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Faculty of Science
Laboratory of Growth Regulators & Department of Botany

A study of the mechanism of action of cytokinins with cytoprotective activity

Summary of the Doctoral thesis

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Contents

1. SUMMARY

This dissertation provides a comprehensive summary of the multifaceted therapeutic effects of cytokinins and their derivatives on health and aging, acting on various molecular domains. The aim of this study was to identify kinetin derivatives with an effect on familial dysautonomia and hereditary Parkinson's disease.

Familial dysautonomia is an autosomal recessive disease caused by a point mutation that results in missplicing of the mRNA and translation of a non-functional ELP1 protein, which is critical for neuronal function. Kinetin corrects the splicing defect. In this study, a series of kinetin derivatives were screened for their ability to enhance exon 20 inclusion in ELP1 pre-mRNA. Several novel derivatives demonstrated improved efficacy in correcting splicing defect and exhibited favorable pharmacokinetic properties *in vitro*. A detailed structure-activity relationship study is presented.

Type of early onset familial Parkinsonism (PARK6) caused by mutation G309D in the PINK1 gene encode a kinase essential for mitochondrial quality control which and leads to the loss of dopaminergic neurons in the *substantia nigra pars compacta*. Kinetin, after intracellular conversion to kinetin riboside-5´-triphosphate was reported to act as a neosubstrate for the mutated kinase. However, while previous studies suggested promising results, this dissertation was unable to replicate the reported protective effects of kinetin in cellular models, warranting further research into alternative modulators.

The aim of this study was to identify kinetin derivatives with an effect on familial dysautonomia and hereditary Parkinson's disease using molecular biology techniques, transcriptome analysis, and pharmacokinetic profiling.

2. INTRODUCTION

The primary function of phytohormone cytokinins (CKs) in plants is the regulation of cell division and thus CKs are present in all rapidly dividing tissues. Other functions of CKs include a significant slowing leaf senescence, maintenance of high metabolic activity in tissues or suppression of apical dominance. CKs acts in concert with other classes of phytohormones. A well-documented example is their effect on organ regeneration. A balanced ratio cytokinins and auxins leads to the formation of an undifferentiated tissue called a callus. An overabundance of cytokinins (CKs) leads to the regeneration of shoots, while an excess of auxins results in root formation. Surprisingly, their presence has been confirmed in all kingdoms of life except Archaea which lends support to the hypothesis that artificial manipulation has a wide range of applications.

Phytohormones, such as cytokinins, have been observed to possess the capacity to decelerate the process of cellular senescence in tissue culture of animal cells, with some studies demonstrating their ability to extend the lifespan of certain invertebrates. Their protective effect against diverse forms of stress has been evidenced in both *in vitro* and *in vivo* models. Consequently, these hormones have found application in the field of therapeutic cosmetics. The present study explores two distinct research areas: firstly, the cytoprotection of cytokinins based on splicing correction of mRNA of ELP1 in cases of familial dysautonomia (FD) a rarer hereditary disease, and secondly, the potential of cytokinins for neuroprotection in familial early onset parkinsonism (PD) through PINK1 kinase.

3. AIMS OF THIS WORK

Studies since 1950 have shown that CKs also have a variety of interesting activities in cell lines, animal models and humans. The primary objective of this study was to elucidate the effect of kinetin in Familial dysautonomy (FD) and Familial parkinsonism PARK6 (PD) *in vitro* models and identify derivatives with improved activity. In light of the comprehensive array of natural phytohormones and their derivatives housed within our laboratory, coupled with a review of pertinent literature, two potential avenues of inquiry were identified as worthy of investigation. This work has endeavored to address these two research fronts.

Familial dysautonomy

a. Structure-activity relationship study.
b. Transcriptomic study of selected derivative's action mechanism.
c. Analysis of select derivatives on panel ADME assay.

Familial Parkinsonism

a. Study of metabolic activation of cytokinins.
b. Identification of kinetin derivatives capable of protecting fibroblasts obtained from patients suffering from an inherited form of early-onset Parkinson's disease PARK6 caused by PINK1 mutations from stress.

4. THEORETICAL BACKGROUND

4.1 Cytokinins (CKs)

4.1.1 Structure and occurrence

Cytokinins can be divided into isoprenoid and aromatic types based on the nature of the N^6-substituent. Isoprenoid cytokinins include N-isopentenyladenine (iP), dihydrozeatin (DHZ), and zeatin (Z), while aromatic cytokinins comprise N^6-benzyladenine and its hydroxylated derivatives. In plants, cytokinins exist as free bases, ribosides, ribotides, N-glucosides, and amino acid conjugates. iP is a modified base in tRNA[Ser]Sec, aiding protein translation in both plants and humans. Cytokinins are primarily synthesized in the root apical meristem and transported via xylem to aerial parts, spreading further through the phloem[2-4].

CK biosynthesis has also been identified in bacteria, fungi, and nematodes[5-18]. These organisms interact with plants, with CKs functioning as interkingdom signaling molecules and exhibiting bioactive roles beyond plant interactions. CKs have been found in algae, yeasts, insects, mosses, mammals, and various animal tissues, including human urine and transgenic mouse models[19-35]. Some synthetic compounds, such as diphenylurea (DPU) and thidiazuron (TDZ), also exhibit cytokinin activity[29,35].

4.1.2 Activity in plants

Cytokinins (CKs) are essential phytohormones that regulate plant growth by influencing cytokinesis, organ regeneration, stress resistance, and shoot-to-root development depending on their concentration ratio with auxins[3,36,37]. To date, over 30 natural cytokinins (CKs) have been discovered, along with hundreds of their synthetic derivatives[5]. Currently, there are also several libraries of synthetic cytokinin derivatives, e.g., benzyladenines[38,39].

4.1.3 Synthesis and degradation

There are two pathways of isoprenoid CKs synthesis: direct and indirect. The indirect one is associated with isopentenylation of adenine in some tRNAs, while free cytokinins are released after their degradation. In the direct pathway, the free adenine nucleotide is isopentenylated. In higher plants, adenosine-5'-monophosphate and dimethylallyl pyrophosphate (DMAPP) are synthesized to create isopentenyladenosine-5-monophosphate (iPMP)[40]. While isoprenoid cytokinin metabolism is well understood, knowledge of aromatic cytokinin metabolism remains limited[41]. CKs are irreversibly degraded by cytokinin dehydrogenase (CKX), producing adenine and an aldehyde[42].

4.1.4 Cytokinin signalling pathways in plants

Cytokinin signaling, resembling a bacterial two-component system, involves phosphate transfer between histidine receptors and aspartate residues, regulating gene transcription; for details see Mok[43], Kakimoto[44] and Spíchal *et al*. [45].

