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REVIEW ARTICLE

Behavioral and neurochemical effects of proline

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Abstract Proline is an amino acid with an essential role for primary metabolism and physiologic functions. Hyperprolinemia results from the deficiency of specific enzymes for proline catabolism, leading to tissue accumulation of this amino acid. Hyperprolinemic patients can present neurological symptoms and brain abnormalities, whose aetiopathogenesis is poorly understood. This review addresses some of the findings obtained, mainly from animal studies, indicating that high proline levels may be associated to neuropathophysiology of some disorders. In this context, it has been suggested that energy metabolism deficit, Na^+,K^+-ATPase, kinase creatine, oxidative stress, excitotoxicity, lipid content, as well as purinergic and cholinergic systems are involved in the effect of proline on brain damage and spatial memory deficit. The discussion focuses on the relatively low antioxidant defenses of the brain and the vulnerability of neural tissue to reactive species. This offers new perspectives for potential therapeutic strategies for this condition, which may include the early use of appropriate antioxidants as a novel adjuvant therapy, besides the usual treatment based on special diets poor in proline.

Keywords Proline · Hyperprolinemia · Brain damage · Antioxidants · Alpha-tocopherol · Ascorbic acid

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Introduction

L-Proline (Pro) is a non-essential amino acid for human infants and adults (Hiramatsu et al. 1994; Young and El-Khoury 1995). It can be endogenously synthesized either from glutamate or ornithine, but these synthetic pathways are not utilized to provide substrate for protein synthesis because Pro is also present in food regularly consumed from the diet. Low levels of Pro (51–271 μM) are normally found in the plasma (Phang et al. 2001). However, genetic defects can be found in the enzymes of Pro metabolism that can lead to the increase in Pro levels, namely hyperprolinemia. Mutations in proline oxidase and delta-1-pyrroline-5-carboxylate dehydrogenase are associated with excess levels of Pro (>500 μM), mental retardation and epilepsy. Although these mutations are rare, mild or high elevations of Pro levels have been associated with cancer and predispositions to psychiatric disease (Phang et al. 2001). However, to understand the potential relevance of the role of Pro in the central nervous system, it is important to briefly review pathways involved in metabolism of this amino acid.

Proline metabolism—an overview

In contrast to other amino acids, Pro has no primary amino group but an imino group, since only possesses one hydrogen atom inserted in its pyrroline ring, giving rise to a molecule with an exceptional conformational rigidity. Based on this fact, Pro is excluded from the pyridoxal-5-phosphate coenzyme catalyzed decarboxylation and transaminations reactions that are important for amino acid metabolism. As such, Pro is metabolized by enzymes with properties and regulatory mechanisms

that are independent of those used by other amino acids (Phang et al. 2001).

As described by Hu and colleagues (2008), the Pro metabolism (Pro cycle) in mammals involves two other amino acid, glutamate and ornithine, and five enzymes namely delta-1-pyrroline-5-carboxylase reductase, proline oxidase, delta-1-pyrroline-5-carboxylate dehydrogenase, delta-1-pyrroline-5-carboxylate synthase and ornithine aminotransferase (Fig. 1).

As shown in Fig. 1, ornithine and glutamate are the precursors of Pro, with delta-1-pyrroline-5-carboxylate (P5C) or glutamic-gamma-semialdehyde as the common intermediate (Adams 1970; Ross et al. 1978; Smith and Phang 1979; Strecker 1957). P5C, a precursor and the degradation product of Pro, is found both intracellularly and also circulating in plasma. In Pro synthesis, P5C is released from mitochondria and is converted to Pro by cytosolic P5C reductase, an enzyme found in low concentrations in all tissues that utilize either NADH or NADPH as a cofactor, since it has a higher affinity for NADPH (Phang et al. 2001). Thus, the Pro cycle, via P5C redutase, participates and activates the metabolism of glucose through the pentose phosphate pathway (Phang et al. 1980; Phang et al. 2008b). With the exception of conversion of P5C to Pro by P5C reductase found in cytosol, all other reactions involved in Pro synthesis occur in the mitochondria.

