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Coenzyme A, more than 'just' a metabolic cofactor

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Abstract

In all organisms biomolecules play a vital role to enable proper cellular metabolism. Alteration of metabolite homoeostasis disrupts the physiology of cells, leading to various diseases [DeBerardinis and Thompson (2012) Cell, 148, 1132–1144]. Recent studies advances our understanding that some metabolites are not only involved in cellular metabolism, but also have other molecular functions. It has become evident that similar to multifunctional 'moonlighting proteins', 'moonlighting metabolites' also exists. One clear example is nicotinamide adenine dinucleotide (NAD). NAD is a ubiquitous molecule with a well-known function in many metabolic reactions, but it also has become clear that NAD is involved in the regulation of sirtuins. Sirtuins play a role in cancer, diabetes, and cardiovascular, neurodegenerative and other diseases [Donmez and Outeiro (2013) EMBO Mol. Med. 5, 344–352] and the deacetylation capacity of sirtuin proteins is NAD-dependent. This direct role of NAD in age-related diseases could not be anticipated when NAD was initially discovered as a metabolic cofactor [Donmez and Outeiro (2013) EMBO Mol. Med. 5, 344–352; Mouchiroud et al. (2013) Crit. Rev. Biochem. Mol. Biol. 48, 397–408]. Recent findings now also indicate that CoA (coenzyme A), another metabolic cofactor, can be considered as being more than 'just' a metabolic cofactor, and altered CoA levels lead to severe and complex effects.

Renewed attention for CoA

CoA (coenzyme A) was first described in 1947, as a coenzyme functioning as an acyl carrier [1]. In a series of publications it has been described that CoA is an essential metabolic cofactor for all living organisms, involved in over 100 metabolic reactions, such as the citric acid cycle and fatty acid metabolism [2]. The *de novo* CoA biosynthesis is carried out by the action of specific enzymes in several steps starting from pantothenic acid, also known as pantothenate or vitamin B_5 (Figure 1). Vitamin B_5 is present in sufficient quantities in the diet and it is also produced by bacteria in human intestines. The enzymatic steps of the canonical CoA *de novo* biosynthesis route are well conserved and genes encoding these enzymes have been identified in various organisms [3 – 8]. CoA regained new attention after the discovery that one of the CoA biosynthetic enzymes PANK (pantothenate kinase) was found to be associated with a neurodegenerative disease characterized with very specific features. This neurodegenerative disease was already described in 1922, and in 2001, after the discovery of the causative gene *PANK2*, the disease was named PKAN (PANK-associated neurodegeneration) [9]. PKAN is a subform of NBIA (neurodegeneration with brain iron accumulation), which is a group of disorders all characterized by iron accumulation in the brain [10]. Several seemingly unrelated genes (including *PANK2*) have been characterized, which, when mutated, are causative for specific subforms of NBIA [11,12]. PKAN is characterized by a progressive loss of extrapyramidal and pyramidal functions and patients suffer often from dystonia, dysarthria and intellectual disabilities [13]. The identification of the causative gene for PKAN indicated a clear link between neurodegeneration and CoA *de novo* biosynthesis, and suggests that intact homoeostasis of CoA levels is highly essential for normal brain function. However, to date, the pathophysiology of this disease is largely unknown, a therapy is lacking and why impaired *de novo* biosynthesis of CoA leads to PKAN is still unclear.

Drosophila to understand the link between CoA and neurodegeneration

In order to investigate functions of CoA and consequences of impaired *de novo* CoA biosynthesis, several model organisms have been used, such as *Arabidopsis thaliana* [14], PANK-knockout mice [15,16], *Schizosaccharomyces pombe* [17] and *Drosophila melanogaster* [3,7,18]. In the present mini-review we focus on the multicellular eukaryote model organism *D. melanogaster* (fruitfly) and its potential aid in understanding the link between CoA and neurodegeneration is summarized and discussed.

In 2001, a few months before *PANK2* was identified as the causative gene for PKAN, Wasserman and co-workers described the phenotype of *D. melanogaster* carrying mutations in the gene *fumble*, coding for PANK [3]. *fumble* is also referred to as *dPANK/fbl* (*Drosophila* PANK/*fumble*).

Key words: coenzyme A (CoA), metabolic cofactor, NAD, neurodegeneration, pantothenate kinase (PANK).

Abbreviations: ATM, ataxia telangiectasia; CaMKII, calcium/calmodulin-dependent protein kinase II; COASY, CoA synthase; CoPAN, COASY protein-associated neurodegeneration; *dPANK/fbl*, *Drosophila* PANK/*fumble*; DPCK, dephospho-CoA-kinase; dPPAT-DPCK, *Drosophila* PPAT-DPCK; dPPCS, *Drosophila* PPCS; EP300, E1A-binding protein p300; HDAC, histone deacetylase; NBIA, neurodegeneration with brain iron accumulation; PANK, pantothenate kinase; PKAN, PANK-associated neurodegeneration; PPAT, 4′-phosphopantetheine adenylyltransferase; PPCDC, (*R*)-4′-phospho-*N*-pantothenoylcysteine decarboxylase; PPCS, phosphopantothenoylcysteine synthetase.