4.2 Cytotoxic and antiproliferative activity in animals

Certain cytokinin ribosides, such as N^{6}-isopentenyladenosine (iPR)[46-62], and kinetin riboside (KR)[63-76]; N^{6}-benzyladenosine (BAPR)[48,55,77-80], *ortho*-topolin riboside (*o*TR)[81-83], alongside their derivatives[84-97], demonstrate cytotoxicity, showing promise as antitumor agents. In contrast to plants, where cytokinin bases at high concentrations show cytotoxic activity[77,78,98-101], bases corresponding to cytotoxic ribosides are not toxic for majority of cell lines. Compounds with strong anticancer activity due to cyclin dependent kinase inhibition can be obtained by substitution of cytokinin bases by alkyl or cycloalkyl at the atom N9 in combination with a 2-hydroxyalkyl substitution (for examples olomoucine, roscovitine)[47-52].

4.3 Protective effects in animal models

A more comprehensive overview of the numerous effects of cytokinins on animal models and cells can be found in the overview table in Supplement 3 of the dissertation.

Rattan *et* Clark[102] demonstrated that fibroblasts cultured with kinetin (K) maintained an early-passage (young) cell morphology, cell size, showing reduced lipofuscin accumulation and youthful cytoskeletal organisation. Similarly, *trans*-zeatin (*t*Z) exhibited gerontomodulatory effects, preserving cell juvenile phenotype and reducing intracellular debris[103]. Kinetin has also been shown to enhance catalase activity and extend the lifespan of *Zaprionus sp*.[104], while offering protection against glyco-oxidative stress in rat astrocytes[105]. In *C. elegans*, kinetin improves lifespan and stress resistance[106]. Additionally, kinetin from sprouted barley extracts improved glucose tolerance and lowered glycosylated hemoglobin in type 2 diabetes patients[107]. Kinetin also enhances immune function and delays aging in rats[108].

Kinetin's benefits extend to skin health. Clinical trials have shown that kinetin-based creams improve skin texture, reduce fine lines, and enhance barrier function[109]. It also protects against UV-induced photoaging, enhancing AQP3 expression and inhibiting collagenase activity[110,111]. Kinetin's antioxidant activity, including its ability to form copper complexes and reduce oxidative damage, further supports its therapeutic potential[112,113]. Kinetin also mitigates oxidative damage from cisplatin and improves cryopreservation of sperm[114,115]. In mouse models, K has been shown to protect ovaries and reduce anxiety[116,117].

4.3.1 Other activities

Recent studies have shown that cytokinins (CKs) have antiviral effects against viruses like EV-A71 and SARS-CoV-2[118-122], as well as anti-adipogenic properties, antithrombotic activity, anti-inflammatory effects, and the ability to inhibit HSC activation, with evidence of their benefits in various models of disease, including hepatic fibrosis[123-130].

4.3.2 Neuroprotection

Cytokinins, such as zeatin and kinetin, have demonstrated neuroprotective effects through their antioxidant properties, improving oxidative damage in nerve cells and acting via A_{2A} adenosine receptors and acetylcholinesterase inhibition[131,142]. A another effect is the suppression of acetylcholinesterase by inhibitors which can modulate the PI3K/AKT pathway, the important cascade for neuronal survival (AD)[141,142]. Bowie *et al.*[143] and Maiuri *et al.*[144] have outlined the benefits of kinetin for models of Huntington's disease. Additionally, kinetin influences alternative splicing events, correcting splicing defects in neurofibromatosis type 1 and familial dysautonomia, highlighting its potential therapeutic role in neurological diseases[144-146]. The familial dysautonomia splicing neurological disease, for which kinetin has been demonstrated to have a beneficial effect, and is the main subject of this research, is described in detail in the following chapter Part I. FD.

Part I. Familial dysautonomia

Familial dysautonomia (FD), also known as Riley Day syndrome or hereditary sensory and autonomic neuropathy type III, is a congenital neurodegenerative disorder impacting neurons in the sensory and autonomic nervous systems. The condition is characterised by abnormal pain and heat perception, inability to produce tears, and difficulties with speech and swallowing, alongside optic neuropathy, corneal opacification, labile blood pressure, and gastrointestinal dysfunction. Vomiting crises, leading to pneumonia, are a major cause of mortality, and affected individuals exhibit impaired motor skills but retain intelligence[147-151]. The disease predominantly affects Ashkenazi Jews, with over 99% of cases caused by a recessive mutation in the ELP1 gene (IVS20+6T→C)[152,153]. This mutation has been shown to result in reduced splicing efficiency and a truncated ELP1 protein, leading to impaired neuronal function[154,155]. Stress has been observed to further decrease ELP1 gene expression, resulting in tissue-specific effects[156]. ELP1 is a component of the elongator complex, influencing transcription and various neural processes, including cell migration, cytoskeletal dynamics, and myelin formation. It also regulates the JNK signaling pathway, which is impaired in FD due to the mutation[157-179]. Recent studies on FD models, including induced pluripotent stem cells and humanized mice, reveal insights into the molecular consequences of ELP1 dysfunction. These studies show abnormal neuronal development, stress and apoptosis[180-189].

While no known therapy exists, experimental treatments targeting the splicing of ELP1 mRNA have shown promise in preclinical studies[190-193].

Current therapies for familial dysautonomia focus on symptomatic treatment, but experimental evidence suggests that pharmacological correction of abnormal ELP1 pre-mRNA splicing could benefit patients across all age groups. Several approaches, such as using antisense oligonucleotides targeting splicing sites and modified U1 snRNAs, have shown promise in affected neurons[190-192]. In addition, small molecules, such as epigallocatechin gallate (EGCG), have been found to increase exon 20 inclusion, thereby enhancing ELP1 expression[193,194]. Furthermore, cotreatment with tocotrienol has been observed to upregulate ELP1 transcription, thereby enhancing the therapeutic effect[193,195].

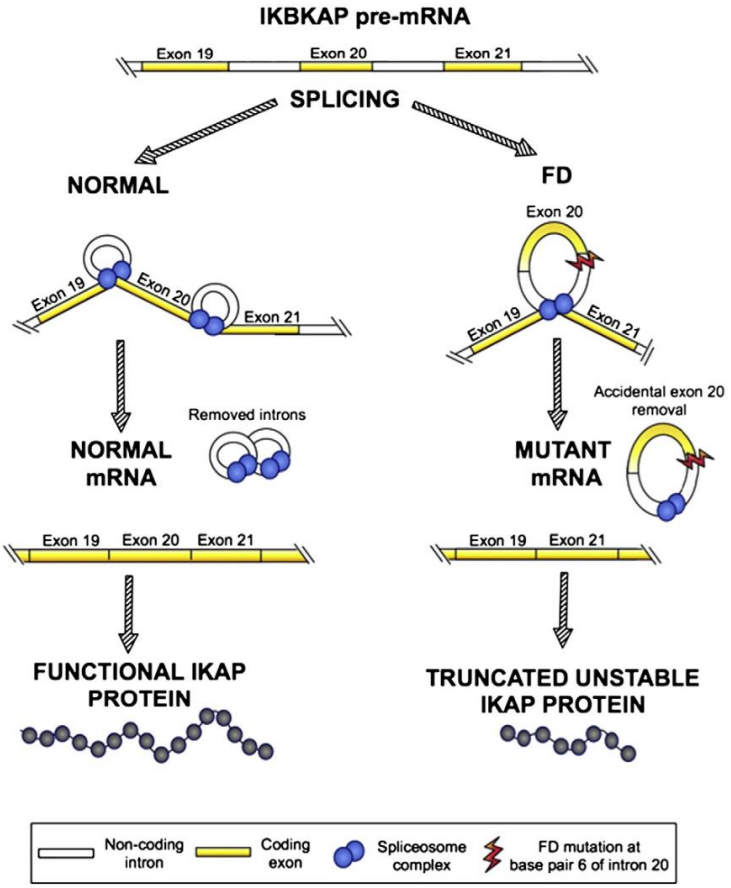

Figure 1. Schema of ELP1 mRNA splicing: normal versus abnormal (acquired from Norcliffe-Kaufmann *et* Kaufmann[196]).

Other compounds that promote exon 20 inclusion include isoflavones genistein and daidzein, cardiac glycosides, and proteasome inhibitors such as BPN-15477 and carfilzomib, though the latter requires toxic concentrations for effectiveness[197-200]. Phosphatidylserine has also demonstrated neuroprotective effects by reducing histone deacetylase activity in affected neurons, leading to increased α-tubulin acetylation[184,201-203]. Kinetin, a compound with beneficial effects on splicing, has been used to correct

splicing defects in FD. When administered orally, kinetin improved exon 20 inclusion in various tissues, including the brain and liver[204-206]. Its derivative, 2-chlorokinetin (2ClK), has been shown to enhance phosphorylation of splicing factor SRSF6, further promoting exon inclusion[207,208]. Kinetin combined with phosphatidylserine and other agents has demonstrated enhanced therapeutic effects[209].

However, clinical trials have shown a dose-dependent increase in normal ELP1 mRNA, although adverse effects like nausea and vomiting were also noted[205]. Caution is advised, as kinetin's furan moiety may be metabolized to toxic compounds[210-212]. Further research into the regulatory mechanisms of ELP1 expression and the development of additional therapeutics is necessary[190].

Part II. Familial parkinsonism

Mitochondrial dysfunction has been identified as a key pathogenic mechanism in Parkinson's disease and other neurodegenerative disorders[213]. Studies have indicated correlations between mitochondrial DNA haplotypes, polymorphisms, and the development of PD[214,215]. PD is the second most prevalent neurodegenerative disorder, affecting over 1% of individuals >60 years and 4% >80 years[216,217]. It has been shown to have a significant impact on quality of life, manifesting as motor symptoms (e.g. tremors, muscle rigidity, slow movements, balance issues) and non-motor symptoms, including gastrointestinal, autonomic, neuropsychiatric and sensory dysfunctions.

Parkinson's disease typically manifests between the ages of 60 and 70 (late-onset), but 5–10% of cases occur before 40 (early-onset). Early-onset PD is characterised by a more protracted progression, a favourable response to dopaminergic therapy, and an earlier emergence of drug-induced dyskinesias, accompanied by relatively preserved cognitive function. The disease is marked by dopaminergic neuron loss in the *substantia nigra pars compacta* (SNc), α-synuclein aggregation (Lewy bodies) and neuromelanin loss. At the molecular level, α-synuclein aggregation[218], disruptions in the ubiquitin–proteasome system[219], mitochondrial dysfunction, oxidative stress, inflammation[220], cell cycle dysregulation[221], and apoptosis abnormalities[222] are observed. Environmental factors[223], ageing[224], and genetic mutations[225] contribute to pathogenesis. While monogenic mutations account for 5–10% of PD cases, sporadic cases involve genetic polymorphisms. The hereditary nature of PD has been noted for over a century, with 12 loci and 8 genes identified in monogenic PD. The PDGene database provides updated genetic associations. Mitochondria, a major reactive oxygen species (ROS) source, experience mtDNA damage in PD. Patients exhibit increased mtDNA deletions in the SNc. Furthermore, POLG1 mutations, linked to progressive external ophthalmoplegia, heighten PD susceptibility.

Dopamine replacement (e.g., levodopa) remains the primary PD therapy, but it induces dyskinesia and does not stop disease progression[226,227]. No disease-modifying treatments exist, though research is ongoing[228,229]. The lack of biomarkers complicates

therapy development[230]. Deep brain stimulation offers a non-pharmacological alternative[231].

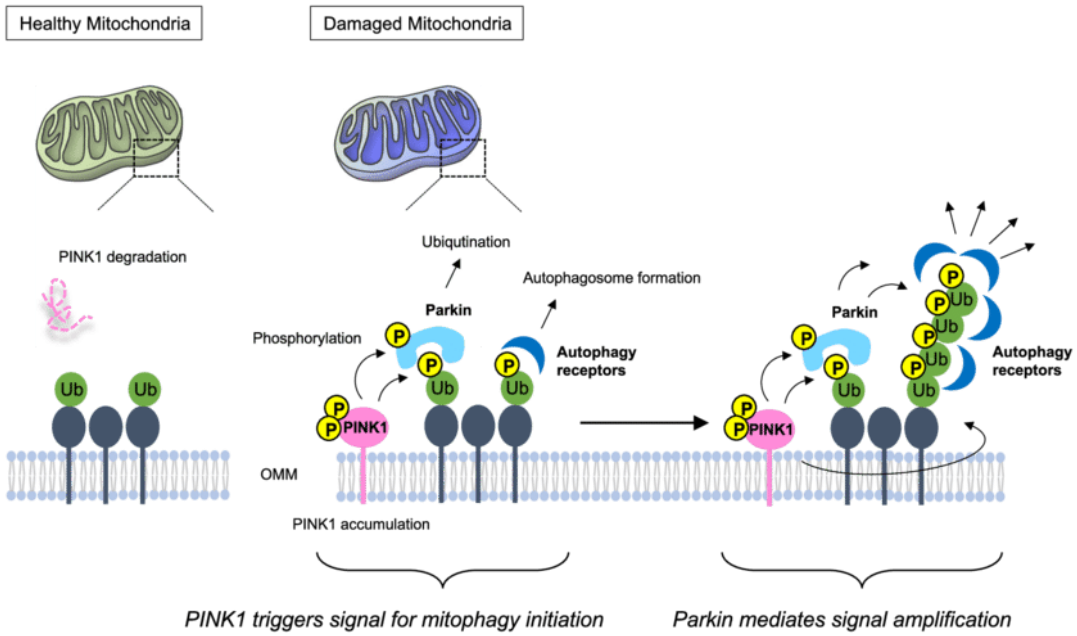

Figure 2. Overview of PINK1/Parkin-mediated mitophagy (acquired from Sekine *et* Youle[232]).
PINK1 plays a pivotal role in mitochondrial quality control, specifically in identifying damaged mitochondria and directing them for degradation. In mitochondria with an intact membrane potential, PINK1 import is dependent on the correct potential; however, when this potential is compromised, PINK1 accumulates in the mitochondrial outer membrane. In such a scenario, PINK1 facilitates the recruitment of parkin, which targets damaged mitochondria for degradation via autophagy. PINK1 also exerts control over mitochondrial quality through its involvement in the fission process, which often results in the formation of daughter mitochondria with unequal potentials. In the absence of PINK1, parkin is unable to effectively localise damaged mitochondria. Conversely, elevated PINK1 expression can result in parkin localising healthy mitochondria as well[232].

PINK1 Protein – PARK6 Disease

One genetic cause of Parkinson's disease is the mutation of the PINK1 gene, leading to the accumulation of misfolded proteins in the mitochondria. PINK1, a serine/threonine mitochondrial kinase, has antiapoptotic properties and is found in Lewy bodies[233]. It has been demonstrated to reduce cytochrome c release and inhibit caspase 3 activation[234]. PINK1 interacts with Parkin, influencing mitochondrial morphology and function, with mutations leading to mitophagy[235,236]. These mutations, often in the kinase domain, suggest loss of kinase activity as the main pathogenic mechanism[237]. PINK1 and the E3 ubiquitin ligase Parkin play key roles in mitophagy[238,239]. PINK1, located on the outer mitochondrial membrane, recruits Parkin upon mitochondrial depolarization, thereby inhibiting mitochondrial transport and fusion[240-242]. PINK1 (63 kDA) is cleaved by PARL to a 53 kDA product (103 Ala–104 Phe). It contains an N-terminal mitochondrial localization sequence, a transmembrane domain, and a kinase domain. In response to depolarization, PINK1 phosphorylates Bcl-xL at Ser62, thereby preventing the formation of proapoptotic forms[243]. It is noteworthy that more than 40 PINK1 variants have been identified, with

mutations being present in 4–5% of familial early-onset PD cases and 1–2% of sporadic cases[244]. A prevalent mutation, G309D, has been observed to reduce kinase activity by 70%[234,245]. Hertz *et al*.[1] demonstrated that kinetin riboside triphosphate (KRTP) restores PINK1 G309D function, and that kinetin protects against mitochondrial toxins, reducing apoptosis[1]. However, it should be noted that high concentrations of kinetin are toxic[79]. ProTides of kinetin, developed by Osgerby *et al*.[246], may offer safer alternatives. Recent findings suggest broader kinase targets for kinetin-based therapies[246].

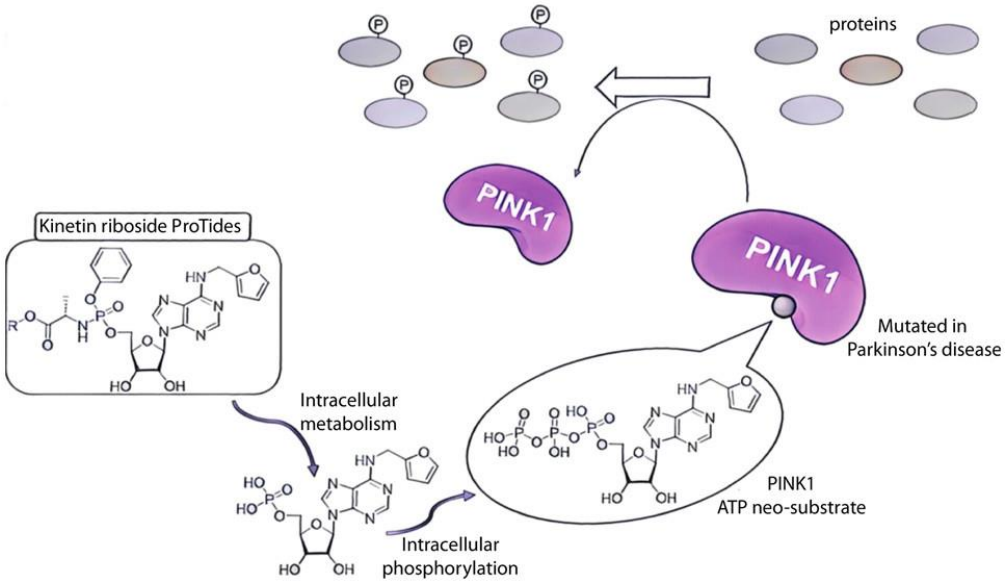

Figure 3a. The activation of PINK1 in cell lines independent of mitochondrial depolarisation was observed to be inducible by the ProTides and kinetin riboside. These observations suggest that modified nucleosides and their phosphate prodrugs have potential as therapeutic agents for neurodegenerative diseases.

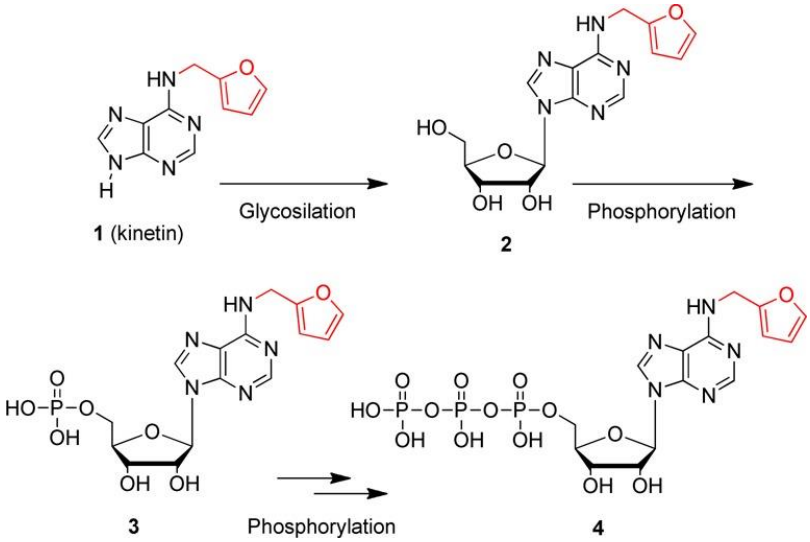

Figure 3b. Chemical structure of kinetin (1) and its metabolism in cells to generate the active substrate kinetin riboside triphosphate (4). Pictures 3a+3b and description acquired from Osgerby *et al*.[246].