The first step in proline degradation is catalyzed by proline oxidase (POX), also named proline dehydrogenase (PRODH), a flavoenzyme localized at the inner mitochondrial membranes that convert proline to P5C. In this reaction, the transfer of electrons occurs from Pro to FAD (flavine adenine dinucleotide) and generates $FADH_2$, which delivers its electrons into the complex II of the electron transport chain and ATP is formed by oxidative phosphorylation through the subsequent transfer of these electrons, via cytochrome c. Thus, Pro can be a direct substrate for ATP production (Adams and Frank 1980; Hagedorn and Phang 1983; Phang et al. 2001). The second non-enzymatic step involves the conversion of P5C to glutamic-gamma-semialdehyde, which is converted to ornithine in the reversible reaction catalyzed by ornithine amino transferase (OAT) or to glutamate by enzyme delta-1-pyrroline-5-carboxylate dehydrogenase (P5C dehydrogenase), which use NAD^+ (nicotinamide adenine dinucleotide) as an electron acceptor and generate NADH, delivering electrons for mitochondrial respiration. This reaction is a component of the pathway connecting the urea (ornithine/arginine) and tricarboxylic acid cycles (glutamate/alpha-ketoglutarate). With the exception of OAT, which catalyzes a reversible reaction, the other four enzymes catalyze irreversible reactions. With the exception of proline oxidase, which is inserted in the inner membrane, the other reactions of Pro degradation occur primarily in matrix mitochondria. Mitochondrial P5C can be recycled to Pro in the cytosol by P5C redutase.

Roles of L-proline

Pro has important roles in synthesis and structure of protein and metabolism (particularly the synthesis of arginine, polyamines, and glutamate via P5C). Pro is one of most abundant amino acids, being readily available from the breakdown of the extracellular matrix, which is composed predominately of collagen and 25% of the amino acids of this protein are Pro and/or its derivative hydroxyproline (Li et al. 2006). Due its predominance in collagen and milk, the requirements for Pro are the greatest among all amino acids (Wu et al. 2010). In addition, the cycling of P5C and Pro between mitochondria and cytosol can transfer reducing potential, which can contribute to ATP production (Yeh and Phang 1988). In addition, the Pro degradative pathway can generate gluta-

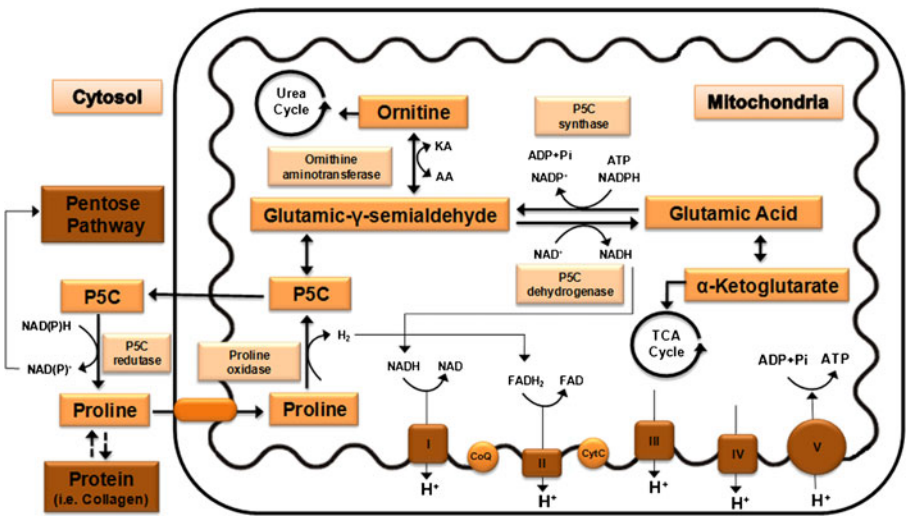

Fig. 1 Schematic Proline Cycle. Abbreviations: *P5C*: delta-1-pyrroline-5-carboxylic acid; *CoQ*: coenzyme Q; *Cyt c*: cytochrome c; *I–IV*: complexes of electron transport chain and *V*: FoFi-ATP synthase; *AA*: amino acid; *KA*: α-ketoacid (Adapted from Phang et al., 2001)

mate and alpha-ketoglutarate, which can play an anaplerotic role in the Krebs cycle (Phang 1985). Based on this, it has been suggested that Pro metabolism can be activated under stress conditions providing accessory mechanisms for bioenergetic and redox reactions (Pandhare et al. 2009).