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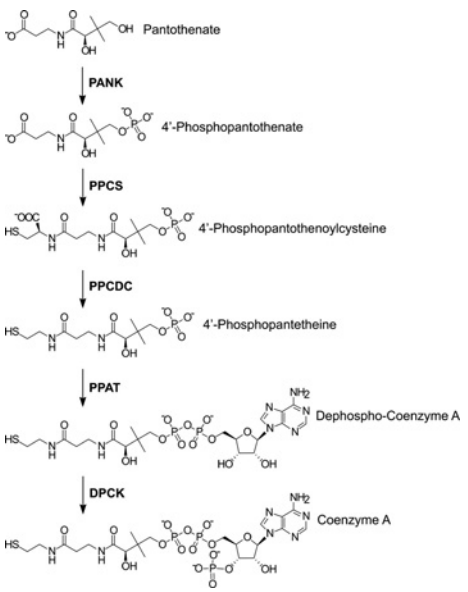
Figure 1 | **Simplified scheme of the *de novo* CoA biosynthesis route**



Although the researchers focused in this study on the male sterile phenotype, they also noticed the locomotor impairment of the mutant flies and the gene and the mutant were named after this phenotype: '*fumble*'. Wasserman and co-workers, therefore, were the first to reveal the link between impaired PANK function and locomotor abnormalities. In addition to the locomotor defects, in *dPANK/fbl* mutant flies a decreased number of mitotic neuroblasts and an increase in abnormal (lagging chromosomes and anaphase bridges) mitotic chromosomes are observed [3]. In addition, defects in cytokinesis and chromosome segregation were also observed in spermatocytes. Why mutations in *dPANK/fbl* are associated with such specific phenotypes has not yet been resolved. Later in the same year, the Hayflick laboratory identified human *PANK2* as a causative gene for the severe autosomal recessive neurodegenerative disorder PKAN, further establishing a link between impaired CoA biosynthesis and abnormal locomotor functions [9]. However, PKAN is still surrounded by unresolved basic questions such as the following. Why do patients with mutations in PANK2 suffer from neurological symptoms? What are the mechanisms behind the specific symptoms? Why is the nervous system affected in particular?

D. melanogaster is a versatile and genetically modifiable model organism. It is widely used to study basic mechanisms in the life sciences at various levels (molecular, cellular, tissue, developmental and behavioural) and it is also used as a model to study human diseases [19 – 21]. Similarly to many diseases with a genetic cause, a *Drosophila* PKAN model was explored and *dPANK/fbl* mutants were further investigated to understand the link between neurodegeneration and CoA biosynthesis. First, the *Drosophila* genes coding for enzymes required for the *de novo* biosynthesis of CoA were annotated by *in silico* analysis and five *Drosophila* loci were identified coding for structural orthologues of PANK (*dPANK/fbl*), PPCS [phosphopantothenoylcysteine synthetase; *dPPCS* (*Drosophila* PPCS)], PPCDC [(*R*)-4′-phospho-*N*-pantothenoylcysteine decarboxylase; *dPPCDC* (*Drosophila* PPCDC)] and a bifunctional PPAT (4′-phosphopantetheine adenylyltransferase)-DPCK (dephospho-CoA-kinase) [*dPPAT-DPCK* (*Drosophila* PPAT-DPCK)] and a single *dDPCK* (*Drosophila* DPCK) [7]. It was demonstrated that *Drosophila* mutants carrying mutations in *dPANK/fbl*, *dPPCS* and *dPPAT-DPCK* show a comparable phenotype, strongly suggesting that this shared phenotype is caused by impaired CoA biosynthesis. All mutants show abnormal locomotor function (impaired climbing and flying behaviour) which worsens upon aging, a decreased lifespan, abnormal lipid homoeostasis, increased sensitivity to ROS (reactive oxygen species)-inducing agents, increased apoptotic cells in the brain and increased sensitivity to DNA-damaging agents. Moreover, consistent with the previous results from Wasserman and co-workers [3], all of the *Drosophila* CoA mutants investigated show increased number of cells with abnormal mitotic chromosomes in larval brains. The phenotypes were comparable; however, the severity of the phenotypes varied between the mutants, most likely because the mutants are hypomorphs and therefore the rest activity of each affected enzyme may be different. One key issue that could be addressed with the usage of the *Drosophila dPANK/fbl* mutant was to investigate whether impaired function of *dPANK/fbl* actually leads to decreased levels of CoA. If so, this suggests that decreased levels of the end product CoA is the primary cause of the reported defects. CoA levels were measured and found to be decreased in *dPANK/fbl* fly mutants and in *dPANK/fbl* (by RNAi) depleted *Drosophila* cultured cells [22]. Replenishing CoA levels by the compound pantethine partly rescued lifespan, neurodegeneration and locomotor defects in *dPANK/fbl* mutant flies [22]. These data suggest that decreased levels of CoA may be causative for the observed neurodegenerative symptoms and predicted that patients who carry mutations in other CoA biosynthesis enzymes may also suffer from a comparable disorder such as PKAN. Indeed, the recent finding of a new form of NBIA, referred to as CoPAN [COASY (CoA synthase) protein-associated neurodegeneration], associated with mutations in the gene coding for the last enzyme in the CoA biosynthesis pathway, PPAT-DPCK or COASY, further indicates that impairment of CoA homoeostasis is strongly associated with neurodegeneration [23]. It remains to be investigated whether CoA levels are actually decreased in parts of the brain affected in patients with PKAN and CoPAN.

