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Review Article

# Metabolic Disturbances in Diseases with Neurological Involvement

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**ABSTRACT: Degeneration of specific neuronal populations and progressive nervous system dysfunction characterize neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. These findings are also reported in inherited diseases such as phenylketonuria and glutaric aciduria type I. The involvement of mitochondrial dysfunction in these diseases was reported, elicited by genetic alterations, exogenous toxins or buildup of toxic metabolites. In this review we shall discuss some metabolic alterations related to the pathophysiology of diseases with neurological involvement and aging process. These findings may help identifying early disease biomarkers and lead to more effective therapies to improve the quality of life of the patients affected by these devastating illnesses.**

***Key words:*** neurodegenerative diseases; inherited diseases; brain metabolism

Neurodegenerative disorders are progressive diseases characterized by the loss of specific neuronal populations resulting in different clinical phenotypes. These diseases are also recognized as conformational diseases or disorders of protein aggregation or catabolism and are classified according to the main pathophysiological processes involved. Examples include Alzheimer's disease (AD), Parkinson's disease (PD), and others [1]. In most of these disorders, the cause of protein aggregation remains unknown. However, it might be attributed to autophagic dysfunction, since the autophagy consists of a proteolytic system in which cytosolic components are degraded in lysosomes and is pivotal to cellular survival [2].

The main risk factor for neurodegenerative diseases is aging. Many of these diseases share chronic pro-inflammatory environment as a common feature. The trigger of chronic inflammation in most of cases remains unclear, although it may be the interplay between innate and adaptive responses against certain stimuli, such as aggregated proteins, heat shock proteins, and other local danger-associated molecular patterns that may contribute to a final pathogenic pathway [3]. The selective expression of mutant proteins associated with neurodegenerative diseases in astrocytes [4], along with microglia [5], may contribute to the chronic neuroinflammation.

Mitochondrial alterations also play a role in these diseases, elicited by either genetic alterations (mitochondrial or nuclear DNA) or exogenous toxins affecting mitochondrial functioning [6]. In this scenario, mitochondrial DNA mutations cause enzymatic defects of the respiratory chain complexes, which render cells devoid of energy; these changes tend to affect systems

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with high energy demands, including brain, skeletal muscle and heart [7,8]. Furthermore, disruption of key steps of energy metabolism was previously shown in neurodegenerative diseases, particularly for respiratory chain complexes [9-13]. It should, however, emphasized that the mitochondrial involvement linked to the pathophysiology of neurodegenderative diseases is not restricted to defects in energy metabolism and DNA mutations, but also oxidative stress [14-16] and alterations in mitochondrial shape and distribution [17-19], as well as metabolic communication with other organelles [20].

Neurodegeneration and mitochondrial dysfunction are also found in many genetic disorders, including inborn errors of metabolism such as glutaric aciduria type I (GA I), phenylketonuria (PKU), methylmalonic acidemia (MMAemia), and Niemann-Pick type C (NPC) disease. Data from patients and animal models evidenced that energy dysfunction may play a role in the pathophysiology of the characteristic brain damage found in these diseases. The evidence points out bioenergetic impairments as one of the most important biochemical events that lead to neurodegeneration in these metabolic disorders.

This review will discuss some metabolic alterations related to the pathophysiology of certain diseases with neurological involvement and aging process.

## Bioenergetic alterations in inherited metabolic diseases with CNS involvement

### *Glutaric acidemia type I*

GA I is a severe disease caused by the inherited deficiency of glutaryl-CoA dehydrogenase activity, a mitochondrial enzyme that participates in the lysine and tryptophan catabolism pathways [21]. Patients affected by GA I present increased levels of glutaric (GA), 3-hydroxyglutaric (3HGA) and trans-glutaconic (tGA) acids in tissues and body fluids [21,22]. The main clinical presentation includes progressive macrocephaly and striatal necrosis (medium-spiny neurons) following episodes of metabolic decompensation, basal ganglia degeneration, frontotemporal hypoplasia, and delayed myelination/hypomyelination [23-24]. Currently, excitotoxicity, oxidative stress and alterations of bioenergetics are suggested to play a role in the pathophysiology of the characteristic neurodegeneration observed in GA I patients.

