



Plant-derived compounds, vitagens, vitagenes and mitochondrial function

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ABSTRACT

There is great interest in identifying natural products that can be approved as nutraceuticals. A good option is to induce transcription of vitagenes, which would lead to increased expression of proteins that provide the means to maintain homeostasis. In fact, the induction of vitagenes is considered relevant during aging, especially if aging is accompanied by neurodegenerative diseases. Care must be taken to avoid confusing vitagenes, which are genes, and vitagens, which are vitamin-like low-molecular weight compounds; both concepts are recalled here. Although mitochondria are key factors in several chronic diseases of the nervous system, the amount of vitagenes that is associated with better mitochondrial function (bioenergetics, oxidative stress, biogenesis, dynamics, etc.) is limited. Plant molecules have been used for centuries to improve well-being, and some have a directly or indirectly impact on mitochondrial function. However, there is little knowledge about whether plant-derived products can induce vitagenes related to the enhancement of the multiple actions exerted by mitochondria; studies are needed to detect natural plant compounds that increase the transcription of genes related to the function of this cellular organelle. This study is expected to identify new vitagenes whose induction provides benefits in aging and/or neurodegenerative diseases.

1. Close relationship between mitochondrial alterations and chronic diseases of the nervous system

Several diseases including obesity, cardiomyopathy, diabetes mellitus or age-induced cognitive disabilities course with mitochondrial alterations due to mechanisms that, often, are not well deciphered. Mammalian cells are very resilient to mitochondrial damage, but in the long run the excess of oxidative stress and/or the failure to provide enough adenosine triphosphate (ATP) leads to cell death. In fact, age induces a decay of all cell components and processes, and the mitochondrion arises as a key factor in age-related diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), the most common neurodegenerative pathologies. Neurons are dependent of glucose supply and the proper functionality of mitochondrial electron chain transport. Faulty operation of mitochondria in aged neurons results in oxidative stress and, consequently, in a reduction of ATP production

which compromises neuronal survival. In addition, mitochondrial alterations have been detected in other chronic diseases of the nervous (e. g. multiple sclerosis, see [1–6] for review) and of other body systems (see [7–10] for review).

The involvement of mitochondrial dysfunction in AD pathogenesis has been revealed during the past decades. In fact, a large body of evidence suggests that mitochondrial alterations appear early in the course of the disease [11]. Some gene expression and proteomic studies have demonstrated disruptions in mitochondrial bioenergetics in AD. On the one hand, different microarray studies have found that nuclear genes encoding for mitochondrial electron transport chain subunits and those involved in glycolytic, tricarboxylic acid (TCA) cycle, oxidative phosphorylation (OXPHOS) and associated pathways were significantly downregulated in some brain areas of AD patients, e.g. in hippocampus [12–14]. On the other hand, proteomic data describe a similar picture when comparing mitochondrial enzymatic activities of samples from AD

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease.

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brains and aged-matched controls, e.g. a decrease in the activity of cyclooxygenase (COX) or mitochondrial ATP synthase [15–17]. Impaired mitochondrial functional integrity in neurons is also related with a compromised activity of enzyme of the antioxidant machinery (e.g. glutathione and peroxiredoxin 6), or a disturbed mitochondrial genome [18–21]. Mutations and modifications in mtDNA may compromise mitochondrial function, resulting in cell death and in changes in cognitive functions similar to those found in AD [20,22]. Our experience with transgenic models of AD allowed to detect a high percentage of altered mitochondrial proteins upon aging. Animals that express mutated forms of the human amyloid precursor protein (APP) are born without any major significant neurological alteration. However, they display severe cognitive deficits upon aging. Since APP mutations have been reported in the brain of AD patients, those animals are used as models of the disease [23–26]. Taking advantage of this model, we analyzed the hippocampal proteome of the Tg2576 transgenic mice at two ages: i) at 7 months when cognitive symptoms are not yet present and amyloid- β protein (A β) levels begin to increase, and ii) at 16 months when mice show features similar to those found in AD. The percentage of proteins differentially expressed was higher in the mitochondria than in the rest of cell components. Mitochondrial dysfunction was evident in 7-month-old mice as confirmed by the impairment of cytochrome c oxidase function and the alteration of inner membrane integrity. Another of the mitochondrial proteins whose expression is altered in AD models is the voltage-dependent anion channel 1 (VDAC1) which mediates the release of apoptotic proteins involved in programmed cell death. Apart from overexpression in the hippocampus of amyloidogenic mice models, the protein is enriched in post-mortem brain samples from AD patients [27].

