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Review

A bacterial novel quinone participating in multiple functions in higher organisms

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The quinoproteins are a group of enzymes that use as cofactor to a quinone novel, pyrroloquinoline quinone (PQQ). The most widely enzymes studied are the bacterial periplasmic dehydrogenases that oxidize sugars, alcohols, aldehydes and some decarboxylases and oxidases containing PQQ have been studied also. In higher organisms have been reported multiple functions that involved the PQQ, such as free radical scavenger, inhibitor of cataracts, as promoter of animal and plant growth and development. Also It increases the cognitive capacity and favors the energy metabolism on having increased the number of mitocondrias in the tissues, among others. The present review trying to approach some of the most relevant aspects of the role of a novel quinone (PQQ) in higher organisms.

Keywords: PQQ, Quinoprotein, Quinone, Enzymes.

INTRODUCTION

Enzymes use cofactors that may be organic or inorganic. In recent years a group of proteins that posses a novel quinone cofactor called pyrroloquinoline quinone (PQQ) (collectivally known as PQQ-quinoproteins) have been intensively studied (Duine, 1989; McIntire, 1994; Misra et al. 2012). Most of the enzymes involved in cell metabolism require nicotine adenine or flavin adenine dinucleotides (NAD^+, $FADH^+$), but do not require the quinoproteins. PQQ-quinoproteins include dehydrogenases, oxydases and decarboxylases (Matsushita et al., 1994). Bacterial dehydrogenases have been the most studied. PQQ-glucose dehydrogenase (PQQ G-DH) has been isolated from Gram-negative barterial as *Gluconobacter suboxydans* and *Klebsiella aerogenes*. This enzyme was found to be associated to the membrane located on the periplasmic side of the cytoplasmic membrane and functionally linked to respiratory chain. PQQ G-DH is able to donate electrons to ubiquinone-6 (Q_6) or ubiquinone-9 (Q_9) (Matsushita et al., 1994; Meyer et al., 2013). This structural and functional orientation is consistent with membrane PQQ G-DH which serving as a low impedance energy generating system (Neijssel et al., 1989). Gluconic acid production by *G. suboxydans* has been shown to be mainly due to the activity of membrane-bound PQQ-G-

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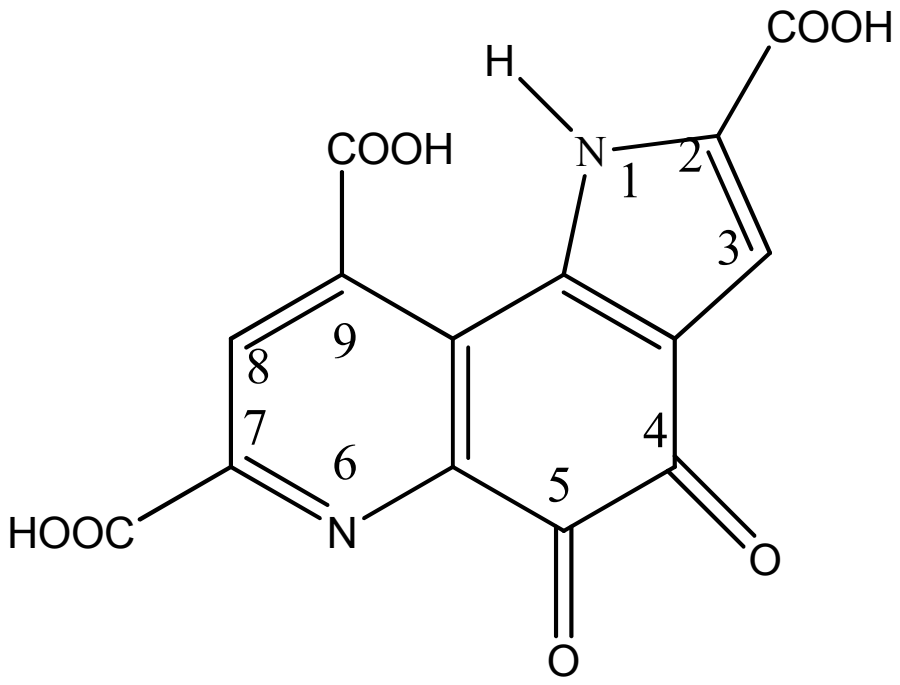

Figure 1. Structure of PQQ.