Patients affected by this disease excrete increased levels of lactate and dicarboxylic acids, indicating a possible role of mitochondrial dysfunction in GA I patients [25-26]. Evidence from animal models of GA I demonstrate that brain energy metabolism is severely affected. Koeller and colleagues [27] showed alterations of the expression of genes involved in mitochondrial energy metabolism and transport in cerebral cortex from a knock out mouse model. Many studies reported that GA, and 3-HGA elicit bioenergetics dysfunction both *in vivo* and in vitro, while tGA did not affect mitochondrial metabolism [28]. GA and 3HGA showed an inhibitory effect on complexes of mitochondrial respiratory chain in rat brain and chick embryonic neurons [29-31]. This impairment of mitochondrial function causes energy failure in the brain, which may lead to secondary excitotoxicity and oxidative stress [32-35]. These organic acids were also shown to decrease cellular phosphocreatine levels and creatine kinase (CK) activity, as well as glucose and pyruvate oxidation in cerebral cortex, striatum, midbrain and hippocampus in rats [29,31,36,37], similar to Alzheimer's, Parkinson's and Huntington's diseases brain areas affected (see bellow), reinforcing the idea that energy metabolism impairment may be an important mechanism involved in the characteristic striatal degeneration found in GA I patients.

### *Phenylketonuria*

PKU is a genetic disease caused by an abnormal phenylalanine (Phe) metabolism due to a phenylalanine hydroxylase deficiency. This enzymatic deficiency leads to increased levels of Phe, phenyllactate (PLA), phenylpyruvate (PPA), and phenylacetate (PAA) in tissues, plasma and urine of affected patients [38]. Severe neurological impairment is the main characteristic of phenylketonuric patients, which appears to be a direct consequence of neuronal cell loss, white matter abnormalities, and reduction of synaptic density [38-41].

Many efforts have been made in order to identify the underlying mechanisms of the pathophysiology of the severe brain damage found in phenylketonuric patients. Studies in patients and animal models suggest that the accumulating metabolites exert neurotoxic effects, particularly Phe. Phe and its metabolites cause DNA damage in patient blood and brain of animals submitted to an animal model of PKU [42,43] and cell apoptosis in cultured neurons [44-46]. It has been suggested that one of the main mechanisms responsible for this neuronal damage may be an energy metabolism impairment. In this context, Wasserstein and colleagues [47] demonstrated by positron emission tomography (PET) that phenylketonuric patients had decreased relative glucose metabolic rates in cortical regions. On the other hand, the same authors showed an increased activity in subcortical regions including the striatum and limbic system. Moreover, a MRS study in vivo with adult patients demonstrated subtle abnormalities of cerebral energy metabolism in PKU steady-state conditions, such as increased ADP and decreased inorganic phosphate

content. Furthermore, these abnormalities were accentuated by an increased dietary Phe load [48].

Studies using animal models also described deleterious effects of Phe, PLA, PPA and PAA on important markers of bioenergetics activity. Costabeber and colleagues [49] demonstrated that Phe significantly inhibited CK activity in vitro and in vivo in brain of young rats. In addition, Phe decreased pyruvate kinase (PK) activity, glucose utilization, and lactate release, and increased ADP brain levels [50,51]. Moreover, chronic Phe administration inhibited respiratory chain complexes I-III and succinate dehydrogenase (SDH) activities in cerebral cortex of rats [52]. Taken together, these studies suggest that Phe is the main toxic metabolite in PKU and that bioenergetics imbalance contributes to its toxicity.

### *Methylmalonic Acidemia*

MMAemia is an organic acidemia caused by the deficiency of L-methylmalonil-CoA mutase activity, a mitochondrial enzyme involved in the catabolism of the amino acids isoleucine, valine, methionine and threonine, as well as thymine, odd carbon number fatty acids, and cholesterol [53]. The lack of L-methylmalonil-CoA mutase activity increases methylmalonic acid (MMA) levels in tissues and body fluids of patients, especially in the brain. Patients affected by MMA present predominantly with neurological signs and symptoms, with marked bilateral destruction of the globus pallidus [53-55].