Based on these results, we hypothesized that individuals with fragile mitochondria due to genetic or environmental factors would be more likely to suffer from AD. Then, we performed an experimental design to investigate whether intact cognitive mothers but carrying the mutant APP in heterozygosity could transmit a "mitochondrial trait" to offspring. As indicated in the work, we analyzed the *"phenotype of the offspring with or without the transgene resulting from crossing young Tg2576 females with wild-type males were compared with those of the offspring resulting from crossing wild-type females with Tg2576 males"* [28]. The difference was in the sex of the progenitor carrying the transgene. It should be noted that the AD-like features occur only in aged homozygous but not in aged heterozygous mice. We found that cognitive alterations and other symptoms displayed by wild-type animals generated from Tg2576 females were similar to those exhibited by Tg2576 heterozygous mice [28]. These findings suggest that maternal imprinting confers a greater facility to develop AD-like phenotypes; undoubtedly this would be due to fragile mitochondria transmitted to offspring. Positron emission tomography images to assess cerebral glucose consumption (in humans) show reduced glucose metabolism in individuals whose mothers have non-hereditary late-onset AD (LOAD) compared to those of fathers with LOAD history. This reinforces the opinion that the mitochondria transmitted by the mother have some peculiarities that affect the risk of undergoing LOAD (see [21,29]).

The link of PD and defective mitochondrial distribution and function has been known for years. Indeed, mitochondrial dynamics in neurons are altered in the disease irrespective of whether it is idiopathic or resulting from gene defects. In fact, many of the familial forms of PD are caused by mutations in genes that directly or indirectly impact on mitochondria [30]. It should be noted that a mitochondrial membrane protein, Miro, is key for axonal transport and dynamics of mitochondria in neurons (see [31] for review). Apart from metabolic alterations [32], the changes affecting mitochondria in this disease are manifold, e.g. deficiencies in mitochondrial protein import [33] or structural membrane alterations by α -synuclein/lipid interactions [34]. A recent review describes potential interventions to manage the disease by targeting mitochondrial dysfunction [35]. What remains a mystery is why this specific disease affects a very precise region, the substantia nigra; Is it

because the environment in dopamine-producing neurons is more damaging to the mitochondria? or Is it because these cells/mitochondria are more vulnerable?

2. Vitagens versus vitagenes

While the word "vitagene" has been mostly used in the 21st Century, the term "vitagen" (usually used in plural: vitagens) began to be used in the twenties i.e., one Century ago. Vitagens were considered molecules that are not vitamins but are necessary, in a broad sense, for human life. Like vitamins, vitagens are low molecular-weight compounds which means that they are not and cannot be genes nor gene products.

We have traced back words that were proposed to denominate "accessory food components" in a Meeting of the British Medical Association in Cambridge in 1920. Dr. Brown proposed "vitoids" and "biogens" since he preferred them over "vitagens" and other potential names such as vitoids, vitines, advitans, vitases, vitaferes, or biofers [36]. Around twenty years later, vitamins were well defined and vitagens lasted for some years to describe low molecular-weight molecules that are needed for either life or healthy life. To our knowledge, the best definition was provided by Rosenberg, who wrote that vitagens *"are required for normal growth and maintenance of life of animals, including man, who, as a rule are unable to synthesize (them) ..."* He pointed out that a molecule with these properties was a vitagen, as long as it did not fall within the definition of a vitamin [37,38].

Vitagens were considered important as adjuvants of physical exercise to maintain health [39], for children nutrition [40] and for management of liver disease [41]. In summary, vitagens have no relationship with genes and, in spite of the word has been (apparently) forgotten, we believe it would still be appropriate to describe essential nutrients, for instance omega-3 and omega-6 fatty acids [42,43]. A rather notable exception to this general neglect is to consider that the organic compounds produced by probiotics are vitagens [44,45].

Despite they are conceptually very different, the term vitagens is incorrectly used in some publications in which the correct word would be vitagenes [46–50].