5. MATERIALS AND METHODS

5.1 Cell lines and Cultivation procedure (FD, PD)

GM04663 and GM02343 fibroblasts (homozygous for the 2507+6T>C ELP1 mutation) were obtained from the Coriell Repository. BJ fibroblasts, ARPE-19 epithelial cells, and HaCaT keratinocytes were sourced from ATCC and DKFZ. SH-SY5Y (from bone tumor) and PARK E/F fibroblasts were used for PD experiments. Cells were cultured in DMEM or DMEM/F12 (ARPE-19) with glucose, L-glutamine, antibiotics, and 10% fetal calf serum. Knocked-down cells included puromycin. Standard conditions: 5.5% CO_2, 37 °C, 100% humidity. Subculturing occurred twice weekly.

5.2 Viability test (FD, PD)

The toxicity of compounds in GM04663, BJ, HaCaT, and ARPE-19 cells was assessed using a resazurin-based metabolic assay. Cells were plated in 96-well plates (10.000 GM04663, 10.500 HaCaT/ARPE-19, 7.500 BJ per well) and treated with test compounds (50 μM) or DMSO (control) after 24 h. After 48 h, resazurin (100 μM) was added, and fluorescence (ex 570 nm, em 610 nm) was measured after 1 h (ARPE-19) or 3 h (others) using a plate reader. Compounds showing toxicity at 50 μM were retested at 10 μM. This study aimed to optimize the resazurin assay for various cell lines.

5.3 PCR (FD)

GM04663 cells (500.000 per 10 cm Petri dish) were seeded and grown overnight before treatment. Cells were exposed to compounds (10, 50, 100 μM) for 24 h to assess dose response. For time course analysis, cells were treated with kinetin and 2ClK and harvested after 24 h. RNA was extracted using TRIzol and purified via phenol-chloroform extraction. RNA was precipitated with isopropanol, washed with 75% ethanol, and resuspended in DEPC water for storage at -80 °C. cDNA synthesis followed the High Capacity cDNA Reverse Transcription Kit protocol. PCR was performed using primers 5'-CAGGTGTCGCTTTTTCATCA-3' and 5'-CATTTCCAAGAAACACCTTAGGG-3' to amplify an ELP1 cDNA segment (nt 2194–2593, NM_003640.5). Thermal cycling conditions included initial denaturation (94 °C, 5 min), 34 cycles of denaturation (94 °C, 40 s), annealing (63.8 °C, 30 s), elongation (72 °C, 90 s), and final elongation (72 °C, 5 min). PCR products (wild-type: 422 bp; exon 20-lacking: 348 bp) were analyzed via 1.5% agarose gel electrophoresis and GelRed staining. For final validation, microfluidic electrophoresis (Agilent 2100 Bioanalyzer, DNA 1000 LabChip kit) was used. Peak area calculations in 2100 Expert Software allowed precise quantification of wild-type and aberrant transcripts by comparison with internal standards.

5.4 Imunodetection (FD, PD)

Cells were lysed in RIPA buffer, boiled for 2 min, and stored at -80 °C. Protein lysates (25-40 μg per well) were separated by SDS-PAGE (10% PAA) and transferred to a PVDF membrane. Blocking was done in 5% milk or BSA + PBS-Tween for 1 h. Membranes were incubated with anti-ELP1 and Bcl-xl (1:1000, Sigma Aldrich) and β-actin (1:2000, Santa Cruz), followed by washes. A secondary HRP-conjugated antibody (1:2000, Cell Signaling) was applied for 60 min. Detection was performed using Clarity Western ECL (Bio-Rad) and an Odyssey Imaging System (Li-Core).

5.5 Transcriptome sequencing (samples preparation, IMTM Ilumina, FD)

A total of 500.000 GM04663 cells were seeded into 10 cm Petri dishes and treated with 100 μM of compound 48 (8-aminokinetin) and kinetin (1), with DMSO serving as a control. Following a 24 h incubation period, total RNA was extracted using Trizol and subsequently utilised for the preparation of cDNA libraries (Illumina® TruSeq®). Subsequent to this, sequencing was performed on the Illumina HiSeq 2000 (100-base paired-end). Three replicates were utilised for the majority of the samples; however, for the kinetin treatment, five samples were used. Reads were quality-trimmed (Cutadapt v2.1), aligned to hg38 (STAR v2.7.11b), and splice isoforms were reconstructed (Stringtie v2.2.0). Gene expression was then quantified using Salmon v1.10.2 and analysed using Sleuth v0.30.0, with differentially expressed genes being identified as those with a $|b| > 2$ and $p < 0.05$. Gene Ontology analysis was performed using ClusterProfiler, org.Hs.eg.db, and GO.db. Heat maps were generated with pheatmap. The differential expression analysis was conducted by Petr Vojta and Jiří Voller.

5.6 Stress assays (PD)

SH-SY5Y (wt and PINK1 knockdown) cells (4.000/well, 96-well plate) were seeded in RPMI with 10% FBS (puromycin for knockdown) and incubated overnight. PARK E, PARK F (high passage, homozygous) and BJ fibroblasts (2.500/well) were prepared similarly in DMEM. Cells were treated in triplicate with stressors at six concentrations. Adenine and kinetin (25/50 μM) were applied as pretreatments, followed by stressor addition after 24 h. Various conditions (doses, durations, co-treatments) were tested for optimisation, and viability was assessed via resazurin.

Table 1. List of stressors and their established concentrations and dilutions for stress assays

Stressor	Stress effect	Concentration range [μM]
Bortezomib	Selective inhibitor of 20S proteasome	0.6 - 20
CCCP	Induction of activation of PINK1 Iinhibition of oxidative phosphorylation	6 - 200
Glyoxal	Production of ROS Decline of membrane potential of the mitochondria	3 - 3000
H_2O_2	Production of ROS	6 - 600
Menadione	Aldehyde oxidase inhibitor Generate ROS	0.02 - 20
MG132	Proteasome inhibitor	1.5 - 50
MPP^+	Irreversible mitochondrial complex I inhibitor	156 - 5000
Paraquat	Decreased superoxide dismutase (SOD) activity Elevated the level of malondialdehyde (MDA)	200 - 1500
Rotenone	Inhibitions of electron transfer from Fe-S centers in complex I to ubiquinone	0.2 - 50

5.7 Design of novel derivatives (library, synthesis, commercial)

Cytokinin derivatives were prepared in the Laboratory of Growth Regulators, Palacký University in Olomouc. Compounds from a chemical library of LGR were screened, and some of these compounds were newly synthesised.

The testing substances were kindly provided by the authors Lenka Zahajská, Václav Mik, Marek Zatloukal, Kamil Paruch, Libor Havlíček, Miroslav Soural, Zoila Gándara Barreiro or were purchased from OlChemIm Ltd.

5.8 Enzymatic Production of KMP *in vitro* (PD)

A solution of 0.5 mM adenine, kinetin, or 9-methylkinetin (negative control) was prepared by combining 100 mM Tris-HCl (pH 7.5), 10 mM $MgCl_2$, and 2 mM phosphoribosyl pyrophosphate (PRPP) in buffer. The reaction mixture (500 μl) was then incubated at 37 °C with gentle agitation. The reactions were then stopped at 5, 10, 15, 20, and 60 min by adding equal volumes of 0.1% trifluoroacetic acid (TFA) with 50 mM EDTA. The samples were then vortexed, centrifugated, and analysed via UPLC-MS. AMP and KMP concentrations were calculated by comparing peak areas with standards.

5.9 Enzymatic Production of KMP in cells (PD)

The cells were seeded in 10 ml of DMEM with 10% FBS per Petri dish, with the test substances added at 100 μM and the control receiving the vehicle. After 24 h, the cells were harvested by trypsinization, centrifugated, and resuspended in 1.2 ml of medium. Then, 100 μl of 1M TCA and 250 μl of oil were added to the microtubes with the cell

suspension and centrifuged. The supernatant was aspirated, and TCA was removed using ether, repeated three times. The samples were stored at -80 °C.

5.10 Data analysis

Molecular descriptors, including clogP, were calculated using the Rdkit Python package (https://www.rdkit.org). Data management, analysis, and visualisation were conducted using R (https://www.r-project.org), with the exception of *in vitro* pharmacology parameters, which were calculated in Microsoft Excel (analysis done by J. Voller). The effects of compounds on the wild-type to total ELP1 transcript ratio were analysed using a non-parametric method with correction for multiple testing, as described by Konietschke *et al.*[247] and implemented in the nparcomp R library. Statistical significance was defined by corrected p-values < 0.05.Standard errors for drug efflux ratios were calculated using the delta method, as described by Wu *et al.*[248].

5.11 *In vitro* pharmacology (FD)

The pharmacological analysis of the synthetic derivatives was carried out under the supervision of Barbora Lišková and Martina Medvědíková (Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University, Hněvotínská 3, CZ-77515 Olomouc, Czech Republic). For a more detailed exposition of the methodology, please refer to the dissertation. The bioavailability of the active ingredients was determined by methods: chemical stability, stability in human plasma, microsomal stability, parallel artificial membrane permeability assay, protein plasma binding assay, studies of the transport across Caco-2 and MDR-MDCK cell monolayers.

5.12 Compounds

A total of 264 compounds were tested, comprising both commercially available products and those synthesised by our chemists over the years.

6. RESULTS

Familial Dysautonomia (FD):

- **Current treatment** - Only symptomatic, no cure available.
- **Disease genotype** - Recessive point mutation in the donor splice site of intron 20 (IVS20+6T→C) of the ELP1 gene.
- **Potential therapies** - Kinetin and 2ClK. Use as positive controls.
- **Aim** - Identification of kinetin derivatives capable to rectify abnormal ELP1 pre-mRNA splicing.
- **Experimental approach**
  - PCR, agarose gel electrophoresis and capillary electrophoresis used to quantify transcripts, imunodetection of level of ELP1, viability assay of test substances.
  - 264 compounds were tested; 40 active, 36 borderline active.
- **Structure-Activity Relationship of this study**
  - Substitutions at position 2 (Cl, F) retained activity
  - Position 8 tolerates a variety of substituents, indicating it is outside the active site.
  - Positions 3 and 9 lost activity.
  - Isosteric replacements of the purine for the pyrimidine or imidazole rings
  - Several 4-chloropyrimidine derivatives were active
  - Substitution on the N^6-furfuryl side chain inactive.
  - Active/inactive complicated modifications of N^6-sidechain can be seen in disertation theses. Simplified the aromatic ring of kinetin (and BAP) can be replaced by a variety of heteroaromatic rings, particularly when the C2 atom is substituted with chlorine or a five-membered aliphatic ring. Acyclic derivatives and those in which the cycle incorporates or directly binds to the adenine amino group were inactive.
  - The investigation of TG003 (a SF2/ASF-dependent splicing modulator) and others did not elucidate the underlying mechanism of effect.
  - Several years later, a study was published that showed that 2ClK, which is structurally related, indeed binds to CLK and increases its activity[208].
  - Exon 20 inclusion requires phosphorylation of SRSF6 via CLK (interacts with 2ClK).
- **Pharmacokinetics (ADME) for active compounds by Dr. Lišková**
  - Compounds stable at neutral pH and in human plasma.
  - Variable stability in human liver microsomes and plasma protein binding.
  - Predicted to cross biological barriers, including the blood-brain barrier.
  - Parent compound (kinetin) was the most bioavailable.
- **Transcriptomics**
  - It was performed an RNA-seq analysis with *de novo* assembly to assess the effects of kinetin and equimolar 8-aminokinetin (compound 48).

- The complete list of differentially expressed transcripts and Gene Ontology (GO) analysis is available in the supplementary materials.
- Overrepresented GO categories for compound 48 included “spliceosome complex” and four categories related to translation.
- Upregulated LUC7L and downregulated WDR70.
- Other significant categories included chromatin remodeling and phosphatidylinositol binding.
- Bioinformatics was performed by Jiří Voller and Petr Vojta.