Observations in MMAemia-affected patients and animal models of the disease suggest that mitochondrial dysfunction is an important process participating in the neurodegeneration found in this condition. In this scenario, lactic acid levels are elevated in the globus pallidus, cerebrospinal fluid (CSF), and urine of patients [56]; citric acid cycle intermediates were also elevated in the blood [53], suggesting impairment of mitochondrial metabolism. Indeed, mitochondrial abnormalities and inhibition of respiratory chain complexes were observed in various tissues from MMAemia-affected patients [57-60].

Studies in vitro demonstrated that MMA inhibited succinate-supported oxygen consumption in intact isolated mitochondria by inhibiting mitochondrial succinate transport through dicarboxylate carrier [61]. In the same way, malate transport by the same transporter is also impaired by MMA [62]. Furthermore, important enzyme activities involved in energy metabolism are affected by metabolites accumulating in MMAemia, including respiratory chain complexes in brain homogenates [63,64]. Utter and colleagues [65] observed that MMA is a competitive inhibitor of pyruvate carboxylase activity. This organic acid also inhibits brain mitochondrial utilization of ketone bodies and lactate through competitive inhibition of β-hydroxybutyrate [66,67] and lactate dehydrogenases [68]. Moreover, Schuck and colleagues [69] reported decreased CK activity by MMA in rat brain homogenates. In addition, MMA blocks aerobic glucose oxidation due to a reduction of $CO_2$ production from [2-$^{14}$C] glucose and [U-$^{14}$C] acetate and increased lactate synthesis in rat brain slices [70]. MMA also induces cell death by inhibiting mitochondrial permeability transition pore [71-72], a structure formed by proteins as ATP synthase and adenine nucleotide traslocase and whose activity control cell death by apoptosis and superoxide generation. Furthermore, Sauer and colleagues [73] demonstrated that methylmalonyl-CoA (precursor of MMA) decreased pyruvate and α-ketoglutarate dehydrogenase activities.

These experimental evidences suggest that MMA, the main metabolite accumulating in MMAemia, impairs brain bioenergetics and this impairment may collaborate to neurodegeneration found in MMAemia patients.

### *Niemann-Pick type C disease (NPC)*

NPC is a fatal lipid storage disorder characterized by cholesterol accumulation in endosomal/ lysosomal compartments [74]. The disease is caused by mutations in the Npc1 or Npc2 genes [75]. Clinical findings include difficulty with speaking and swallowing, cerebellar ataxia, and progressive dementia [74,76-78]. Similarly to other neurodegenerative diseases, NPC presents altered metabolism of amyloid precursor protein [79] and levels of total-tau (T-tau) in cerebrospinal fluid of patient [80], toxic proteins involved in axonal degeneration, oxidative stress induction and bioenergetics impairment. Furthermore, extensive and progressive neuronal death is found, especially in the cerebellum [81].

Evidence obtained from serum of NPC patients and animal models demonstrated diminished antioxidant defenses and Coenzyme Q10 concentrations, an important component of mitochondrial respiratory chain and mitochondrial glutathione content depletion, suggesting a role for oxidative stress in the pathophysiology of NPC [82,83]. In this context, Yu and colleagues [84] demonstrated that mitochondrial metabolism impairment and subsequent ATP deficiency might be responsible for the neuronal impairment in NPC disease. The same authors also showed that the brains of NPC animal model contained smaller mitochondria, decreased ATP levels and higher cholesterol content in mitochondria [84-86]. Considering the link between oxidative stress and mitochondrial dysfunction, it is tempting to speculate that bioenergetics impairment could also participate in the neurodegeneration found in NPC patients.

## Metabolic alterations in aging and neurodegenerative diseases

### *Aging*

According to the Free Radical Theory to Aging, age-related neurodegenerative diseases are mainly attributed to oxidation of cellular components by free radicals, catalyzed by oxidative enzymes and traces of metal ions [87].