3. Direct and indirect relationships between vitagenes and mitochondria

Certainly, vitagenes are genes. However, neither a consensual list of vitagenes is available and no entry for "vitagene" appears in encyclopedias (e.g., Encyclopedia Britannica). A Google search leads to Amazon pages, as the company sells products that appear to be reagents to "analyze" the level of vitagenes. Besides making little sense, in our opinion, these commercial initiatives reflect the lack of an adequate and precise definition. Companies market these reagents advertising them as products able to measure the levels of important genes to be healthy or to reduce the risk of acquiring some diseases.

Likewise, there are very few manuscripts having the word vitagene in the title. In the review of Calabrese et al., the term "vitagenes" appears in the title and is defined as: *"a group of genes involved in preserving cellular homeostasis during stressful conditions"* [51]. This definition is good as long as the conditions and underlying mechanisms are specified. First, all genes of the human genome are required for homeostasis. Secondly, the main operators are not genes themselves but gene products. Also, any condition that alters homeostasis leads to compensations that may affect a wide range of genes. Intense exercise by an athlete is physiological or stressful? Both the individuals that do train intensely and athletes have preserved cell homeostasis but the levels of the gene products maintaining homeostasis are different. Hence, which are the genes that deserve to be considered as "vitagenes".

One situation in which there is a low expression of vitagenes and, therefore, interventions to increase the level of vitagene products would be necessary is malnutrition. Nutrition is essential for human life and malnutrition leads to alterations in the overall homeostasis. Depending

on the characteristics of malnutrition different tissues may be differentially affected. In this context, vitagenes would be those genes whose transcription should be enhanced to return to a healthy life. In this specific case, the simple fact of coming back to a correct nutrition would lead to rebalancing the system.

Another situation in which vitagenes make all the sense is aging. Even in physiological aging, there is a decay in overall performance, from the cell level to the organism one. Accordingly, vitagenes are among those genes whose expression levels decrease with age, thus requiring of some interventions (from making exercise to taking food supplements) in an attempt to increase their transcription for achieve healthy aging and for being more active. Interestingly, the number of genes that may be considered as vitagenes increases if aging is accompanied by a disease, the so-called pathological aging. Despite the fact that (as indicated above) there is no consensual list of vitagenes, there are candidates whose increased transcription would be beneficial to the elderly; those genes are also known as gerontogenes (see [52]).

In conclusion, current research focuses on interventions that lead to increased levels of vitagenes. On the one hand, the benefits are due to the gene products of the vitagenes, not the vitagenes themselves, that is, the benefit is due to a higher transcription of the vitagenes (obviously, the level of genes does not change). On the other hand, some natural molecules of plant origin should be capable of inducing the transcription of vitagenes. For well-being, and considering that the mitochondria is key to maintaining homeostasis, plant-derived compounds that affect mitochondrial function are of great interest.

4. Do plant-derived compounds improve mitochondrial function?

In the absence of any gross change in gene expression, there are plant-derived molecules beneficial for mitochondrial function. Actually, animals have evolved eating plant products. The potential of plants to refill components of the innate detoxification mechanisms (of mammals) and to directly supply components that participate in mitochondrial actions are presented elsewhere [53].

Some examples of plant-derived compounds that are beneficial for mitochondria are here provided. An exhaustive review is out of the scope of the present work. First of all, essential fatty acids, which were considered vitagens [42], are needed for all human cells and all cell components. Similarly, essential amino acids can be vitagens; they can be obtained from animals but also from plants, as vegans well know. A high percentage of plant molecules with demonstrated benefits to maintain homeostasis conditions is directly or indirectly helping mitochondrial function. A good example is the case of vitamins. They are mainly present in plant-derived products and are required to synthesize enzyme cofactors/coenzymes, for example, those needed by enzymes of the Krebs cycle, which takes place in mitochondria. Four representative examples are given below.

The deficit of vitamin B₆ (pyridoxine), a vitamin required to synthesize the prosthetic group of transaminases (pyridoxal phosphate), reduces glutamate-oxaloacetate transaminase activity thus altering the homeostatic levels of oxaloacetate, an intermediate in the Krebs cycle. Actually, the first reaction of the Krebs cycle is citric acid formation, using oxaloacetate and acetyl-coenzyme A, in a process that requires the intake of Pantothenic acid (vitamin B₅). The fuel for this metabolic cycle is the reducing power in form of NADH, i.e. of a compound whose synthesis needs niacin (vitamin B₃). Last but not least, correct operation of the mitochondrial electron chain transport requires a suitable amount of coenzyme Q10 (also known as ubiquinol/ubiquinone), which is obtained from foods of animal or vegetal origin. All these molecules are present in an equilibrated diet, although they are also available as dietary supplements.

Plants contain thousands of molecules that surely impact on human Biology in multiple ways. Three of the most populated families of plant compounds are alkaloids, terpenoids and flavonoids. Alkaloids of the

methylxanthine type such as caffeine, theophylline or theobromine provide health benefits but not related to mitochondrial action [54]. Some polyphenols, which belong to the flavonoid family, are considered antioxidants able to reduce oxidative stress, impacting on mitochondrial function in an indirect way. However, there is controversy on whether dietary plant-derived antioxidants are acting as such or they are boosting the innate mechanisms of detoxification (of mammals) [53]. If the latter were true, these compounds would serve less as vitagens and more as inducers of vitagene transcription.

Are there examples of compounds able to increase the transcription of vitagenes and that ultimately impact on mitochondrial function? Yes, but, as of today, not too many. Curcumin, which is enriched in the rhizome of *Curcuma longa*, increases the transcription of the *HMOX1* gene in astrocytes, probably via Nrf2 transcription factor [55–57]. *HMOX1* codes for heme oxygenase-1 (HO-1), the first enzyme of heme catabolism. HO-1 is considered a key component of the major heat stress/shock cell response [58], it is induced under conditions of oxidative stress [57], and also mediates the resolution of neuro-inflammation [59]. In the cerebral cortex and hippocampus of AD patients, HO-1 immunoreactivity is increased in neurons and astrocytes, and colocalizes with pathological AD hallmarks [60]. Later, the same laboratory reported that: “In Parkinson disease, HO-1 decorates Lewy bodies of affected dopaminergic neurons and is highly overexpressed in astrocytes residing within the substantia nigra. The ho-1 gene is also upregulated in glial cells within multiple sclerosis plaques; in the vicinity of human cerebral infarcts, haemorrhages, and contusions; and in various other degenerative and nondegenerative human CNS disorders” [61]. In summary, increased expression of this enzyme is a common factor in several diseases of the central nervous system, including inherited ones such as Huntington’s disease [62]. Supposedly, HO-1 reduces oxidative stress thus allowing a better performance of mitochondria. The antioxidant role of the enzyme can be challenged because HO-1 produces NADPH⁺ from its reduced form, NADPH, which is necessary to reduce oxidative stress in other contexts. Therefore, it is rare that an agent that consumes NADPH acts in antioxidant processes. For instance, in the pro-oxidant environment of a red blood cell there is a mechanism of detoxification in which glutathione is the means to use NADPH to maintain homeostasis. Furthermore, the levels of NADPH are kept high by glucose consumption and by the activity of glucose-6-phosphate dehydrogenase whose gene, *G6PD*, may be considered a vitagene, at least for the erythrocyte. Then, it is strange that a vitagene product is acting by reducing cell levels of NADPH. The underlying mechanism of action of HO-1 is not fully elucidated and, actually, a controversy has arisen because data in cultured astrocytes show that increased enzyme action leads to enhanced oxidative stress and mitochondrial membrane damage [63]. This example reflects that: i) under some circumstances and/or in certain cell types, one of the most studied vitagenes may not be acting as a vitagene, and ii) the link(s) between the product of a vitagene and mitochondrial function should be better delineated.

Another example to highlight is the case of hydroxytyrosol (HT), a polyphenol from virgin olive oil, that has been recently studied in a cellular model of A β toxicity that mimics the mitochondrial dysfunction of AD. The authors provide evidence that HT initiates mitochondrial activity and improves the altered energy state characteristic of 7PA2 cells [64]. In fact, 24 h of HT treatment are sufficient to increase cellular ATP concentrations respect to those in untreated cells. Interestingly, the analysis of mRNA levels and protein expression of the nuclear transcription factor PGC-1 α (Peroxisome proliferator-activated receptor Gamma Coactivator-1 α) as well as the mtDNA copy number in HT-treated cells suggests that the reversion of the energetic deficit in 7PA2 cells seems to be related with increased mitochondrial biogenesis already detectable at eight hours of treatment [64]. These findings are in line with other in vivo and in vitro studies in which it has been described that HT induces the expression of OXPHOS complexes or mitochondrial ATP synthase [65–67]. In addition, recent evidence suggests that other olive polyphenols, oleocanthal and ligstroside, are able to induce

Table 1

Vitagenes, vitagene products and their functions in the mitochondria.