DH. This enzyme has been found in wide variety of Gram-negative bacteria including facultative anaerobes such as enteric and strictly aerobic bacteria such as *Pseudomonas sp.* as well as acetic acid bacteria (Matsushita et al., 1994; Meyer et al., 2013). PQQ cytochrome-*c* alcohol dehydrogenase (PQQ A-DH) isolated from G*luconacetobacter aceti* and other bacteria is a membrane enzyme and contain membrane-bound cytochrome-*c* and PQQ (Matsushita et al., 1990; Matsushita et al., 1992). In *G. polyoxogenes* the enzyme contains one mole of PQQ together with three moles of heme C, per mole of enzyme complex (Matsushita et al., 1994). PQQ A-DH is an oxidative alcohol-system of acetic acid bacteria that plays a main role in vinager production (Ameyama et al., 1991; Duine, 1989; Flores et al., 2004; Goodwin et al., 1998; Matsushita et al., 1994).

On other hand, PQQ was first obtained by denaturing the enzyme methanol dehydrogenase (M-DH) (Anthony et al., 1994). Many bacteria produce it in large quantities and excrete it (Matsushita et al., 1994). The amount of excreted PQQ can range from 1 micrograms/mL to 1 mg/mL, depending on the composition of the growth media (McIntire, 1994; Misra et al., 2012). The C-5 position of PQQ carbonyl group is very reactive and susceptible to nucleophilic attack (Figure 1) (Anthony, 1996). PQQ forms very stable complexes in the presence of benzylamine, hydroxylamine, hydrazine, phenylhydrazine and semicarbazide, acetone, aminoguanidine, urea, *o*-phenylenediamine, sulfite, malononitrile and Cu^{2+}, Ca^{2+} and Mg^{2+} ions. With strong acids, PQQ promotes the formation of a lactone (Gong et al., 2012; Ohshiro and Itoh, 1993). PQQ knowledge in bacteria is widespread, however little is known about the function of PQQ in higher organisms. This review shows the most relevant aspects of the involvement of a bacterial novel quinone cofactor (PQQ) participants in multiples functions in higher organisms.

Bacterial PQQ-dependent enzymes

In the past 30 years, many new cofactors have appeared on the biochemical scene. In the late 70´s various proteins were found containing PQQ (McIntire, 1994). The PQQ-quinoproteins cover a wide range of bacterial dehydrogenases, oxidases and decarboxylases (Matsushita et al., 2002). The first case found was methanol dehydrogenase isolated from *Methylobacterium extorquens* (Table 1) (Avezoux et al., 1995). Table 1 shows some examples of the PQQ-containing enzymes (including dehydrogenases and oxidases) that have been found in bacteria (Ameyama and Adachi, 1982; Anthony, 1993; Attwood et al., 1991; Chan and Anthony, 1991; Flores et al., 1999; Flores et al., 2004; Galar and Boiardi, 1995; Hommel and Kleber, 1990; Matsushita et al., 1990; Van der Meer et al., 1989). In the case of dehydrogenases, they oxidize a wide variety of alcohols, aldehydes, organic acids and sugars. They are present in the periplasmatic membrane side of Gram-negative bacteria. These enzymes are important because they are involved in substrate oxidation from outside the cell and apparently the process is coupled to the respiratory chain

Table 1. Quinoprotein enzymes found in bacteria.