Bioenergetic changes, mainly mitochondria-related alterations, comprise a more recent approach that may help to understand the aging process. Mitochondria are the organelles responsible by ATP generation, $Ca^{2+}$ uptake and storage, and generation and detoxification of reactive oxygen species (ROS). Such functions are influenced by the mitochondrial membrane potential ($\Delta\psi m$), while many apoptotic signals are triggered by cytochrome c release into the cytoplasm [88]. On the basis of putative ROS generation by mitochondria, the mitochondrial theory of aging was developed. This theory considers somatic mutations of mitochondrial DNA (mtDNA) induced by reactive species as the primary cause of age-related energy dysfunction. The complex I is thought to be mostly affected, becoming strongly rate limiting for electron transfer [89], which leads to impaired energy metabolism.

The net ROS production by mitochondria may be the major source of oxidative damage that accumulate with aging and impair multiple mitochondrial functions. The contributing factors appear to include the intrinsic rate of proton leakage across the inner mitochondrial membrane, decreased membrane fluidity, and decreased levels and function of cardiolipin, a compound found mainly in mitochondria that supports the function of many of the proteins of the inner mitochondrial membrane. Furthermore, the enzyme activity of mitochondrial complexes I, III, and IV are decreased with aging [90], as well as mitochondrial membrane potential, respiratory control ratio and cellular $O_2$ uptake [91-92].

Certain nutritional or behavioural measures may improve brain mitochondrial function and reduce ROS production. Indeed, it was shown that calorie restriction may be an effective intervention to delay age-related cognitive decline and diseases in mammals [93-94]. Calorie restriction increases cerebral mitochondrial respiratory capacity [95] and prevents age-related deficit in long-term potentiation in the hippocampus [96,97]. Moreover, a positive relation between physical activity and cognitive performance has been reported in several studies, and may reduce the risk of elderly-associated neurodegenerative disorders [reviewed in 98,99]. Physical activity was shown to increase the number of mitochondria and dendritic spine synapses in the hippocampus [100], to stimulate neurogenesis and to enhance long-term potentiation in the hippocampus [101-105], which results in improved learning and memory in aging [106].

MRS studies in elderly subjects were performed at low magnetic field and focused on the most prominent resonances in $^1$H MR spectra, *i.e. N*-acetylaspartate (NAA), *myo*-inositol, glutamate plus glutamine (overlapped peaks at low MR field), choline and creatine [*e.g.* 107-109]. In experimental animal models, the extended neurochemical profile detectable *in vivo* by high-field $^1$H MRS has been extensively investigated from birth to adulthood. Recently, we studied the evolution of the neurochemical profile in the mouse brain from 3 to 24 months of age in a longitudinal manner [110]. The most important findings were that aging induces general modifications of neurotransmission processes (reduced GABA and glutamate), primary energy metabolism (altered glucose, alanine and lactate) and turnover of lipid membranes (modification of choline-containing compounds and phosphorylethanolamine).

The age-induced reduction in glutamate and GABA in 2-year old mice compared to young adults [110] may be associated with the loss of synaptic efficiency. Decreased density of synaptic proteins was observed in the aged rodent brain, namely SNARE complex proteins, vesicle-mobilizing proteins, vesicular neurotransmitter transporters, post-synaptic proteins and components of the synaptic vesicle cycle [*e.g.* 111,112], which can contribute to brain dysfunction and decline in hippocampal-dependent memory performance [*e.g.* 113-116]. Lower concentrations of neurotransmitters were accompanied by higher levels of *myo*-inositol [110] that were often related to astrogliosis in Alzheimer's disease [discussed in 117]. These age-dependent modifications in the mouse brain resemble those in humans, namely elderly subjects displayed reduction in glutamate and increase in *myo*-inositol concentrations in the brain, compared to young subjects [118]. Reduced neurotransmission imposes lower energy demand and, in fact, aging is associated with reduced cerebral glucose utilization [*e.g.* 119-120] and reduced neuronal and glial mitochondrial metabolism [118]. Lactate levels were found to decrease with age in the mouse brain [110], which suggests modification of the relative rates of cytosolic glycolysis and mitochondrial oxidative metabolism.