On the other hand, Pro has also been considered as an osmoprotectant in bacteria and also an antioxidant in plants (Phang 1985), as well as a bioenergetic substrate for insects during their initiation of flight (Gade and Auerswald 2002; Micheu et al. 2000; Phang et al. 2008a). Although the role of Pro has been recognized in a variety of animals and plants, the mechanisms are unclear. However, it has been suggested that this amino acid has an important role in the co-evolution in both plant and animal species (Phang et al. 2008a).

L-Proline metabolism and diseases

Human inherited disorders of the metabolism of Pro are known as hyperprolinemia type I (HPI), hyperprolinemia type II (HPII), delta-1-pyrroline-5-carboxylate synthase deficiency, ornithine aminotransferase deficiency, hydroxiprolinemia and iminoglycinuria (Mitsubuchi et al. 2008). Inherited disorders in the degradative pathways of proline cause hyperprolinemia in humans (Phang et al. 2001). The first report of the direct effect of the involvement of Pro in human disease was reported by Schafer and colleagues (Schafer et al. 1962) in a family with hyperprolinemia, cerebral dysfunction, renal abnormalities, hereditary nephropathy and deafness. From this time onwards, many families with hyperprolinemia have been reported in the literature (Mitsubuchi et al. 2008) and various studies have been performed in order to understand the biological function (Phang, Hu and David Valle groups and others), behavioural and neurochemical effects (Wyse group and others) and physiopathology of diseases such as hyperprolinemias, cancer and psychiatrics (Phang, Hu, David Valle, Campion and other groups).

Hyperprolinemia is present in two inherited metabolic disorders: type I and type II hyperprolinemias. These disorders are characterized by distinct biochemical and genetic deficiencies in the catabolic pathway (Fig. 1). HPI is a rare inherited autosomal recessive disorder of amino acid metabolism characterized by the hepatic deficiency of proline oxidase (also called proline dehydrogenase), a flavoenzyme localized in the inner mitochondria that converts Pro to P5C, the first step in the Pro catabolic pathway. Tissue accumulation of Pro occurs in affected patients, and Pro levels can range from five- to ten times (700 to 2400 μM) above normal values (51 to 271 μM). Some studies show that mild hyperprolinemia (500 to 1000 μM) may be observed in HPI heterozygotes (Phang et al. 2001). It has been shown that the gene (PRODH1) that encodes POX is localized in the 22q11 chromosomal region. The clinical manifestations in patients with HPI are still not well characterized. Some phenotypes are found in patients with HPI, such as neurological renal, auditory defects, ocular abnormalities, mental retardation and other neurologic alterations, whereas others are asymptomatic (Mitsubuchi et al. 2008; Phang et al. 2001). One case report described a patient with psychomotor delay, right hemiparesis and epilepsy (Humbertclaude et al. 2001) and another described a 10-year-old boy with HPI, neurologic manifestations and abnormalities of the central nervous system white matter (Steinlin et al. 1989). Since HPI is not necessarily associated with clinical manifestations this disorder has been considered a benign condition in most individuals under most circumstances (Phang et al. 2001).

HPII is a rare inherited autosomal recessive disorder of amino acid metabolism, characterized by the hepatic deficiency of delta-1-pyrroline-5-carboxylic acid dehydrogenase activity. This enzyme catalyzes the conversion of P5C, derived from proline or ornithine, to glutamate. This disease is biochemically characterized by accumulating Pro and P5C in plasma, urine and cerebrospinal fluid and, quantitatively, the major metabolite that accumulates in the tissue of patients with HPII is proline and not P5C (Fleming et al. 1984; Flynn et al. 1989; Phang et al. 2001). The plasma concentrations of Pro in HPII are greater than those of HPI, can range from ten to fifteen times (500–3700 μM) above normal values (51 to 271 μM), where in homozygotes, the plasma levels of Pro almost always exceed 1500 μM. In addition, Pro levels in cerebrospinal fluid and urine are correspondingly greater in type II homozygotes than in type I subjects (Phang et al. 2001). The greater Pro concentrations in patients with HPII seem to result from the inhibition of proline oxidase by P5C (Valle et al. 1976). Although asymptomatic hyperprolinemic siblings have been identified in some pedigrees (Pavone et al. 1975; Simila and Visakorpi 1967), a considerable number of hyperprolinemic patients, so far detected, show neurological manifestations including seizures and mental retardation (Di Rosa et al. 2008; Phang et al. 2001). In this context, a relationship between a high concentration of Pro and neurological symptoms has been demonstrated in patients with HPII (Flynn et al. 1989). In contrast to HPI, there is persuasive evidence that HPII is causally associated with neurologic manifestations (Phang et al. 2001).

