constitute a significant cause of neuronal dysfunction and death. They are a notable marker of PD as they are found in high concentrations in postmortem examinations of PD patients.⁸ In PD pathogenesis, mutated α Syn aggregation results in the neurotoxic protein aggregates known as Lewy bodies, which are also associated with dementia.⁹

Sporadic PD lacks a heritable genetic cause and may be caused by other internal and external factors, including environmental factors and concomitant disease. For example, certain species of bacteria may cause the aggregation of alpha-synuclein (αSyn) in the enteric nervous system.^{3, 4}

Progression of Parkinson's disease:

PD is not fatal, but complications of PD, like falls and pneumonia, can lead to death. Over time, however, the symptoms of PD can worsen due to increased neuron death. Subtypes also exist for PD progression. In the brain-first subtype, αSyn primarily aggregates in the brain and the disease progress toward the body. Contrastingly, the body-first subtype is characterized by the entry of αSyn from the gastrointestinal nervous system into the brain; these patients are more likely to exhibit rapid eye movement sleep behavior disorder as a complication.³

There are several hypotheses on how PD progresses. For example, the transmission hypothesis states that aggregated proteins can propagate rapidly between living cells or move in a prion-like mode. As cells die, toxic proteins released into the environment promote further protein misfolding and the death of other cells.^{10,11} Another hypothesis is that reactive oxygen species (ROS) build up over time as a result of dysfunctional mitochondria, and it has been shown that restoring antioxidative mechanisms in brain cells can slow PD progression.¹²

AMPK:

As a central regulator of cell survival, metabolic homeostasis, mitochondrial function, and autophagy, 5' adenosine monophosphate-activated protein kinase (AMPK) have garnered attention as a drug target for neurodegenerative diseases. AMPK stimulation might prevent PD pathogenesis or slow disease progression. However, given the complexity of its function, it is necessary to solidify the specific downstream effects of AMPK that are most beneficial for PD treatment.

AMPK is a highly conserved serine-threonine protein kinase that plays a crucial role in regulating cellular energy levels by controlling rates of lipid metabolism, carbohydrate metabolism, autophagy, and mitochondrial quality control. AMPK is activated in nutrient- and energy-deficient conditions and broadly act to increase catabolism and transform ADP into ATP. AMPK consists of a catalytic alpha subunit, a regulatory beta subunit, and a regulatory gamma subunit. There are two types of the alpha subunit, two types of beta subunit, and three types of gamma subunit in humans, encoded by the *PRKAA1*, *PRKAA2*, *PRKAB1*, *PRKAB2*, *PRKAG1*, *PRKAG2*, and *PRKAG3* genes respectively, allowing for a total of 12 possible combinations of AMPK.¹³ These genes combine differently in different tissue types and can shift in response to cellular physiology (for example, the alpha 2 subunit is highly expressed in neurons). Still, the pathological and functional differences in Parkinson's disease are unspecified.^{13, 14}

As its name suggests, AMPK is also activated when AMP levels are high. A rise in the AMP: ATP ratio similarly indicates reduced energy and nutrient availability in the cell. Through allosteric binding of AMP on the gamma subunit or by phosphorylation of Threonine 172 by Liver Kinase B1 (LKB1, also known as STK11) and calcium-dependent protein

kinase kinase 2 (CaMKK2), AMPK can be directly activated through phosphorylation or indirectly activated through intermediate molecules at elevated AMP levels. In addition, ADP and cyclic AMP (cAMP) can also activate AMPK. ADP typically has a milder effect than AMP, and cAMP has a stronger impact than AMP.

Moreover, AMPK links the different pathways of PD pathogenesis. Experiments using AMPK knockouts on the beta subunit have shown that depletion of AMPK leads to neurodegeneration.¹⁵ An autophagic defect was noted when the gamma subunit mutated, and neuronal death was caused by a mutated beta subunit, demonstrating the necessity of AMPK in preventing PD pathogenesis.^{16,17}

Mutations in the gene *LRRK2* initiate an energy-consuming process of chronic protein translation.¹⁸ AMPK is a regulator of cellular energy level, so it can restore homeostasis by changing the ratio of energy-consuming and energy-generating processes, therefore counteracting some of the pathogenetic impact of mutated *LRRK2* on neuron function.¹⁹

Moreover, suppression of AMPK decreases the levels of microtubule-associated protein 1 light chain 3 phosphatidylethanolamine conjugate (LC3-II) in a PD cell model.²⁰ LC3-II is involved in the formation and maturation of autophagosomes and binds autophagy receptors for selective degradation.²¹ This shows that AMPK is important for autophagy, and a constant amount of AMPK is needed for the clearance of misfolded protein and dysfunctional mitochondria.