Vitagene	Vitagene product	Function of vitagene product in the mitochondria	
<i>BCL2</i>	Bcl-2	Regulation of mitochondrial dynamics Prevention of mitochondrial-dependent apoptosis	[a]
<i>CREB1</i>	CREB-1	Regulation of mitochondrial biogenesis	[b]
<i>GSS</i>	Glutathione synthetase	Defence against respiration-induced reactive oxygen species	[c]
<i>GSR</i>	Glutathione reductase		
<i>GPX1</i>	Glutathione peroxidase 1	Detoxification of lipid hydroperoxides and electrophiles	[d]
<i>HMOX1</i>	Heme oxygenase-1; Hsp32	Regulation of mitochondrial dynamics Mitophagy	
<i>HSP70</i>	Hsp70	Translocation and correct folding of mitochondrial proteins	[e]
<i>SIRT1</i>	Sirtuin-1	Deacetylation of mitochondrial proteins	[f, g]
<i>SIRT3</i>	Sirtuin-3	Regulation of mitochondrial electron transport and β -oxidation	
<i>SIRT4</i>	Sirtuin-4	Regulation of mitochondrial biogenesis and turnover	
<i>SIRT5</i>	Sirtuin-5	Detoxification of respiration-induced reactive oxygen species	[h]
<i>SOD2</i>	Superoxide dismutase [Mn]	Regulation of mitochondrial-dependent apoptosis	
<i>TXNRD2</i>	Thioredoxin reductase 2	Regulation of mitochondrial permeability Detoxification	[i]

Mn: manganese. Refs: a: [73]; b: [74]; c: [75]; d: [76]; e: [77]; f: [70]; g: [78]; h: [79]; i: [80,81].

transcription of genes associated with mitochondrial biogenesis, respiration and antioxidant capacity (*SIRT1*, *CREB1* and *GPX1*, among them), in a cellular model of early AD. More importantly, aged mice fed a diet rich in these two purified compounds exhibit increased brain ATP levels, improved spatial working memory and a life extension compared to aged control animals [68].

A (non-exhaustive) list of vitagenes that are directly or indirectly linked to the Biology of mitochondria in mammals is provided in Table 1. The list has few mitochondrial components and this may be due to lack of vitagene products in mitochondria or lack of *ad hoc* research. Sirtuins have emerged as crucial factors in many physiological and cellular processes (see [69] for review), and few of them exert their function in the mitochondria. Accordingly, some of the genes coding for sirtuins can be considered vitagenes that directly impact on mitochondrial activities [70,71]. These factors participate in the synthesis of the nicotinamide adenine dinucleotide (NAD^+) whose concentration is essential for keeping mitochondria in proper “homeostatic” conditions. Plant-derived components (and nutraceuticals) may furnish NAD^+ precursors but sirtuin activity is necessary for NAD^+ synthesis. In addition, to avoid oxidative stress is necessary to keep the oxidized (NAD^+) and reduced (NADH) forms of this compound in appropriate ratios, something that requires players that could become recognized as vitagene products.

5. Conclusion

Whereas there is multiple evidence of plant products providing benefit for mitochondrial function, there is a lack of appropriate studies addressing whether compounds of plant origin lead to increases in the expression of vitagenes related to mitochondrial function. As an example, we have previously suggested that vicine and convicine from broad/fava beans may increase the activity of glucose-6-phosphate dehydrogenase, thus helping to boost the production of NADPH and to reduce the oxidative stress in erythrocytes [72]. To our knowledge, the study has not been performed. Here, we propose that there is a gap between vitagenes and mitochondrial function, and that eliminating it

would require determining whether or not a given plant-derived compound increases the activity of the products of known vitagenes. We bet that such approach would lead to find novel vitagenes and molecules that may become nutraceuticals able to boost homeostatic mitochondrial functions and to decrease oxidative burden.

Author contributions

Conceptualization (R.F., E.M-P.); formal analysis (R.F.); literature search and compilation (R.F., E.M-P., G.N.); data curation (R.F., E.M-P., G.N.); writing—original draft preparation (R.F.); writing—review and editing (R.F., E.M-P., G.N.); supervision (R.F.); funding acquisition, (R.F., G.N.) All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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