PQQ-Quinoprotein	Enzyme	Bacteria	References
Dehydrogenase	Glucose dehydrogenase	*Pseudomonas aeruginosa*	2,3,7,12
		Gluconobacter suboxydans	3,4,16,36,40
		G. aceti	3,7,14,16,17
		G. diazotrophicus	12,17,18
	Methanol dehydrogenase	*Methylobacterium extorquens*	3,4,5,8,10,22
		Acetobacter methanolicus	3,4,5,8,10,23
	Alcohol dehydrogenase	*Gluconobacter. suboxydans*	
	(Quinocytochrome-*c*)	*G. aceti*	4,16,17,18,34,35,36
		G. diazotrophicus	
	Aldehyde dehydrogenase	*Acetobacter rancens*	
		G. aceti	6,16,18,22,26,32,36
		G. diazotrophicus	
Oxidase	Methylamine oxidase	*Arthrobacter P1*	22,37,38,60
Decarboxylase	Glutamate decarboxylase	*Escherichia coli*	16,18,22,36

and therefore the production of ATP (Anthony, 1996; Gong et al 2012; Matsushita et al., 1994; McIntire, 1994; Meyer et al. 2013). There is only one known example of a bacterial PQQ oxidase: methylamine oxidase found in Gram-positive bacteria *Arthrobacter* P1. Also in fungi, there have been found others such as galactose oxidase (Van der Meer et al., 1989). These enzymes contain Cu^{2+} ions due to the excellent chelating properties of PQQ (McIntire, 1994). In *E. coli* it has been demonstrated the existence of the glutamate decarboxylase, which contains PQQ covalently bound (Duine, 1989). Membrane quinoproteins are anchored to the bacterial cytoplasmic membrane, in which their catalytic sites are oriented toward the the periplasm (Matsushita et al., 1994). These are also known examples of soluble dehydrogenases such as soluble glucose dehydrogenase isolated from *Acinetobacter calcoaceticus* (Matsushita et al., 2002). Because of its location and action, membrane glucose dehydrogenase provides some ecological advantages related to the oxidation process that occurs outside of the bacteria and the accumulating products (Flores et al., 2004). Such is the case of oxidation of glucose in *G. suboxdans*, *G. aceti*, *G. diazotrophicus* and *E. coli*, which the process takes place in the periplasmic space and the reaction product (such as gluconic acid) accumulates acidifying the bacterial environment (Cozier and Anthony, 1995; Cozier et al., 1999; Flores et al., 1999; Meyer et al., 2013). The low pH gives the bacteria some sort of advantage in competition with other microorganisms (Matsushita et al., 1994). These are some of the functions of PQQ that have been reported in bacteria. In higher organisms, PQQ is a protective agent against free radicals, promotes growth and development in animals and plants, for what it has proposed as a new vitamin. In the following section are enumerated some of his more important functions of PQQ.

Protective effect of PQQ in oxidative stress

How it was mentioned, bacterial quinoproteins have PQQ and its presence is important to perform catalysis in many reactions (Anthony, 1996; Duine, 1989; Goodwin and Anthony, 1998; Matsushita et al., 2002). However, it has also been determined that PQQ is present in higher organisms, including mammals and plants (Harrisa et al., 2013; Misra et al., 2012). So in recent years, interest has increased in studying the biological potential of PQQ not only in bacteria but also in eukaryotic organisms due to his clinical potential; for example: the role that PQQ plays in the metabolism of the eye lenses. It was observed that hydrocortisone induced cataracts in chick embryos but it was suppressed by the exogenous administration of PQQ. It what suggests a potential for the prevention of cataracts in human (Ameyama et al., 1991; Katsumata et al., 1988; McIntire, 1998). Catarats are caused by the accumulation of polyol and quinoid compounds (such as dopaquinone and sorbitol) and this could be avoided by using of PQQ, which inhibits the tyrosinase and aldose enzymes that synthesize of the above mentioned compounds, respectively (Katsumata et al., 1988). Other studies have reported the involvement of PQQ as a free radical scavenger (Zhang et al., 2013). The administration of an endotoxin of *E. coli* in rats diminished considerably their mortality after the PQQ's exogenous administration (Matsumoto et al., 1988). *E. coli* endotoxin generates superoxide anions which damage cell membranes and produce disseminated intravenous coagulopathies. This was one of the first tests that provided evidence that PQQ acts as a potent free radical scavenger decreasing mortality in rats (Matsumoto et al., 1988; Zhang et al., 2013). Hamagishi et al. (1988) provided further evidence that PQQ suppresses the production of superoxide radicals, which were produced