Overall, AMPK is an attractive drug target as it relates to multiple PD pathogenesis and progression pathways. This review will summarize studies using AMPK-activating drugs and analyze how these drugs influence the critical PD-related AMPK stimulation pathways to inform researchers developing drugs that can target AMPK without activating other harmful pathways. On a molecular level, finding a balance between molecular pathways of AMPK is significant because activation of AMPK may be neuroprotective, but overactivation of AMPK exerts detrimental effects on cells.

■ Methods

Google Scholar and PubMed were used to search for primary research incorporating AMPK stimulation in Parkinson's disease models. A list of papers published from 2007 to 2022 was selected for screening. The list was filtered so that only papers with both the keywords "AMPK" and "Parkinson's disease" were included. Additionally, STRING (string-db.org) was used to hypothesize protein interactions unspecified in papers. Genecards (genecards.org) and KEGG (genome.jp/kegg/pathway.html) were used to find neurogenetics information on PD models and their relevant pathways. Finally, "ConceptDraw DIAGRAM" was used to draw the two molecular diagrams.

■ Results and Discussion

Table 1: AMPK-activating drugs that have been tested in models of Parkinson's disease. In particular, the impact column act as a quick guide to see the direction of the effect of AMPK activation: an increase or decrease in pathogenesis refers to a significant improvement or worsening in PD-related symptoms after activation of AMPK; increase or a decrease in progression refers to prevention or speeding up of disease onset or cell death in AMPK activated groups. The same experiments in this table will be discussed in detail below.

Type	Model	PD model	Treatment	Molecular Effect	Impact
in vitro	SH-SY5Y cell	α Syn overexpression	Metformin, Acadesine	Neurotoxicity of α Syn ↓, acidic autophagosomes ↑	Progression ↓ ²²
in vivo	Drosophila	Mutant <i>LRRK2</i> and Parkin-null	Metformin, Acadesine	DA neuron count ↑	Progression ↓ ¹⁹
in vivo & in vitro	mouse model, SH-SY5Y cell	MPP+ induced PD	Metformin	ROS ↓, MPP+ induced cytotoxicity ↓, DA level ↑, α Syn expression ↓	Progression ↓ ²³
in vitro	SH-SY5Y cell	Rotenone	Resveratrol	LC3-II levels ↑, SIRT1 deacetylase activity ↓, autophagosome and autophagolysosome structure ↑	Pathogenesis ↓ ²⁰
in vitro	PC12 cell	α Syn expression	Resveratrol	LC3-II level ↑, α Syn degradation ↑	Progression ↓ ²⁰
in vivo	Mouse model	6-OHDA	Metformin	TH expression ↓, Neuronal atrophy ↑	Pathogenesis ↑ ²⁴
in vitro	PC12 cell	A30P and A53T mutation	Trehalose and Rapamycin	Clearance of mutant α Syn ↑, autophagy ↑	Pathogenesis ↓ ²⁵
in vivo	Mouse model	MPTP induced	Trehalose	DA neuron survival ↑, Tyrosine hydroxylase loss ↓, neuroinflammation ↓	Pathogenesis ↓ ²⁶
in vivo	Rat model	A53T mutation	Trehalose	DA neurodegeneration ↓, α Syn aggregation ↓	Pathogenesis ↓ ²⁷
in vitro	Mouse model	MPP+ induced	AMPK Overexpression	nuclear condensation ↑	Pathogenesis ↓ ²⁸
in vitro	SH-SY5Y cell, neuron	MPP+	FCPR16	autophagic vacuoles ↑, ROS ↓	pathogenesis ↓ ²⁹

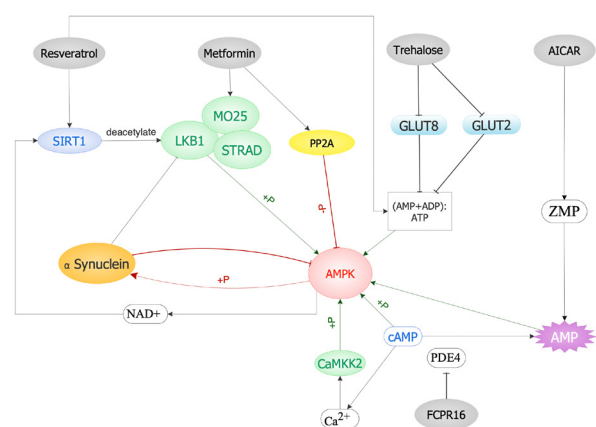


Figure 1: Stimulation of AMPK by the drugs resveratrol, metformin, trehalose, acadesine and FCPR16. Many upstream regulators can be drugged to activate AMPK either by direct phosphorylation or by indirectly increasing the levels of cAMP, AMP, or ADP. For example, resveratrol activates AMPK via binding to SIRT1, an upstream regulator of LKB1, and inhibits AMP's conversion into ATP. Metformin stimulates AMPK by increasing the formation of the LKB1-MO25-STRAD complex and activating PP2A. Trehalose inhibits glucose transporters, leading to less ATP production. Acadesine is metabolized into ZMP, which mimics AMP and

activating PP2A. Trehalose inhibits glucose transporters, leading to less ATP production. Acadesine is metabolized into ZMP, which mimics AMP and thereby leads to AMPK activation. FCPR16 inhibits PDE4, which increases cAMP levels. A normal arrow is activation and upregulation, and a T-shaped arrow is inhibition and downregulation.

Metformin:

Metformin is a common diabetes drug. Metformin stimulates AMPK by inhibiting complex I of the electron transport chain, which increases the AMP:ATP ratio, leading to the activation of AMPK.³⁰ By increased translocation of LKB1 from the nucleus to the cytosol,³¹ metformin also promotes the formation of the LKB1-MO25-STRAD complex, which phosphorylates and activates AMPK (Figure 1).

In a 2016 study by Lu *et al.*, AMPK stimulation by metformin reduces ROS and MPP+ induced cytotoxicity by autophagy.²³ (Table 1). Autophagy, short for macroautophagy, is highly connected to PD as it involves the degradation of α Syn and damaged mitochondria.³² AMPK primarily regulates autophagy through the activation of ULK1, which forms a complex with ATG13 and FIP200.^{33,34} This complex then phosphorylates PI3-kinase-related VPS34 and Beclin 1, which leads to ATG16L1-ATG5-ATG12 complex formation.³⁵ This converts LC3-I to LC3-II by adding it onto the phagophore membrane and initiates autophagosome formation.³³ ULK1 also phosphorylates ATG9, which is involved in phagophore elongation and maturation.³⁶ The absence of AMPK thus prevents autophagy initiation and completion. Finally, AMPK activation promotes the activity of FOXO3 and TFEB, transcription factors that drive the expression of autophagy genes.³⁵ A suitable rate of autophagy prevents neuronal death and slows down PD pathogenesis and progression.

Kim *et al.* (2011) showed that metformin-activated AMPK also inhibits mTOR complex 1 (mTORC1), which normally inhibits ULK1, leading to increased autophagosome formation.³⁷ To do this, AMPK can phosphorylate Raptor, a subunit of the mTORC1 complex, to inhibit complex formation, and AMPK can activate TSC1 and TSC2, which in turn inhibit Rheb, a promoter of mTORC1 (Figure 2). mTORC1 works to increase anabolism (conversion of ATP to ADP) and decrease catabolism (conversion of ADP to ATP). On the other hand, AMPK increases catabolism and decreases anabolism.³⁵ AMPK stimulation by metformin slows PD development by sensing cellular energy levels and increasing autophagy.

Moreover, metformin activation of AMPK reduces the transcription of pro-inflammatory cytokines IL-6 and TNF α , IL-6 and increases the transcription of anti-inflammatory genes IL-4, IL-10, and TGF β .²³ The anti-inflammatory effect of activated AMPK attenuates PD symptoms caused by neuroinflammation.

Conversely, Kim *et al.* (2013) showed that AMPK over-activation by metformin increased neurodegeneration in 6-OHDA-induced PD mouse model.²⁴ AMPK can convert alpha-synuclein into a more active form, pS129- α Syn, which is alpha-synuclein phosphorylated at Serine 129. pS129- α Syn is more prone to aggregation than unphosphorylated alpha-synuclein. The presence of pS129- α Syn can hinder autophagy in PD organisms because it prevents autophago

some formation and lysosome function. Here, the presence of AMPK has a harmful effect and accelerates the pathogenesis of the 6-OHDA-induced PD model. In addition, the above study and the AMPK KO study by Bayliss *et al.* (2016) both yield a neurodegeneration phenotype but have conflicting results regarding AMPK activation. Because the detrimental effect of AMPK may be due to a mechanism specific to the 6-OHDA model, where 6-OHDA is a neurotoxin that mimics DA. I hypothesize that AMPK activation might be inhibiting the mitochondrial inhibition of 6-OHDA, but this should be tested with further experimentation. Thus, the overall effect of AMPK activation or attenuation depends on the specific downstream pathway activated or inhibited. This highlights the need to understand how different PD subtypes react to different treatment strategies.

Acadesine:

Acadesine, or 5-aminoimidazole-4-carboxamide riboside (AICAR), is a naturally occurring intermediate formed during nucleotide synthesis. When used as a drug, it mimics AMP, activating AMPK. A study by Dulovic *et al.* (2014) showed that AMPK stimulators, such as metformin and acadesine, could lead to decreased *in vitro* neurotoxicity of both extracellular α Syn and α Syn resulting from overexpression.²² This pathological effect is amplified by the link between α Syn and AMPK, where α Syn overexpression decreases the phosphorylation of LKB1, therefore decreasing the amount of activated AMPK. This decreases cell survival.

Acadesine demonstrates a similar downstream effect as the mTORC1 inhibition pathway of metformin. When acadesine is applied, PP2A and AMPK concentration increases, leading to reduced neurotoxicity of α Syn. While PP2A normally inhibits AMPK by dephosphorylation, PP2A also inhibits AKT, which inhibits TSC1 and TSC2.³⁸ Thus, the upregulation of PP2A can result in the upregulation of TSC1 and TSC2. AMPK also upregulates TSC1 and TSC2 directly, so the improved PD syndrome of metformin can be partially due to the AMPK-TSC pathway.

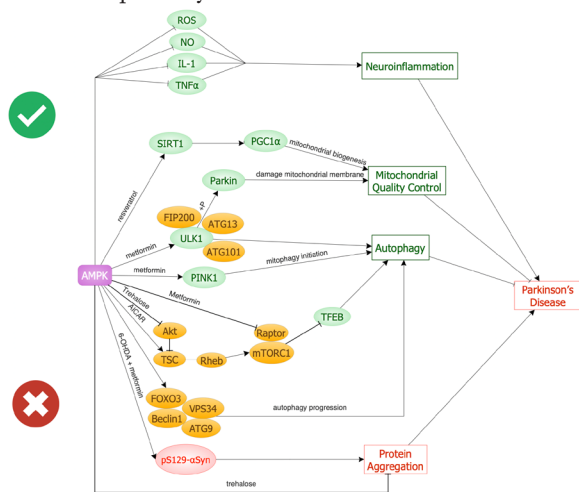


Figure 2: Downstream pathways of AMPK related to PD pathogenesis and progression. AMPK acts on various downstream targets to affect autophagy and mitochondrial quality control, including SIRT1, ULK1, PINK1, and mTOR. AMPK activation also inhibits neuroinflammation via several pathways. AMPK can enhance or reduce α Syn aggregation depending on the PD model.

Resveratrol:

Resveratrol is a natural compound derived from red grapes and other plants. Lan *et al.* (2017) showed that 100 μ M of Resveratrol activates AMPK by inhibiting the function of ATP synthase,³⁹ therefore, increasing the AMP:ATP ratio, which causes an allosteric activation of AMPK on the gamma subunit. Resveratrol also activates SIRT1 by binding to its N-terminal region.^{40, 41} Activation of SIRT1 causes the deacetylation of LKB1, which phosphorylates AMPK, resulting in AMPK activation. Notably, a positive feedback loop forms between SIRT1 and AMPK, in which upregulation of AMPK further activates SIRT1 via NAD⁺.⁴² This positive feedback enhances resveratrol's effect on AMPK. In addition, activated SIRT1 also promotes the transcription of PGC1 α , resulting in an overall increase in mitochondrial biogenesis (Figure 2).