In the mouse brain, concentrations of phosphorylethanolamine and choline-containing phospholipids (glycerylphosphorylcholine and phosphorylcholine) were negatively and positively associated with age, respectively, likely reflecting altered membrane lipid turnover [110,121]. Altered choline levels are also patent in the human brain [reviewed in 117]. Moreover, a $^{31}$P NMR spectroscopy study showed

that the glycerylated forms of such phospholipids increase with age in the human brain [122]. The inverse trajectory in the evolution of phosphorylcholine and phosphorylethanolamine levels and the relative increase in glycerated phospholipids may indeed be related to modifications in cell membrane fluidity in the aging brain [123].

Brain taurine levels were found to be highest after birth and decay during early development until adulthood [121]. During aging, while taurine content is relatively stable in the hippocampus or cortex after reaching adulthood, it continues to decrease in the striatum, where it is most concentrated [110]. Taurine is a neuromodulator and interacts with inhibitory $GABA_A$, $GABA_B$ or glycine receptors thus displaying capability of modulating synaptic plasticity [reviewed in 124]. This inhibitory role of taurine is especially important during the period of cortical synaptogenesis, when brain taurine levels are found to be highest [121,125]. However, as only a small fraction of taurine is involved in neuromodulation, the main role of taurine may be rather related to osmoregulation, balancing modifications that occur in the concentrations of other major neurochemicals [117].

### *Parkinson's Disease*

Parkinson's disease (PD) is a disorder of the central nervous system (CNS) primarily associated with a decrease in dopamine levels in the striatum caused by a degeneration of dopaminergic neurons in the substantia nigra [126]. It has been suggested that mitochondrial dysfunction is involved in the pathogenesis of the degeneration of dopaminergic neurons, particularly a decrease in NADH dehydrogenase (respiratory chain complex I) in the substantia nigra of PD patients in postmortem studies [127]. Furthermore, alterations in complex I activity may also be found in other brain regions of PD patients [128-130] and also in peripheral tissues [131-133]. It was also demonstrated that the administration of complex I inhibitors, including the pesticide rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), triggers neurological changes similar to PD in rats and that genes associated with familial PD are involved in mitochondrial functioning [134-135]. Finally, it was demonstrated in tissues of PD patients or animal models of PD other alterations of energy metabolism than complex I deficiency, including impaired glycolysis, oxidative decarboxylation of pyruvate and other components of oxidative phosphorylation system [136-140].

Decreased NAA to creatine ratio has been extensively observed in different brain areas of patients with PD [reviewed in 117]. Other studies found that PD leads to a reduction in the signal corresponding to choline-containing compounds in cortical areas [141,142] and posterior cingulate [143], and a reduction in glutamate to creatine ratio in the anterior cingulate gyrus [144]. This later study however failed to identify the typical PD-induced reduction in NAA levels. Since mitochondrial dysfunction also contributes to neuronal degeneration in PD [145], a reduction of high-energy phosphates and increased lactate concentration was observed in several brain areas of PD patients when compared to healthy subjects [146,147]. A recent study at high magnetic field found increased GABA levels in the pons and putamen of early PD patients relative to healthy subjects, in the absence of other neurochemical modifications [148]. In this study, the authors further proposed a mechanism for the involvement of GABAergic activity in pontine-nigral-striatal pathways that could be important for developing PD. Most importantly, the detection of increased GABA levels in these areas must be regarded as a putative early biomarker of PD, before substantial degeneration occurs.

Pre-clinical MRS studies of PD have been largely limited to animal models administered with the neurotoxin MPTP or its active metabolite 1-methyl-4-phenylpyridinium ($MPP^+$), leading to destruction of dopaminergic neurons in the substantia nigra, and triggering PD symptoms [147]. After MPTP/$MPP^+$ intoxication, reduced NAA and increased lactate levels were observed in the striatum or substantia nigra of rodents [149-152] and other mammals [reviewed in 117], consistent with neuronal loss and mitochondrial dysfunction. Rats injected with 6-hydroxydopamine and ascorbate in the substantia nigra display phenotypes of PD and reduced NAA to creatine ratio in the frontal cortex, which is associated with synaptic degeneration and dopaminergic loss [153]. GABA was suggested to be either increased [154] or reduced [152] after MPTP/$MPP^+$ treatment. Increased concentration of both glutamate and glutamine was proposed in the striatum of animal models of PD compared to controls [154-156], as consequence of excitotoxicity and/or impaired glutamatergic neurotransmission. These neurochemical modifications were suggested to be restricted to the motor part of the striatum and absent in the nucleus accumbens [157].