Neuropsychiatric disorders associated with hyperprolinemia

A 22q11.2 microdeletion causes velocardiofacial syndrome (VCFS), an autosomal dominant genetic condition (Shprintzen et al. 1981). Most of these deletions occur spontaneously and

its frequency is estimated at 1/4000 live births. Patients affected by this syndrome present symptoms that include cognitive dysfunction with mild mental retardation, and behavioral difficulties (Karayiorgou and Gogos 2004). Among children and adolescents, attention deficit, hyperactivity, obsessive compulsive, mood and autism spectrum disorders have been reported (Baker and Skuse 2005; Fine et al. 2005; Vorstman et al. 2006; Vorstman et al. 2009). In adults, there is an increased (30-fold) risk of schizophrenia (Karayiorgou and Gogos 2004; Mitsubuchi et al. 2008).

The catechol-o-methyltransferase (COMT) and the proline dehydrogenase genes (known as PRODH) are functional candidate genes located in the 22q11 chromosomal region that may be able to modify the psychiatric phenotype of people with 22q11 deletion syndrome and psychiatric disease, including schizophrenia. COMT is an enzyme that inactivates biologically-active catechols, including the important neurotransmitters dopamine, noradrenaline and adrenaline. These neurotransmitters seem to be involved in numerous physiological and physiopatological processes, including psychiatric disorders (Chen et al. 2004; Levy 2009; Tan et al. 2009).

As described above in Pro metabolism, proline oxidase (POX) is a mitochondrial inner membrane, also known as proline dehydrogenase that converts Pro to P5C. The PRODH gene is widely expressed in brain and other tissues (Gogos et al. 1999). Also, it has been established that P5C can be converted to glutamate and GABA, two neurotransmitters implicated in the physiology of schizophrenia and other psychiatric illnesses (Roussos et al. 2009; Van Spronsen and Hoogenraad 2010). In addition, evidence to support the role of Pro in brain function includes the presence of high affinity Pro transporter molecules (Na^+/Cl^--dependent proline transporter-PROT), which belong to a large superfamily of neurotransmitter transporters, in a subset of glutamatergic neurons in the rat brain, including the hippocampus (Schaffer collateral commissural and lateral perforant pathways) (Cohen and Nadler 1997a; Fremeau et al. 1992) and corticostriatal pathways (Renick et al. 1999). Studies also show that mice lacking the PRODH gene present prepulse inhibition and an impairment of learning and memory (Paterlini et al. 2005). It has been demonstrated that moderate hyperprolinemia is an intermediate phenotype associated to certain forms of psychosis such as schizoaffective disorder, but not with schizophrenia or bipolar disorder (Jacquet et al. 2005). On the other hand, a recent study suggests that Pro metabolism is specifically associated with schizophrenia (Oresic et al. 2011). Interestingly, it has been also shown that urinary hydroxyproline and Pro concentrations are influenced by stress and anxiety (Lee et al. 2011).

Behavioral and neurochemical impairments caused by L-proline

Despite the different clinical and neuropathological conditions, the pathomechanisms associated with various diseases that affect the central nervous system (CNS) seem to have a number of common features in their processes. In this context, it has been suggested that energy metabolism dysfunction, glutamate excitotoxicity, oxidative stress, purinergic and cholinergic impairment have an important role in the physiopathology of these disorders, which seem to be associated with cognitive deficits, as observed in Parkinson's and Alzheimer's diseases, cerebral ischemia, amongst others (Abbracchio et al. 2009; Beal 2007; Dumont et al. 2010; Halliwell and Gutteridge 1985; Halliwell and Gutteridge 2007; Kapogiannis and Mattson; Kim et al. 2010; Lees 1993; Lin and Beal 2006; Maragakis and Rothstein 2001; