THE ROLE OF AXONAL TRANSPORT AND MITOCHONDRIAL DYSFUNCTION IN NEURODEGENERATION - FOCUSING ON HUNTINGTON'S DISEASE

Summary of PhD Thesis

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I. Introduction

Neurodegenerative disorders are devastating diseases whose importance for the ageing population is steadily increasing. Despite recent and continuous research efforts the exact pathomechanism which causes neuronal dysfunction and cell death still remains unknown neither in the most common sporadic or familial neurodegenerative diseases, nor in the inherited forms such as Huntington's disease (HD) and there is no specific neuroprotective therapy so far. We investigated some aspects of two pathogenic hallmarks thought to be important in neurodegeneration: disrupted axonal transport and mitochondrial dysfunction.

Huntington's disease is the most common known autosomal dominantly inherited neurodegenerative disorder. Clinically it is characterized by motor dysfunction, cognitive and behavioural impairment and psychiatric disturbances, typically starting in mid-life and progressing relentlessly to death after a course of 10-25 years. HD is caused by expansion of a cytosine-adenine-guanine trinucleotide repeat in the protein coding region of the IT15 gene encoding an elongated polyglutamine tract in the huntingtin (HTT) protein. Neuropathological hallmark of HD is the loss of gamma-aminobutyric acidergic medium-sized spiny neurons (MSNs) in the striatum. The N-terminal fragments of mutant HTT accumulate in the nuclei of the affected neurons and form intranuclear aggregates. Transgenic mice expressing the N-terminal fragment of HTT with 82 CAG repeat, develop progressive neurological symptoms which resemble human pathology. They show decreased spontaneous locomotor activity and reduced explorative behaviour by aging. The brain of these mice exhibits striatal atrophy and neuronal intranuclear inclusions that are immunopositive for huntingtin and ubiquitin.

Axonal transport is a bidirectional process through which materials and signals are exchanged between the neuronal cell body and the synapse. Axonal transport is mediated primarily by microtubule-based molecular motors, large enzymes that use the energy of ATP hydrolysis to generate movement. Cytoplasmic dynein is a large motor protein complex responsible for retrograde axonal transport. Dynein functions in association with a multi-protein regulatory complex called dynactin. One of the most important roles of the dynein/dynactin motor complex is the removal of aggregation-prone proteins from the cell periphery to the place of degradation. Loss of dynein/dynactin function is considered an important factor in the pathogenesis of neurodegenerative diseases. Mutations in the gene encoding the dynein heavy chain (*DYNC1H1*) were found in Charcot-Marie-Tooth disease axonal type 2, in spinal muscular atrophy with lower extremity predominance and in malformations of cortical development. Several lines of evidence suggest that altered axonal

transport and dynein contribute to the pathogenesis of HD. Swollen axons and accumulated vesicular proteins were found in HD patients tissue and in several animal models of HD. Dynein, as well as the dynactin subunit $p150^{Glued}$, are binding partners of HTT and of huntingtin associated protein 1. Moreover, the activity of the dynein complex is positively regulated by wild-type HTT, and strongly decreased by mutant HTT.

Cramping (*Cra*) mice carry a point mutation in the dynein heavy chain gene causing disturbed dynein function. Heterozygous *Cramping* (*Cra/+*) mice develop a characteristic phenotype: they show unusual twisting of the body, hind limb clasping when held by the tail and abnormal gait. This phenotype is partially explained by a relative mild proprioceptive sensory neuropathy observed in these mice.

Mitochondrial dysfunction is an early, active, common contributor to all major neurodegenerative diseases, such as to HD. Peroxisome proliferator-activated receptor (PPAR) gamma coactivator 1 alpha (PGC-1α) is a transcriptional coactivator that plays a key role in coordinating the expression of a wide range of nuclear encoded mitochondrial proteins. Due to this key position in the metabolic regulatory network PGC-1α is labelled as a "master regulator" of mitochondrial respiration and mitochondrial biogenesis. PGC-1α exists in multiple isoforms, among which full length isoform (FL-PGC-1α) is more specialized in increasing mitochondrial biogenesis. PGC-1α knock-out mouse models display several metabolic abnormalities, such as cold intolerance and impaired body weight regulation. Moreover they share many phenotypical similarities to transgenic mouse models of HD. Mice show hind limb clasping, dystonic posturing, stimulus-induced myoclonus and display spongiform-like vacuolization predominantly in the striatum.

There is an increasing number of evidence suggesting the role for PGC-1α function in the pathogenesis of HD. Mutant HTT supresses the expression of PGC-1α. Moreover the genetic ablation of PGC-1α aggravates the phenotype of a knock-in HD mouse model and *in vivo* transfection with PGC-1α can rescue some aspects of the striatal pathology in the R6/2 transgenic HD mice. The clinical significance of the PGC-1α system for HD is demonstrated by that common variants of the *PPARGC1A* gene are associated with a significant delay in onset of motor symptoms in HD patients of several years.

Increased mitochondrial mass is frequently observed in human diseases directly or indirectly involving mitochondrial dysfunction and is usually called "mitochondrial proliferation". It is considered as a compensatory mechanism mitigating a compromised energy metabolism. Consistent with this view, muscle overexpression of FL-PGC-1α, leading to remarkable mitochondrial proliferation, is broadly protective for muscle function in

mitochondrial myopathies, also in amyotrophic lateral sclerosis. Albeit mitochondrial proliferation might also be detrimental through alterations of mitochondrial regulatory functions such as apoptosis, calcium metabolism or oxidative stress. Mechanisms underlying mitochondrial proliferation are unknown. Recently, others from our workgroup showed that the *Cramping* mice develop systemic mitochondrial dysfunction with increased mitochondrial mass accompanied by PGC-1α activation.

An important opportunity provided by the existence of animal models of neurodegenerative diseases is the test of supposed protective agents. One possible candidate is L-carnitine (LC) which has antioxidant properties and is used to improve mitochondrial function. The main role of LC is in cellular energy metabolism, it improves mitochondrial energetics and scavenges free radicals. It plays a role in the transport of long-chain fatty acids into the mitochondria for beta-oxidation, providing energy and acetyl-coenzyme A (CoA) formation. On the other hand, it contributes to the removal of short- and medium-chain fatty acids preventing these toxic accumulation in the mitochondria and leading to an increase of free CoA. Thus, it controls the mitochondrial acetyl-CoA/ CoA ratio which is crucial for mitochondrial metabolism. A double-bind placebo controlled human study did not find any significant changes in HD patients as compared with healthy subjects that upon low dose L-carnitine. We suggested that LC may be effective in higher doses.

II. Aims

The aims of our studies were as follows:

(i) to provide a direct genetic evidence linking cytoplasmic dynein mutation to striatal dysfunction by detailed characterisation of *Cramping* mice bearing a point mutation in the dynein heavy chain 1 gene.

(ii) to study whether the recently showed systemic mitochondrial dysfunction (Eschbach et al., 2013) and compensatory mitochondrial proliferation in *Cramping* mice is FL-PGC-1α dependent. We investigated the effect of FL-PGC-1α ablation in *Cramping* mice with extended characterisation of the phenotype using longitudinally performed behavioural tests, muscle histology, electron microscopy.

(iii) to study whether L-carnitine administration, in high dose, exerts beneficial effects on the survival as well as the behavioural and neuropathological phenotype in N171-82Q transgenic mouse model of HD.

III. Results

The motor phenotype of *Cra*/+ mice is characterized by early muscle weakness, progressive incoordination and hyperactivity

We first performed a battery of motor and behavioural tests in *Cramping* mice (*Cra*/+). *Cra*/+ mice showed reduced total and forelimb muscle grip strength compared with wild-type mice as early as 3 months of age, and suffered from an impairment in motor coordination that mildly increased with aging, as observed using an accelerating rotarod test. *Cra*/+ mice displayed hyperactivity in the open field arena as revealed by increased track length and average velocity. The level of anxiety appeared similar between *Cra*/+ mice and their wild-type littermates as assessed using the elevated plus maze paradigm. We performed the Morris water maze test which showed no spatial memory deficits in *Cra*/+ mice. Taken together, *Cra*/+ mice display muscle weakness and incoordination with increased open field activity in the absence of anxiety and obvious spatial working memory deficits.

Cra/+ mice present with striatal atrophy and lateral ventricle enlargement

We found that forebrain, but not hindbrain, wet weight was decreased in *Cra*/+ mice suggestive of atrophy. The striatum and cerebral cortex of *Cra*/+ mice appeared grossly normal using haematoxylin/eosin staining, and the cortical layer organisation was preserved, suggesting that the defect was not due to abnormal cortical development. *In vivo* brain imaging using MRI showed a significant reduction in the volume of the *Cra*/+ mice striata at both 5 and 10 months of age, while concomitantly, the volumes of the lateral ventricles were significantly increased. Thus, mutation in dynein leads to striatal atrophy in mice.

Progressive astrocytosis in the absence of neurodegeneration in the striatum

Reactive astrocytosis represents a typical marker of neuronal stress and is often a sign of an underlying pathology. Interestingly, reactive astrocytosis, as revealed by glial fibrillary acidic protein (GFAP) immunoreactivity was dramatically increased in the striatum of 8 months old *Cra*/+ mice, and this increase was even higher at 18 months of age. Consistent with this observation, striatal GFAP mRNA levels as measured using RT-qPCR were higher in *Cra*/+ mice than in wild-type littermates at 8 months, but not at 4 months of age. To determine whether astrocytosis was associated to neurodegeneration, we determined the total number of DARPP32 (dopamine and cAMP regulated phosphoprotein of a molecular weight of 32 kDa) positive medium spiny neurons (MSNs), the neuronal population comprising more than 95% of striatal neurons, using stereological analysis. The analysis of DARPP32 positive

MSNs showed a non-significant trend towards decreased number at 6 months of age. These data show that the phenotype of dynein mutant mice is rather due to neuronal dysfunction than to neurodegeneration in the striatum.

Altered dopamine signalling and D1 receptor binding in the striatum of *Cra*/+ mice

D1, but not D2, dopamine receptor mRNA levels were decreased in 8 months old *Cra*/+ mice as shown using RT-qPCR. D1 receptor expressing cells synthesize substance P, whereas D2 receptor expressing cells synthesize pre-proenkephalin. We found that substance P, but not pre-proenkephalin, mRNA levels appeared decreased in 8 months old *Cra*/+ mice, which corroborates the selective down-regulation of the expression of D1 dopamine receptors in striatal neurons. We performed PET analysis of the binding of the D1 receptor selective ligand [^{11}C] SCH-23390 which showed a decrease of the signal in the brains of *Cra*/+ mice. We extended our D1-PET scans by using [^{18}F]Fallypride, a high-affinity selective dopamine D2/3 receptor ligand. We observed a significant reduction of [^{18}F]Fallypride uptake in the striatum of *Cra*/+ mice compared with wild type animals, lending further support for the involvement of the striatal dopaminergic system in the *Cra*/+ pathogenesis.

Mitochondrial proliferation in *Cramping* mice is dependent on endogenous FL-PGC-1α

To determine whether PGC-1α is functionally involved in *Cramping* induced mitochondrial proliferation, we ablated FL-PGC-1α in these mice. We chose FL-PGC-1α ablation as this isoform is more specialized in increasing mitochondrial biogenesis and pan-PGC-1α ablation is very toxic *per se* for muscle physiology. We crossed FL-PGC-1α -/- mice with *Cramping* mice to generate *Cramping* mice deficient in FL-PGC-1α (termed *Cra*/FLα -/- mice). The ablation of FL-PGC-1α in *Cramping* mice completely abolished the previously observed increases in mtDNA levels in muscles. At 6 months of age, *i.e.* an age at which mitochondrial dysfunction is not histologically and biochemically evident in *Cramping* mice, we observed a 20% increase in citrate synthase activity in *Cramping* muscle, which was fully reverted by FL-PGC-1α ablation. This was associated with unchanged mitochondrial respiratory complex activities and normal ratios between respiratory chain complex activities suggesting that mitochondrial proliferation maintained close to normal respiratory activity at that age. From an ultrastructural point of view, the *Cramping* mutation leads to giant mitochondria invading sarcomeres. FL-PGC-1α deficiency reverted this mitochondrial proliferation. Thus, mitochondrial proliferation in *Cramping* mice is fully dependent upon

endogenous FL-PGC-1α and cannot be rescued by the roughly normal expression of NT-PGC-1a in FL-PGC-1α -/- mice.

Endogenous FL-PGC-1α mitigates overall phenotype, mitochondrial dysfunction and the neurological phenotype in *Cramping* mice

We next asked whether ablating the increase in mitochondriogenesis in *Cramping* mice, through FL-PGC-1α ablation, modified the phenotype of the mice. *Cra*/FLα -/- mice displayed a much more severe phenotype than single mutations. They showed prominent kyphosis, and abnormal posture as well as progressive hair loss. Both male and female *Cra*/FLα -/- mice displayed body weight loss as compared with the three other genotypes. Body temperature of *Cra*/FLα -/- mice became progressively lower in females while in males the defect was also present in single FL-PGC-1α -/- mice. At 12 months of age, both single *Cramping* and FL-PGC-1α -/- muscles showed the expected decrease in SDH activity in both tibialis anterior and soleus muscles. The combination of both mutations potently exacerbated this mitochondrial defect.

The *Cramping* mutation leads to a stereotypical neurological phenotype that includes loss of muscle strength and incoordination as prescribed above. As compared with *Cramping* mice, *Cra/*FL*α* -/- mice showed an earlier and stronger loss of grip strength in forelimbs and all limbs. Tremor, a phenotype occasionally observed in *Cramping* or FL-PGC-1α -/- mice after 9 months of age, occurred systematically before 6 months of age in *Cra/*FL*α* -/- mice. Indeed, compound transgenic mice were unable to hang on a string as early as 4 months of age, while *Cramping* mice were still able to do so at least 10 seconds until 9 months of age. Further supporting this point, compound transgenic mice showed profoundly impaired rotarod performance as compared with all three other genotypes at 6, 9 and 12 months of age and decreased rearing activity at 8 and 12 months of age.

L-carnitine administration significantly improved the survival and ameliorated the motor symptoms of N171-82Q mice

Further, we tested the effects of L-carnitine (LC) administration in the N171-82Q transgenic mouse model of HD. The mean of survival of the vehicle-treated transgenic mice was 125.6 days. LC treatment caused a significant increase of 14.91% in the survival time (144.3 days). From the age of 14 weeks the N171-82Q transgenic HD mice started to move more slowly and less compared with wild-type mice in the open field apparatus. This decreased motility was completely reverted by LC administration. LC itself did not have any

influence in wild-type mice mobility. Further, the frequency of rearing was significantly reduced in transgenic mice at the age of 15 weeks but not in the L-carnitine treated group.