### *Alzheimer's Disease*

Alzheimer's disease (AD) is a progressive, severe aging-related neurodegenerative disease and the most common form of dementia. This neurodegenerative disorder is characterized by extracellular deposition of amyloid aggregates and accumulation of neurofibrillary tangles of hyperphosphorylated tau protein, leading to loss of synapses and neuronal death [158]. AD pathophysiology is not yet completely understood, however mitochondrial dysfunction and oxidative stress are implied in it.

Mitochondrial genome mutations and deletions that impair mitochondrial function are associated with AD [159]. In this context, alterations in the expression of mitochondrial fission and fusion proteins were described, indicating an impairment of fusion–fission process [160]. Furthermore, precursor amyloid protein (APP) interferes with important mitochondrial proteins, impairing cell bioenergetics [161]. Studies from animal models and AD patients showed that amyloid protein inhibits respiratory complexes (especially complex IV) and α-ketoglutarate dehydrogenase activities [162,163]. In addition, amyloid protein fragments decreased mitochondrial mass in the neurites of cultured neurons [164].

Mitochondrial dysfunction may also be related to AD pathophysiology due to promotion of tau phosphorylation, participating in the process of tangle formation [165]. Moreover, ATP depletion inhibits the transporter superfamily for toxic peptides (ABC transporters), including β-amyloid, which is highly dependent on ATP availability. In fact, it was recently demonstrated that the molecular alterations are pronounced near the β-amyloid plaques [166]. In this scenario, inhibition of ABC transporters impairs the clearance mechanisms for the removal of toxic peptides and its aggregates, contributing to the progression of AD [167].

The brains of patients with AD have been consistently reported to display reduced NAA and increased *myo*-inositol concentrations compared to cognitively healthy elderly individuals and, furthermore, these findings were often correlated with decline in cognitive performance [reviewed in 117]. While NAA indicates loss of neuronal integrity, *myo*-inositol has been interpreted as marker of astrocyte reactivity. However, the majority of these clinical MRS studies did not provide absolute quantification of neurochemicals but determined ratios of NAA and *myo*-inositol to other peaks in the $^{1}$H MR spectra, namely choline and creatine. Since some studies found altered choline [168-171] or creatine [172,173] levels in certain brain areas of patients with AD compared to controls, care should be taken when interpreting metabolite ratios. Levels of choline-containing compounds are associated to phospholipid turnover and, indeed, increased glycerylphosphorylcholine concentration in post-mortem cortical gray matter measured from severely demented AD brains have been attributed to membrane breakdown [174].

The concentration of NAA in brain areas of patients with mild cognitive impairment was found to be higher than that in the brains of AD patients but also lower than that of healthy subjects [*e.g.* 173,175,176]. Furthermore, NAA decrease has been suggested to correlate with cognitive decline from light dementia to AD [*e.g.* 172,177,178]. These findings suggest a positive correlation between NAA levels and cognitive performance. Thus, in vivo $^{1}$H MRS has given the opportunity to assess metabolic and functional correlates of dementia in research and clinical settings, as well as prediction of future cognitive decline in AD [176].

Patients with AD display impaired cerebral energy metabolism [reviewed in 13]. Accordingly, in addition to these neurochemical markers, after glucose administration, Haley and colleagues [179] measured glucose levels in the brain of AD patients at higher levels than in healthy subjects. These increased brain glucose levels thus likely reflect reduced glucose metabolism, linked to impaired insulin signaling [180].

Mutations in genes associated with β-amyloid precursor protein (APP), presenillin 1 (PS1) and presenillin 2 (PS2) are involved in early-onset familial AD [181]. Mouse models of AD have thus been generated by inserting one or more of these human mutations into the mouse genome and are characterized by β-amyloid deposition in the brain. Double transgenic mice expressing human mutant APP and human mutated PS1 (APP/PS1) display decreased glutamate and NAA concentrations in the brain, particularly in the hippocampus, that were observed at the time where hippocampal volume was already reduced but amyloid plaques were not yet present [182-184]. Later, upon visible amyloid deposits, these mice also presented increased brain *myo*-inositol to creatine ratio, when compared to wild type mice [185], accompanied by astrogliosis [186]. Increased *myo*-inositol and glutamine and decreased NAA and glutamate were reported to occur in the cortex of these mice. Additionally, it was found that once amyloid plaques are observed, NAA levels are inversely associated to the area of cortex occupied by plaques [182]. Dedeoglu and colleagues [187], but not Marjanska and colleagues [183], reproduced these findings in mice possessing only the mutated APP gene. Both authors reported, however, higher cerebral taurine to creatine ratio in the brain of APP transgenic mice compared to wild type mice. These results were confirmed by in vitro NMR spectroscopy of brain extracts, in which glutathione levels were additionally found to be lower than in controls [187].

Recently, high resolution $^{1}$H and $^{31}$P MRS at 14.1 T was used to investigate the brain neurochemistry of the 5xFAD transgenic mouse model of AD [188], which over-expresses APP with 3 different familial mutations and PS1 also with two mutations, resulting in early robust β-amyloid deposition. Compared to wild-type littermates, the hippocampus of 5xFAD mice was characterized by increased *myo*-inositol and decreased NAA and, in addition, decreased concentrations of γ-aminobutyrate (GABA). Furthermore, 5xFAD mice displayed lower brain glucose content associated with higher lactate

levels, suggesting impaired energy metabolism, as occurs in AD patients [179]. However, the rate of creatine kinase and the relative concentrations of phosphorus-containing metabolites were not altered in this AD model [188].

In summary, compared to healthy subjects, AD patients display lower NAA and increased *myo*-inositol in the brain, reflecting disease progression. These observations are also mimicked in animal models of AD. However, contradictory results have appeared regarding some metabolic observations and their regional distribution.

### *Huntington's Disease*

Huntington's disease (HD) is an inherited neurodegenerative disease caused by alterations in the polyglutamine region of the huntingtin protein (Htt), leading to the accumulation of intracellular Htt aggregates, affecting especially GABAergic medium-sized spiny neurons in the striatum [189]. Even though Htt neurotoxicity has been widely studied, the pathophysiological mechanisms of HD have not yet been fully understood.

Mitochondrial dysfunction contributes to the pathogenesis of HD [145,190,191]. Indeed, respiratory chain complex II activity inhibitors administration such as malonate and 3-nitropropionic acid mimics striatal neuronal degeneration found in HD patients [192,193]. Patients and animal models develop several mitochondrial defects, ranging from altered calcium metabolism [194], impaired bioenergetics [195], increased oxidative stress and abnormal trafficking [196] and mitochondrial dynamics [197,198]. Furthermore, $^{1}$H MRS of basal ganglia and cerebral cortex of HD patients showed elevated lactate production, suggesting defects in mitochondrial pyruvate utilization [199]. Additional studies revealed inhibitions of respiratory chain complexes II, III and IV and Krebs cycle enzymes activities in basal ganglia [200-202].

Either chemically induced by 3-nitropropionic or malonate administration or mutant Htt animal models also demonstrated a role for oxidative stress related to mitochondrial dysfunction. In this context, mutant cells presented increased mitochondrial ROS generation and decreased NADPH oxidase and xanthine oxidase activities [203], indicating a redox imbalance, leading to mitochondrial-related apoptosis and excitotoxicity [204].

In addition, data from the literature demonstrated the involvement of impaired function of peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α), a transcriptional master co-regulator of mitochondrial biogenesis, metabolism, and antioxidant defenses, in mitochondrial dysfunction characteristic of HD [205]. In this context, it has been reported that mutant Htt increases Drp1 (an important protein implicated in mitochondrial fission) activity, suggesting that Htt may contribute to mitochondrial fragmentation and dysfunction found in HD patients and animal models [198]. These alterations in mitochondria morphology may enhance cellular susceptibility to apoptosis in HD [197,198].

Reduced NAA and increased *myo*-inositol are known to occur in the brain of HD patients, relative to healthy subjects. In particular, levels of NAA and *myo*-Inositol in the putamen were found to be correlated with measures of HD severity [206]. Association was also found between cognitive dysfunction and both NAA and glutamate levels in the posterior cingulate [207].