Familial parkinsonism (PD):

- **Current treatment** - Only symptomatic, no cure available.
- **Disease genotype** - Homozygous mutation PINK1 G309D on chromosome 1p36 leading to decreased activity of PINK1 kinase.
- **Potential Therapies** - Kinetin, Kinetin riboside.
- **Aim** - Identification of kinetin derivatives capable of protecting cells with mutated kinase PINK1 from stress.
- **Experimental Approach**
  - Stress assays with selected stressors and pretreatments, *in silico* molecular docking, caspase assay, imunodetection, mitophagy detection kit, study of metabolic conversion of cytokinins, analysis of the ability of human phosphoribosyltransferase (PRPT) to catalyse the conversion of cytokinin bases to the corresponding riboside monophosphates.
  - Stability studies of kinetin prodrugs by Dr. Lišková
- **Unexpected Finding**
  - Kinetin not only failed to protect cells but increased stress toxicity.
  - No protective effects were observed.
  - The administration of 100 μM K for 24 h, KRTP was detected at concentrations in the range of 0.5 - 5 μM
  - The conversion of selected cytokinin bases into respective monophoshates by phoshorybosyltransferase *in vitro* after 24h incubation was successful up to 25% product ratio.
- **Controversies and future directions**
  - The present study demonstrated that the combination of kinetin and stressors resulted in a heightened toxicity profile when compared with the separate application of these agents.
  - Future research may focus on kinetin analogs with improved pharmacological properties.
  - A known problem with reproducing scientific results was encountered, despite the use of the same protocols and also the same reagents as detailed in the article by Hertz *et al.*[1]

Publication 1

Maková, B., Mik, V., Lišková, B., Gonzalez, G., Vítek, D., Medvedíková, M., Monfort, B., Ručilová, V., Kadlecová, A., Khirsariya, P., Gándara Barreiro, Z., Havlíček, L., Zatloukal, M., Soural, M., Paruch, K., D'Autréaux, B., Hajdúch, M., Strnad, M. & Voller, J., Cytoprotective activities of kinetin purine isosteres. Biorganic Medicinal Chemistry 2021, 33, 115993.

Abstract

Kinetin (N^6-furfuryladenine), a plant growth substance of the cytokinin family, has been shown to modulate aging and various age-related conditions in animal models. Here we report the synthesis of kinetin isosteres with the purine ring replaced by other bicyclic heterocycles, and the biological evaluation of their activity in several *in vitro* models related to neurodegenerative diseases. Our findings indicate that kinetin isosteres protect Friedreich́s ataxia patient-derived fibroblasts against glutathione depletion, protect neuron-like SH-SY5Y cells from glutamate-induced oxidative damage, and correct aberrant splicing of the ELP1 gene in fibroblasts derived from a familial dysautonomia patient. Although the mechanism of action of kinetin derivatives remains unclear, our data suggest that the cytoprotective activity of some purine isosteres is mediated by their ability to reduce oxidative stress. Further, the studies of permeation across artificial membrane and model gut and blood-brain barriers indicate that the compounds are orally available and can reach central nervous system. Overall, our data demonstrate that isosteric replacement of the kinetin purine scaffold is a fruitful strategy for improving known biological activities of kinetin and discovering novel therapeutic opportunities.

Publication 2

Maková, B., Mik, V., Lišková, B., Dražarová, L., Medvedíková, M., Hořínková, A., Vojta, P., Zatloukal, M., Plíhalová, L., Hönig, M., Doležal, K., Forejt, K., Oždian, T., Hajdúch, M., Strnad, M., & Voller, J. (2025). Correction of aberrant splicing of ELP1 pre-mRNA by kinetin derivatives–a structure activity relationship study. European Journal of Medicinal Chemistry, 284, 117176. https://doi.org/10.1016/J.EJMECH.2024.117176.

Highlights:

- SAR study of 72 kinetin derivatives on ELP-1 mRNA splicing correction.
- ADME panel indicates good oral bioavailability.
- Compound 48 affects mRNA concentrations of mRNA splicing-regulating genes.

Abstract

Familial dysautonomia is a debilitating congenital neurodegenerative disorder with no causative therapy. It is caused by a homozygous mutation in ELP1 gene, resulting in the production of the transcript lacking exon 20. The compounds studied as potential treatments include the clinical candidate kinetin, a plant hormone from the cytokinin family. We explored the relationship between the structure of a set of kinetin derivatives (N = 72) and their ability to correct aberrant splicing of the ELP1 gene. Active compounds can be obtained by the substitution of the purine ring with chlorine and fluorine at the C2 atom, with a small alkyl group at the N7 atom, or with diverse groups at the C8 atom. On the other hand, a substitution at the N3 or N9 atoms resulted in a loss of activity. We successfully tested a hypothesis inspired by the remarkable tolerance of the position C8 to substitution, postulating that the imidazole of the purine moiety is not required for the activity. We also evaluated the activity of phytohormones from other families, but none of them corrected ELP1 mRNA aberrant splicing. A panel of *in vitro* ADME assays, including evaluation of transport across model barriers, stability in plasma and in the presence of liver microsomal fraction as well as plasma protein binding, was used for an initial estimation of the potential bioavailability of the active compounds. Finally, a RNA-seq data suggest that 8-aminokinetin modulates expression spliceosome components.

7. CONCLUSIONS

Familial dysautonomia is a debilitating hereditary neurodegenerative disease for which current treatment is only symptomatic. Although the standard ELP1 transcript persists in cells, its wild type levels are diminished. Research has identified kinetin, a cytokinin, as a promising candidate to bolster full-length transcript levels. Slaugenhaupt *et al*.[204] demonstrated that kinetin, and Yoshida *et al.*[251] showed that 2ClK (2) can correct exon 20 skipping in mutant ELP1 transcripts—findings corroborated in animal models and initial human studies.

To further investigate, were screened a broad set of N^6-substituted adenines for their ability to correct aberrant splicing of mutant ELP1[252,253]. Two splicing-regulating kinase inhibitors, TG003 and PF-670462, were also tested to elucidate the underlying mechanism. However, the observed effect was contrary to that anticipated. Unexpectedly, inclusion of exon 20 required phosphorylation of splicing factor SRSF6 via CLK, which interacts with 2ClK[208]. Structure–activity studies revealed that substitution at position 2 with chlorine or fluorine produced active compounds, whereas modifications at positions 3 or 9 abolished activity. Position 7 tolerated small alkyl groups and position 8 accepted diverse substituents, suggesting that position 8 lies outside the active site. Additionally, derivatives lacking the 5-membered ring proved active. *In vitro* ADME assays indicated that while compounds were stable at neutral pH and in plasma, their liver microsomal stability and protein binding varied. Most derivatives were predicted to cross the blood–brain barrier, though the parent compound was most bioavailable, with active efflux limiting some compounds (notably 2-chlorokinetin, improved by 8-amino substitution).