L-carnitine treatment was neuroprotective in N171-82Q HD mice

L-carnitine treatment also ameliorated the striatal neuronal atrophy in transgenic HD mice. Our quantitative analysis demonstrated that the LC-treated transgenic animals had a significantly higher number of surviving striatal neurons concerning cresyl violet-staining relative to the vehicle-treated group. Moreover we quantified the huntingtin-immunoreactive (IR) aggregates visualized by EM48 polyclonal antibody in the outer lamina of the pyriform cortex (layer II), which is an important area of the N171-82Q transgenic mice and within the lateral striatum. The EM48-IR aggregates were much more prominent within the cortex as compared with the neostriatum. In the L-carnitine-treated group, fewer huntingtin aggregates were detected in both areas compared with the vehicle-treated transgenic group. LC treatment significantly reduced the numbers of cortical aggregates. In the lateral striatum LC treatment induced a slight, but not significant decrease of the huntingtin-IR aggregates.

IV. Discussion

In this PhD work we showed additional evidence of the involvement of the molecular motor dynein and mitochondrial dysfunction in the pathogenesis of neurodegenerative diseases.

First, we demonstrated the *in vivo* requirement of cytoplasmic dynein in the function of the striatum. *Cramping* mice display early onset motor and behavioural abnormalities such as abnormal gait, hind limb clasping, motor incoordination, muscle weakness and hyperactivity. A relatively mild proprioceptive neuropathy was proved previously in dynein mutant mice but this does not explain the overall behavioural disturbances observed here. Our findings confirmed a striatal involvement in *Cramping* mice. We found the selective down-regulation of D1 dopamine receptors expression, striatal atrophy, accompanied with enlargement of lateral ventricles, decreased binding to either D1 or D2 dopamine receptors and prominent astrocytosis in the striatum of *Cra*/+ mice.

Interestingly, the behavioural phenotype of *Cra*/+ mice and striatal atrophy detected by MRI, appeared between 3 and 5 months of age, while astrocytosis, decreased gene expression of D1 receptors and decreased binding potential of D1, D2 receptors were detectable later, after 8 months of age. The fact that behavioural abnormalities forego marked histopathological and biochemical changes in the striatum is not without precedent. For

instance, previous studies reported that motor dysfunction in huntingtin knock-in mice occurred long before any clear signs of striatal lesions. We did not detect decreased DARPP32 neuronal counts, showing that the striatal phenotype was not associated with cell death of MSNs. Our data however does not exclude the occurrence of a very slow and subtle process of striatal neurodegeneration that would be difficult to detect. Also, astrocytosis itself might be an astrocyte-autonomous event. Dynein expression and function in astrocytes has been poorly characterized and the elucidation of astrocytic dynein to the phenotype of dynein mutant mice will require the generation of conditional knock out mice.

In summary, we showed that *Cramping* mice bearing a point mutation in the molecular motor dynein display striatal dysfunction which can better explain the phenotype observed in these mice. Our findings provide direct evidence of the involvement of axonal transport machinery, notably dynein in the maintenance of striatal function and may have major implications for our understanding of the pathogenesis of HD.

Besides dynein disruption we investigated the role of mitochondrial dysfunction in neurodegeneration. **We showed that full length PGC-1α is absolutely required for compensatory mitochondrial proliferation occurring in *Cramping* mice, confirmed by the fact that its ablation strongly exacerbates metabolic and neurological phenotype in these mice.** Others from our workgroup previously described decreased mitochondrial respiration along with increased mtDNA levels in *Cramping* mice. Interestingly, this compensatory response was not observed in cultured embryonic striatal neurons or fibroblasts, even in homozygous *Cramping* cells. Thus, mtDNA copy number is increased *in vivo* in *Cramping* mice as a possible compensatory response. The activation of PGC-1α, a transcriptional coactivator responsible for mitochondrial biogenesis, was hypothesized to underlie these observations.