CoA and its influence on protein-acetylation levels

The next question that arises is: why do decreased levels of CoA lead to neurodegeneration? It is yet unresolved whether decreased levels of CoA only cause metabolic defects or also

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lead to defects in non-metabolic processes in cells. Studies in mice showed that decreased levels of CoA influence the metabolic state of an organism [16,24], therefore most likely part of the neurodegeneration is caused by abnormalities in metabolic reactions. However, the influence of altered CoA homoeostasis on other than metabolic reactions became evident by a series of experiments, demonstrating that acetyl-CoA levels influence protein acetylation. Acetyl-CoA provided the acetyl-group transferred by acetyltransferases to enable protein acetylation. Protein acetylation is a post-translational modification with a large influence on protein function [25,26]. In *Saccharomyces cerevisiae*, or budding yeast, it is reported that acetyl-CoA synthetase mutants have decreased levels of histone acetylation [27]. Reduced levels of acetyl-CoA evoked by inactivation of the *S. cerevisiae* orthologue of AMPK (AMP-activated protein kinase) also resulted in decreased histone acetylation and reduced fitness and stress resistance [28]. In addition, two studies also show a link between acetyl-CoA and autophagy. In *S. cerevisiae*, it was demonstrated that acetyl-CoA is a suppressor of autophagy and down-regulation of acetyl-CoA synthetase in flies enhances autophagy and increases lifespan [29]. The second study in mice and human cells showed that starvation leads to decreased levels of acetyl-CoA, a reduction of acetylation of cytoplasmic proteins and induction of autophagy [30]. When acetyl-CoA levels were manipulated under these conditions and kept at a higher level, autophagy was suppressed. This suppression of autophagy was dependent on EP300 (E1A-binding protein p300) acyltransferase activity, suggesting that EP300 is regulated via acetyl-CoA levels [30]. Acetyl-CoA levels can also influence cell-cycle progression in *S. cerevisiae* as demonstrated by acetyl-CoA promoting acetylation of histones in the regulatory domain of the G_1 cyclin CLN3 (cyclin 3) and, consequently, promoting cell-cycle progression [31]. Protein acetylation levels are not only influenced by manipulation of acetyl-CoA levels, as demonstrated in the above-mentioned studies, but manipulating the CoA level itself can also influence protein acetylation levels. This was demonstrated by the observation that decreased CoA levels, by down-regulating *Drosophila dPANK/fbl* via RNAi, by using the PANK chemical inhibitor HoPAN and in *dPANK/fbl* mutant flies, are associated with decreased levels of acetylated histones and tubulin. Restoration of CoA levels reverted this phenotype [32]. Together these data indicate a strong link between CoA and/or acetyl-CoA in regulating the acetylation of specific proteins.

Link between decreased histone and tubulin acetylation and neurodegeneration

Decreased histone and tubulin acetylation levels are associated with neurodegenerative diseases and, therefore, the decreased levels of protein acetylation may explain part of the neurodegenerative phenotype of *dPANK/fbl* mutant flies. There is strong link between cognitive function and histone acetylation [33]. Histone acetylation is also linked with motor neuron function [34]. Few, but nonetheless compelling, research studies have reported the association between tubulin acetylation and neuronal function. Tubulin hyperacetylation has been shown to be associated with protection against axonal degeneration [35] and tubulin acetylation is required for the touch response in *Caenorhabditis elegans* [32]. In APPPS1-21 mice (a mouse model for Alzheimer's disease), levels of acetylated tubulin are decreased and restored after knockdown of the deacetylase HDAC6 (histone deacetylase 6). In these APPPS1-21-HDAC6$^{-/-}$ mice improvement of associative and spatial memory is observed compared with APPPS1-21 mice [36].