Parallel studies about Parkinson's disease aimed to identify cytoprotective compounds for typ of early onset PD hereditary PARK6 mutation. PINK1, a mitochondrial Ser/Thr kinase that protects substantia nigra neurons, is impaired by PARK6 mutations[239,255,256]. Attempts to reproduce Hertz *et al*.'s[1] findings in mutant PINK1 models revealed no protection, with kinetin even enhancing stressor toxicity. No protective effect was observed. Given the potential limitations of the model, including the relevance of the mutation or the state of the cells, it was decided to leave the results unreported.The idea of Prodrug strategies and further modifications was supported by observation from *C. elegans* metabolism that been demonstrated to efficiently metabolise certain N9-substitued kinetin derivatives into kinetin and its ribosylated forms[106] This direction of research still holds promise, for example derivatives with other cyclic ethers in position 9 could be explored.

8. LIST OF PUBLISHED PAPERS AND OTHER CONTRIBUTIONS

Papers in journals with impact factor

Maková, B., Mik, V., Lišková, B., Gonzalez, G., Vítek, D., Medvedíková, M., Monfort, B., Ručilová, V., Kadlecová, A., Khirsariya, P., Gándara Barreiro, Z., Havlíček, L., Zatloukal, M., Soural, M., Paruch, K., D'Autréaux, B., Hajdúch, M., Strnad, M. & Voller, J., Cytoprotective activities of kinetin purine isosteres. Biorganic Medicinal Chemistry 2021, 33, 115993.

Maková, B., Mik, V., Lišková, B., Dražarová, L., Medvedíková, M., Hořínková, A., Vojta, P., Zatloukal, M., Plíhalová, L., Hönig, M., Doležal, K., Forejt, K., Oždian, T., Hajdúch, M., Strnad, M., & Voller, J. (2025). Correction of aberrant splicing of ELP1 pre-mRNA by kinetin derivatives–a structure activity relationship study. European Journal of Medicinal Chemistry, 284, 117176. https://doi.org/10.1016/J.EJMECH.2024.117176.

Kadlecová, A., **Maková, B**., Artal-Sanz, M., Strnad, M., & Voller, J. (2019). The plant hormone kinetin in disease therapy and healthy aging. Ageing research reviews, 55, 100958.

Book chapter

Voller, J., **Maková, B**., Kadlecová, A., Gonzalez, G., & Strnad, M. (2017). Plant hormone cytokinins for modulating human aging and age-related diseases. *Hormones in ageing and longevity*, 311-335.

Conference contributions

I. **Nardelli, B**. Biological activity of cytokinin bases. Biotechnology of Phytohormones and Natural Substances, Malá Morávka, 2015. Oral presentation.

II. Voller, J., Plíhalová, L., Zahájská, L., Zatloukal, M., **Nardelli, B**., Kadlecová, A., Grúz, J., Schubert, D., Spíchal, L., Strnad, M. Anti-aging activity of phytohormones cytokinins. Healthy Aging: From Molecules to Organisms, Hinxton, 2015. Poster.

III. **Nardelli, B**. Cytokinin derivatives for splicing modulation. Growth regulators on the way, Malá Morávka, 2016. Oral presentation.

IV. Voller, J., **Maková, B**. Kadlecová, A., Zahájská, L., Plíhalová, L., Grúz, J., Zatloukal, M., Schubert, D., Spíchal, L., Strnad, M. Antiaging activity of plant hormones cytokinins. The future of aging, Warsaw, 2016. Poster.

V. **Maková, B**., Voller, J. Cytokinin derivatives for splicing modulation. The future of aging, Warsaw, 2016. Poster.

VI. **B. Maková**, A. Dudková, V. Mik, L. Zahájská, M. Zatloukal, K. Paruch, G. Gonzáles, M. Strnad, J. Voller. Modulation of alternative splicing by phytohormones, 1st International Caparica Conference in Splicing, Caparica, 2016. Abstract in the book of abstracts.

VII. Voller, J., **Maková, B**., Kadlecová, A., Zahájská, L., Plíhalová, L., Grúz, J., Zatloukal, M., Schubert, D., Spíchal, L., Strnad, M. Antiaging activity of plant hormones cytokinins. Trends in Natural Product Research – PSE Young Scientists' Meeting, Natural Products in Health, Agro-Food and Cosmetics, Lille 2017. Poster.

VIII. **Maková, B.** Cytokinin derivatives for therapy of neurodegenerative diseases. Chemistry and Biology of Phytohormones and Related Substances, Kouty nad Desnou, 2017. Oral presentation.

IX. 21. 6. - 22. 6. 2018 Meeting of young scientists of the Faculty of Medicine UPOL – oral presentation.

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9. SOUHRN (in Czech)

Studium mechanismu účinku cytoprotektivních cytokininů

Tato disertační práce poskytuje komplexní souhrn mnohostranných terapeutických účinků cytokininů a jejich derivátů na zdraví a stárnutí, působících na různé molekulární domény. Cílem této studie bylo identifikovat deriváty kinetinu s účinkem na familiární dysatonomii a hereditární Parkinsonovu nemoc.

Familiární dysautonomie je autozomálně recesivní onemocnění způsobené bodovou mutací, která vede k nesprávnému sestřihu mRNA a translaci nefunkčního proteinu ELP1, který je kritický pro funkci neuronů. Kinetin koriguje defekt sestřihu. V této studii byla sledována řada kinetinových derivátů na jejich schopnost zvýšit inkluzi exonu 20 v pre-mRNA ELP1. Několik nových derivátů prokázalo zlepšenou účinnost při korekci defektů sestřihu a vykazovalo příznivé farmakokinetické vlastnosti *in vitro*.

Typ časného nástupu familiárního parkinsonismu (PARK6) způsobený mutací G309D v genu PINK1 kóduje kinázu nezbytnou pro kontrolu mitochondriální kvality, která vede ke ztrátě dopaminergních neuronů v *substantia nigra pars compacta*. Bylo popsáno, že kinetin po intracelulární přeměně na kinetin ribosid-5´-trifosfát působí jako neosubstrát pro mutovanou kinázu. Nicméně, zatímco předchozí studie naznačovaly slibné výsledky, tato disertační práce nebyla schopna replikovat uváděné ochranné účinky kinetinu v buněčných modelech, což vyžaduje další výzkum alternativních modulátorů.

Cílem této studie bylo identifikovat deriváty kinetinu s vlivem na familiární dysatonomii a hereditární Parkinsonovu chorobu za použití technik molekulární biologie, analýzy transkriptomů a farmakokinetického profilování.

Klíčová slova: cytokininy, kinetin, sestřih mRNA, familiární dysautonomie, PINK1, neuroprotekce, farmakokinetika

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