by intraperitoneal administration of chemicals or by enzymatic reaction with xanthine oxidase (Hamagishi et al., 1988).

It is known that free radicals generated by oxidative stress have been proposed as a cause of neurodegenerative diseases (Ohwada et al., 2008). PQQ is also known because it increases the production of nerve growth factor (NGF) and protects aspartate receptor, NMDA (N-methyl-D-aspartate) by the direct oxidation of the redox site receptor (Aizenman et al., 1992; Gong et al., 2012; Ohwada et al., 2008; Zhang et al., 2013). Its function is neuroprotective because it removes peroxynitrite radical and stimulates the production of NGF and prevent lipoperoxidation (Harrisa et al., 2013; Yamaguchi et al., 1993; Zhang and Rosenberg, 2002). Oxidative damage in the nervous system caused by free radicals leads to cognitive deficits due to a dysfunction in neurotransmission. In recent years there have been some studies that have shown that vitamin E is a powerful antioxidant that can be used as a dietary supplement in patients with cognitive impairment (Chan et al., 2004; Ohwada et al., 2008). Similarly, it has been shown in rats that other antioxidants such as beta-carotene and vitamin C can prevent learning and memory deficits (Delwing et al., 2006). Ohwada et al. (2008) provided some data regarding the effect of PQQ on cognition in rats that were fed with diets supplemented with PQQ and/or ubiquinone-10 (Q_{10}) and normal diets (Ohwada et al., 2008). The results indicated that rats fed with the diet containing PQQ showed greater learning ability than rats fed with a diet devoid of PQQ. Nevertheless, no synergistic effect was seen when PQQ and Q_{10} were added simultaneously in diet. Vitamin E deficiency in young rats reduces learning ability, similar to what has been observed in older rats (Ohwada et al., 2008). However, the use of a diet supplemented with PQQ showed a significant change in the learning (Fukui et al., 2001; Harrisa et al., 2013; Ohwada et al., 2008). This provides valuable data and the use of PQQ and vitamin E may contribute significantly to cognitive processes, especially when there is a deficiency of the latter. It is known that 6-hydroxydopamine (6-OHDA), paraquat and rotenone are potent neurotoxins that affect the mitochondrial complex I producing free radicals such as superoxide, hydroxyl radical and hydrogen peroxide (Lucas and Marín, 2007; Maita et al., 2008; Taira et al., 2004). Reactive nitrogen species such as nitrogen oxide (NO) and peroxynitrite also cause damage to cells, including neuronal cells. PQQ has been reported as a free radical scavenger like superoxide and hydroxyl radicals *in vitro* and suppresses the formation of peroxynitrite-induced neurotoxicity and NO (Misra et al., 2004; Zhang and Rosenberg, 2002). Nunome et al. (2008) conducted studies in a dopaminergic cell line of neuroblastoma (SH -SY5Y) and in rat neurons. They showed that PQQ prevents cell death induced by H2O2 and 6-OHDA and that its protective effect is even greater than that of vitamins C and E (Numome et al., 2008). The reaction mechanism is unknown. Nunome et al. (2008) provided some evidence that the addition of PQQ significantly increased the degree of reduction of a regulatory protein called mitochondrial complex I DJ-1. The results suggested that PQQ prevents oxidative status change of DJ-1 (induced by oxidative stress), so the neuroprotective effect of PQQ on neurons subjected to oxidative stress could be attributed in part to the increase in the level of reduction of the DJ-1 protein (Hepner et al., 2004; Numone et al., 2008; Park et al., 2005). To date, antioxidant mechanism of PQQ is not known; however it has been proposed to activate certain signaling pathways linked to proto-oncogene *ras* and that these should affect the oxidation state of DJ-1 (Kumazawa et al., 2007). It appears to be that DJ-1 is an important protein in the cells, as well as a modulator of the mitochondrial complex I, involved in transcriptional regulation and as a chaperone (Hepner et al., 2004; Taira et al., 2004).