Different transgenic mouse models with mutated huntingtin have been used to investigate the mechanisms of HD. In the R6/2 transgenic mouse model of HD, striatal concentrations of creatine, glycerophosphorylcholine, glutamine and glutathione were found to be increased and NAA levels decreased [208,209]. Further development of the disease leads to additional modifications, namely increased concentrations of phosphocreatine, taurine, ascorbate, glutamate, lactate and *myo*-inositol and decreased phosphorylethanolamine [208,210]. From all these alterations, reduced NAA concentration was consistently found to correlate with neuron dysfunction and to be accentuated by the length of polyglutamine expansions and the progression of the neuropathological phenotype [211]. Interestingly, these neurochemical modifications in the R6/2 mouse were found not only in the striatum but also in cortical areas, and preceded significant shrinkage of cortical and striatal volume, as measured *in vivo* from MR images [210].

In another model of HD, the zQ175 knock-in mouse, concentrations of the neurotransmitters glutamate and GABA were found reduced in the striatum between 4 and 8 months of age, but recover to control levels at one year of age [212]. At this age, glutamine, creatine and taurine were also increased relative to wild-type mice. Levels of NAA in the striatum were always lower in zQ175 mice, probably reflecting the reduced number and density of neurons that also resulted in reduced striatum volume [212].

Glutamine, glutamate and GABA alterations suggest the impaired neurotransmission and glutamate/GABA-glutamine cycles, while increased creatine and phosphocreatine are indicative of impaired mitochondrial bioenergetics and reduced oxidative phosphorylation [191]. Changes in membrane properties of medium-sized spiny neurons that compromise integrity of the membrane potential could be the cause for the observed alterations in phospholipid levels [213]. Increased GSH, ascorbate and taurine were suggested to be a counter-regulatory response to HD associated oxidative stress [214].

Inhibitors of the complex II of mitochondrial respiratory chain, namely 3-nitropropionic acid and malonate, effectively trigger behavioral changes and selective striatal lesions in animals, thus mimicking symptoms of HD. In fact, like in the striatum of R6/2 or zQ175 transgenic mice, rats treated with 3-nitropropionic acid display reduced striatal NAA levels [reviewed in 215]. In this case, the mitochondrial dysfunction caused by chemical inhibition of the respiratory chain leads to increased lactate concentration [*e.g.* 151,199,215,216]. Table 1 summarizes the main metabolic modifications in aging and neurodegenerative disorders measured by MRS in affected brain areas of patients and/or animal models.

**Table 1.** Summary of main metabolic modifications in aging and neurodegenerative disorders measured by MRS in affected brain areas of patients and/or animal models.

| Metabolite | Aging | AD | PD | HD |
|---|---|---|---|---|
| NAA | | ↓ | ↓ | ↓ |
| *myo*-Inositol | ↑ | ↑ | | ↑ |
| Glutamate | ↓ | ↓ | ↑ | ↑ |
| Glutamine | | ↑ | ↑ | ↑ |
| GABA | ↓ | ↓ | | |
| Choline-containing phospholipids | ↑ | | ↓ | ↑ |
| Phosphorylethanolamine | ↓ | | | |
| Taurine | ↓ | | | ↑ |
| Lactate | | ↑ | ↑ | ↑ |

NAA= *N*-acetylaspartate; GABA= γ-aminobutyrate; AD= Alzheimer's disease; PD= Parkinson's disease; HD= Huntington's disease.
Direction of the arrow indicates either increase (↑) or decrease (↓) of metabolite concentration.

## Summary

Extensive research efforts are underway aiming at unraveling the molecular basis of metabolic alterations in the pathophysiology of neurodegenerative diseases, both common (such as Alzheimer, Parkinson and Huntington diseases) and inherited metabolic diseases. The identification of the exact mechanisms involved in these diseases shall help to identify early disease biomarkers as well as more effective therapies (which may include energy compounds, antioxidant therapy – particularly targeted to mitochondria – and modulators of mitochondrial dynamics), preventing or slowing the progression of neurodegeneration and improving the quality of life of the patients affected by these devastating illnesses.

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