These data show that normal levels of tubulin and histone acetylation are required for neuronal function. Therefore the decreased levels of histone and tubulin acetylation as observed in the *dPANK/fbl* mutants could partly explain the neurodegenerative phenotype. Addition of the HDAC inhibitor valproic acid restored the decreased histone and tubulin acetylation levels and partly restored locomotor function of mutant *dPANK/fbl* larvae, demonstrating that impaired acetylation is associated with the observed phenotypes [32]. *dPANK/fbl* mutants also show increased sensitivity to DNA-damaging agents and increased accumulation of DNA damage. This phenotype could also be explained by impaired histone acetylation, because normal histone acetylation kinetics are required for DNA-damage responses as demonstrated in various organisms [25,37–41]. In *dPANK/fbl*-depleted cultured *Drosophila* cells, after ionizing radiation, the kinetics of histone acetylation are abnormal compared with control cells, which coincides with decreased survival of the cells after ionizing radiation. The HDAC inhibitor TSA rescues the decrease in protein acetylation and partly rescues the radiation sensitivity [32]. Therefore it may be possible that part of the neurodegenerative phenotype observed in *Drosophila* CoA mutants is because of defects in DNA-damage-repair pathways, causing accumulation of damaged DNA in the brain. Impaired DNA-damage repair and neurodegeneration is strongly linked in several human diseases such as ATM (ataxia telangiectasia), AT-LD (ATM-like disorder), NBS (Nijmegen breakage syndrome) and others [42,43]. Although it is tempting to hypothesize that accumulation of damaged DNA in non-dividing neuronal cells leads to cell death and tissue loss, this order of events has not been convincingly demonstrated and why DNA damage leads to neurodegeneration is an unresolved puzzle [44].

CoA as an anti-apoptotic signalling molecule

In addition to the influence of CoA levels on metabolism and protein-acetylation levels, the metabolic cofactor CoA has shown to directly influence other cellular functions as well. McCoy et al. [45] demonstrated that CoA can bind directly to CaMKII (calcium/calmodulin-dependent protein kinase II) and, thereby, CAMKII is activated in *Xenopus laevis*

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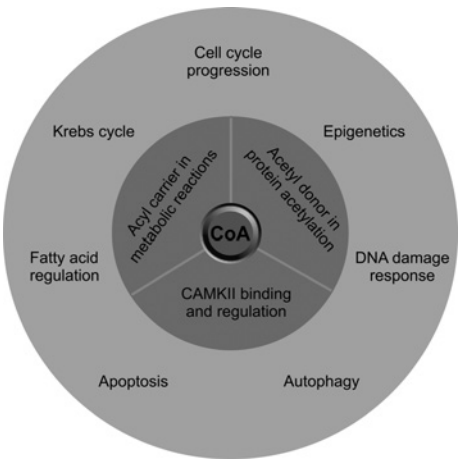
Figure 2 | Schematic representation of diverse roles of CoA in cellular physiology



oocytes promoting oocyte survival via phosphorylation and inactivation of caspase 2. Moreover, they showed that this mechanism is conserved in mammalian oocytes [45]. These data reveal a signalling function of CoA independent from its role in cellular metabolism. Impaired CAMKII has also been shown to have a causative role in neurotoxicity [46]. Since *Drosophila* CoA mutants showed increased apoptotic cells in the brain, it is possible that altered CoA–CAMKII interaction is increasing the vulnerability of cells, especially in brain tissue. The recently discovered effect of CoA–CAMKII interaction is now provoking interest as to whether CoA itself can directly bind or interact with other proteins and thereby regulate their function. The mechanism behind why and how this interaction is regulated will be of importance to reveal some aspects of vital cellular physiology.

Concluding remarks

With the knowledge that CoA is not only a key molecule in metabolism playing a role in over 100 metabolic reactions, but that it also modulates the epigenome and activates at least one specific kinase, the influence of this molecule in health and disease is most likely larger than anticipated previously (Figure 2). Whether the specific disease characteristics of patients with PKAN and CoPAN and the phenotypes of CoA *Drosophila* mutants are caused by impaired metabolism, abnormal protein acetylation, impaired activation of CaMKII or possible other proteins or a combinatorial effect remains to be investigated. This present mini-review summarized the diverse functionality of CoA, apart from its most classically known metabolic role. It is now necessary for the future to understand the complex consequences of impaired CoA *de novo* biosynthesis in diseases including neurodegeneration. Resolving such a challenge can be aided both by implementing reliable analytical methods to understand the CoA flux inside the cellular environment and by using genetically modifiable model organisms to get a clearer picture regarding the multifaceted influence of CoA.

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