Importance of PQQ in animal growth and development

Although the function of PQQ in animals remains uncertain, its ability to carry out a continuous redox recycling suggests a role as a cofactor, a neuroprotector and especially as a powerfull antioxidant (Gong et al., 2012; Ohwada et al., 2008; Zhang et al., 2012; Zhang and Rosenberg, 2002). In animal models, some studies have found that the size and number of mitochondria present in the tissues are affected by a deficiency of PQQ. For example, in PQQ-deficient mice model it was evident that the number of mitochondria decreased by 30 to 40% compared with mice whose diet was supplemented with PQQ (Steinberg et al., 1994; Stites et al., 2000; Stites et al., 2006). It was also observed that in mice fed with chemically defined diets devoid of PQQ have an abnormal neonatal growth, evidence of bleeding, weak skin, decreased fertility and defects in the immune response, decrease in the levels of interleukin-2 (IL-2) and loss of sensitivity of B and T lymphocytes to mitogens (Steinberg et al., 1994; Stites et al., 2006). In contrast, the addition of PQQ in the diet significantly improved growth and maximum growth was recorded when 1 nmol of PQQ or 300 ng of PQQ per gram of diet was added (Steinberg et al., 1994). Cell cultures have shown that PQQ stimulates growth and proliferation at concentrations as low as 3 nmol PQQ/L of culture media or 3 nmol PQQ per gram of diet. These concentrations of PQQ are closely related to the physiological range of cytokines and growth factors (Naito et al., 1993). At concentrations of 15 to 30 micromolar uM of PQQ per kilogram of weigth, PQQ functions as an antioxidant, as

a derivative called imidazole pyrroloquinone (IPQ). A study found that at these concentrations PQQ and IPQ protect rats from acute liver damage induced by ethanol or CCl_4 (Tsuchida et al., 1993; Urakami et al., 1997). In a rat model in which inflammation and edema was induced using carrageenan, the use of 10 to 30 mg of PQQ per kilogram of weight, allowed a 39% decrease inflammation and edema by 76%.

PQQ, a new factor that promotes plant growth

As mentioned above PQQ promotes the growth and proliferation of animal cells. Recent studies have provided evidence that PQQ also stimulates the vegetal growth (Minorsky, 2008). Rhizobacteria (bacteria that colonize the roots of many plants) stimulate plant growth through different mechanisms. Rhizobacteria are the basis for sustainable agriculture; its use can replace pesticides and chemical fertilizers, which are highly toxic and therefore costly (Tikhonovich and Provorov, 2007). They have been proposed as biofertilizers, since they are easy to grow, managed and obtained. The beneficial effects observed on the ground due to the use of bio-fertilizers are an increase in dry weight and foliage, the number of flowers and fruits, as well as the total weight of the fruit, reducing the chances of environmental pollution and costs of production (Lucy et al., 2004). Examples of bacteria that have been used for these purposes are *Rhizobium sp.*, *Agrobacterium tumefaciens*, *Azospirillum sp*, *Pseudomonas sp.*, among others (Cheng, 2008). These bacteria make mainly symbiosis with plants of legumes and grasses. *Pseudomonas fluorescens* B16 has been found to be associated with the roots of grasses and other plants. Bacteria stimulate the growth of the plant and also produce some antibacterial substances that are effective against certain radicular pathogens (Choi et al., 2008; Thomashow, 1996). Choi et al. (2008) reported that *Ps. fluorescens* B16 produces PQQ, which is an important factor in promoting plant growth. The addition of 5 nM of PQQ to 1 micromolar uM of PQQ notably favors vegetal fresh weight (Choi et al., 2008). Its role was confirmed by observing that the PQQ lacking mutants of *P. fluorescens* B16 are unable to stimulate growth. In plants, it was also shown that the use of *P. fluorescens* B16 and PQQ, favors the reduction of free radicals and H_2O_2, suggesting that PQQ acts as an antioxidant agent in plants.

The role of PQQ: a new vitamin

It appears to be that PQQ is present in most living organisms. As can be seen PQQ is found in bacteria, animals, plants, and surely must be present in protists and fungi. In addition to its roles as a neuroprotective and antioxidant agent, PQQ has been proposed as a new vitamin and redox cofactor present in mammals and plants (Takaoki and Tadafumi, 2003). Like adenine and flavin dinucleotides PQQ is acquired through the diet and has been proposed that it could also be acquired by intestinal absorption from PQQ produced by bacteria in the digestive tract (Stites et al., 2000). In relation to diet, it has been possible to quantify PQQ in some foods. For example, the concentration of PQQ (microgram per liter or µgram per kilogram) has been reported in products such as white vinegar (0.3-2.0), cow milk (3.4), egg whites (4.1), apples (6.0), oranges (7), tomatos (9), bananas (13), carrots (17), papaya (27), kiwi (27), cucumber (28), fermented soybean (61), chicken breast (140-180), and cocoa powder (800) (Misra et al., 2012; Stites et al., 2000). Other authors have proposed that PQQ is synthesized in the tissues of living beings, but there is a lot of controversy about it. Although PQQ is present in tissues, metabolic pathways that can participate are unknown. Takaoki and Tadafumi (2003) identified in mice a PQQ-dependent dehydrogenase, which is important for the degradation of lysine (Takaoki and Tadafumi, 2003). In animals, lysine is an essential amino acid that is degraded into saccharopine, and then converted to 2-aminoadipic-6 -semialdehyde (ASA) acid. ASA is then oxidized to 2-aminoadipic acid (AAA). These authors have proposed that PQQ is required by the AAS-dehydrogenase enzyme, which catalyzes the oxidation of 2-aminoadipic-6-semialdehyde-2-aminoadipic acid (Takaoki and Tadafumi, 2003). Therefore, many it is necessary for being glimpsed on the role of PQQ in cell metabolism in different organisms, but it is important to mention that this quinone confers significant protection to nerve cells and it is believed to be a powerful free radical scavenger, protecting them of oxidative stress.

CONCLUSIONS

Pyrroloquinoline quinone (PQQ) has been proposed as a new vitamin and redox cofactor that it is present in most living organisms. PQQ was first discovered in methylotrophic bacteria and it is involved in direct oxidation of sugars, alcohols, aldehydes and other important metabolites. So far, there is no evidence that PQQ is synthesized in mammals, for what has proposed that it is obtained by intestinal absorption from the diet and bacterial normal flora. Trace amounts of PQQ have been found in human and rat tissue; in plants there is no exception. This suggests that PQQ is a micronutrient with biological activity in mammals, however the metabolic pathways that need of PQQ are yet known. So far is has been indicated that the physiological role of PQQ varies and that it can act as a efficiently free radical scavenger that destroying superoxide and hydroxyl. It has also been observed that it is able to inhibit lipoperoxidation, maintained the reduced state of some regulatory compo-

nents of the cell such as protein DJ-1. PQQ has been also used in high-dose of PQQ has been used to protect the brain from damage by hypoxia or ischemia; to reduce inflammation and edema induced by carrageenan and to protect the liver from damage caused by ethanol or CCl_4, among others. It can be concluded that PQQ has special properties and a great biological potential, so PQQ must be presented in future years as a possible alternative for the treatment of some of the neurodegenerative diseases of our time.

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