Wu *et al.* (2011) also showed that resveratrol increased neuronal survival and slowed PD progression due to increased α Syn degradation, likely due to increased autophagy.²⁰ The combined effect of AMPK by autophagy and mitochondrial biogenesis enhances mitochondrial quality control, therefore reducing cell death caused by aggregation of mitochondria. AMPK promotes the binding of DRP1 on MFF to increase mitochondrial fission. In addition, active AMPK leads to increased phosphorylation of ULK1, which triggers mitophagy (the selective autophagy of mitochondria);⁷ accumulation of PINK1 on the mitochondrial membrane also causes phosphorylation of Parkin, which triggers mitophagy.^{14, 40} The formation of new functional mitochondria and the degradation of dysfunctional mitochondria together may mitigate the pathogenesis of PD since it helps maintain energy production while avoiding the accumulation of reactive oxygen species (ROS).

Trehalose and other pathways:

Trehalose is a naturally occurring disaccharide consisting of two molecules of glucose.⁴³ Trehalose activates AMPK by inhibiting glucose and fructose (GLUT) transporters.⁴⁴ Reduction in cellular glucose reduces ATP level, which mimics an energy starvation environment responsible for AMPK activation. In a study by He *et al.* (2015), a rat model of PD was treated with trehalose. It was found that a 2-5% concentration of trehalose provided in rat drinking water was protective against dopaminergic neurodegeneration.²⁷

Trehalose also enhances the clearance of mutated α Syn via autophagy. That is because trehalose increases the expression and activation of TFEB, leading to increased autophagy. The beneficial effects of trehalose may also be due to its inhibition of Akt, which inhibits the mTORC1 pathway (Figure 2). Trehalose also activates ULK1, favoring autophagosome biogenesis and aggregated protein clearance.⁴⁵ Trehalose's stimulating effect on autophagy attenuates PD pathogenesis and progression.

Sarkar *et al.* (2007) showed that AMPK activation and clearance of α Syn were enhanced when combined with inhibiting the mTOR pathway by rapamycin, an mTOR inhibitor.²⁵ Another activator of AMPK, FCPR16, inhibits the PDE4-mediated transformation of cAMP to AMP, resulting in the upregulation of AMPK.²⁹ Overexpression of the AMPK

genes in the MPP(+)-induced PD cell model was also shown to increase cell survival, showing the direct linkage between AMPK and PD.²⁸

■ Conclusion

This review solidifies the connection between the multi-functional regulator AMPK and Parkinson's disease. Various drugs, such as metformin, acadesine, resveratrol, and trehalose, have stimulated AMPK and ameliorated PD pathogenesis and progression in cell and animal models. Therefore, it can be hypothesized that AMPK stimulation would have a similar role in human PD; therefore, such drugs might be used in patients to prevent PD onset or slow disease progression. However, while most AMPK upregulation has a neuroprotective effect, AMPK may increase PD pathogenesis under certain circumstances, namely, Kim *et al.* (2013). It is thus essential to find a balance between the neuroprotective pathways of AMPK and its undesired phosphorylation of α Syn.

AMPK activators have a growing therapeutic potential in PD drug development as these activators are already tested in preclinical PD models and clinical trials for other diseases. Metformin, acadesine, and trehalose have already been used as anti-diabetic drugs, leukemia treatment, and safe food ingredients, respectively.^{27,46,47} As a cellular energy sensor, AMPK has the potential to act as a therapeutic target for various other diseases, including type two diabetes, obesity, cardiovascular disease, multiple tumors, kidney disease, and other neurodegenerative diseases.⁴⁸ However, given the variability in AMPK function, more experiments can be done to determine (1) the optimum amount of AMPK activation that would have a neuroprotective effect while avoiding overactivation, (2) how well can cell, rodent, and drosophila models replicate human PD, (3) drug combinations to minimize off-target effects, and (4) clinical data of the safety and efficacy of long-term dosage with AMPK stimulating drugs. To achieve this, it is first necessary to have a precise understanding of the pathways that regulate and are regulated by AMPK and how they relate to PD.

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