Here we showed that FL-PGC-1α ablation, and subsequent loss of mitochondrial proliferation, strongly exacerbated the previously observed abnormalities of *Cramping* mice, both metabolic (muscle mitochondrial function) and neurological (grip strength, rotarod, tremors). New defects appeared in *Cra/*FL*α -/-* mice which were absent in single transgenic mice, in particular a pronounced kyphosis, profound hair and weight loss and inability to rear. Thus, the mitochondrial proliferation elicited by FL-PGC-1α increased activity is able to mitigate the phenotype of *Cramping* mice. This is in line with other experiments that showed that transgenic overexpression of FL-PGC-1α is able to attenuate symptoms of mitochondrial diseases in a tissue specific manner. Moreover PGC-1α overexpression selectively in skeletal muscle of transgenic mouse model of ALS improved muscle endurance and locomotor

activity at symptomatic stages of the disease. Lentiviral-mediated expression of PGC-1α in the striatum of R6/2 transgenic mouse model of HD was neuroprotective preventing neuronal atrophy in these mice. On the other hand crossbreeding PGC-1α knock-out mice with HD knock-in mice worsened significantly the behavioural and neuropathological abnormalities, which deleterious effect was even more profound after 3-NP administration.

In all, we demonstrated here that the FL-PGC-1α is required for disease induced mitochondrial proliferation. We also showed the protective potential of FL-PGC-1α against mitochondrial dysfunction, which has major implications in neurodegeneration and might provide potential therapeutic targets.

An indirect way to support mitochondrial involvement in neurodegeneration is via therapeutic interventions with drugs affecting mitochondrial function. **We found that in higher doses L-carnitine (LC) produced significant improvement in survival and locomotor activity (including total distance moved, immobility time and velocity) in the N171/82Q transgenic mouse model of HD.** Though in an earlier human study, no significant changes were observed upon low dose LC on the abnormal involuntary movement scale, the mini-mental status, the reaction time and verbal fluency in HD patients. In our experiment, the improvement in survival of 14,91% is nearly equivalent to the effects of other compounds with antioxidant properties, such as BN82451, remacemide and coenzyme Q10, although slightly less than the effects of creatine and cysteamine. Others demonstrated 25% neuronal cell loss and a 20% decrease in striatal cell volume in the striatum of N171-82Q mice at 16 weeks of age. We also reproduced this striatal neuronal loss in vehicle-treated transgenic HD mice compared with wild-type animals. This decline was significantly reverted under LC treatment. The N-terminal fragments of mutant HTT accumulate in the nucleus of affected neurons and form intranuclear aggregates. In our results there was a significant decrease in EM48 immunoreactivity in the pyriform cortex of LC-treated N171-82Q mice and a slight decrease in the striatum relative to the vehicle-treated group.

LC and its acetyl ester, acetyl-LC (ALC) were found to be neuroprotective in different animal models of neuronal dysfunction / neurodegeneration, such as in spinal cord injury, mitochondrial toxin models induced by 3-NP, rotenone and methamphetamine induced neurotoxicity. ALC showed neuroprotective properties in rats exposed to global hypoxia via inducing PGC-1α and nuclear respiratory factor-1 mediated mitochondrial biogenesis. Recent data obtained from patients with inherited neurometabolic diseases confirmed the involvement of L-carnitine in the pathogenesis and supposed LC supplementation as beneficial. Several studies were performed in AD and dementia, and however preclinical

studies and earlier clinical studies suggested a protective effect of ALC treatment, a Cochrane meta-analysis revealed that there is no evidence of benefit for ALC treatment in dementia and AD. Though recently published data of a phase II randomized clinical trial with combinatorial nutritional supplementation (also including ALC) is promising, confirming a significant improvement in dementia rating scale.

The importance of reactive oxygen species (ROS) and free radicals has an increased attention in the last decade, since these molecules are aggravating factors in cellular injury and aging processes. There is a strong evidence of a role of excitotoxicity and oxidative damage in the HD pathogenesis. It has been demonstrated that the expression of mutant HTT in neuronal and non-neuronal cells causes increased ROS, which contributes to cell death. They raise the possibility that agents, which have antioxidative activity, may be useful as therapies to slow the progression of neurodegeneration in HD.

We demonstrated that L-carnitine administration to N171-82Q transgenic mice extends the survival, ameliorates the motor performance, preserves striatal neuron count and decreases the number of intranuclear HTT aggregates, these parameters being important in the pathomechanism of HD. We suggest that L-carnitine may develop its effect through decreasing the oxidative damage. While the exact mechanism responsible for the beneficial effects of LC in N171-82Q mice is uncertain, our data suggest that L-carnitine is neuroprotective and may possibly be beneficial in the treatment of HD.

In all, our findings highlight the role of the molecular motor dynein and mitochondrial dysfunction in neurodegeneration, notably in Huntington's disease. These data contribute to better understanding of the pathomechanism of neurodegenerative diseases and offer potential therapeutic ways.

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VI. List of abbreviations

3-NP	3-nitropropionic acid
ALC	acetyl-L-carnitine
CoA	Coenzyme A
Cra	*Cramping* allele of the *Dync1h1* gene (p.Y1055C mutation)
DARPP32	dopamine and cAMP regulated phosphoprotein of a molecular weight of 32 kDa
DYNC1H1	dynein heavy chain gene 1
EM48	polyclonal antibody recognizing the first 256 amino acids of human huntingtin
FL	full length
GFAP	glial fibrillary acidic protein
HD	Huntington's disease
HTT	huntingtin
IR	immunoreactive
LC	L-carnitine
MRI	magnetic resonance imaging
MSNs	medium sized spiny neurons
mtDNA	mitochondrial DNA
PET	positron emission tomography
PGC-1 α	PPARγ coactivator 1 alpha, encoded by the *PPARGC1A* gene
PPAR	peroxisome proliferator-activated receptor
SDH	succinate dehydrogenase

Publications directly related to the thesis

I. Braunstein KE*, Eschbach J*, **Róna-Vörös K***, Soylu R, Mikrouli E, Larmet Y, René F, De Aguilar JL, Loeffler JP, Müller HP, Bucher S, Kaulisch T, Niessen HG, Tillmanns J, Fischer K, Schwalenstöcker B, Kassubek J, Pichler B, Stiller D, Petersen A, Ludolph AC, Dupuis L (2010): A point mutation in the dynein heavy chain gene leads to striatal atrophy and compromises neurite outgrowth of striatal neurons. Hum Mol Genet 19: 4385-98 (original paper; **IF: 8,058**)

II. Róna-Vörös K, Eschbach J, Vernay A, Wiesner D, Schwalenstocker B, Geniquet P, Mousson De Camaret B, Echaniz-Laguna A, Loeffler JP, Ludolph AC, Weydt P, Dupuis L (2013): Full-length PGC-1α salvages the phenotype of a mouse model of human neuropathy through mitochondrial proliferation. Hum Mol Genet 22: 5096-106 (original paper; **IF: 6,677**)

III. Vámos E, **Vörös K**, Vécsei L, Klivényi P (2010): Neuroprotective effects of L-carnitine in a transgenic animal model of Huntington's disease. Biomed Pharmacother 64: 282-6 (original paper; **IF: 2,208**)

Total impact factor of original papers directly related to the thesis: **16,943**

Publications not directly related to the thesis

I. Róna-Vörös K, Weydt P (2010): The role of PGC-1α in the pathogenesis of neurodegenerative disorders. Curr Drug Targets 11: 1262-9 (review; **IF: 3,061**)

II. Vámos E, **Vörös K**, Zádori D, Vécsei L, Klivényi P (2009): Neuroprotective effects of probenecid in a transgenic animal model of Huntington's disease. J Neural Transm 116: 1079-86 (original paper; **IF: 2,259**)

Cumulative impact factor: **22,263**

** The authors wish it to be known that, in their opinion, the first 3 authors should be regarded as joined First Authors and are listed in alphabetical order.*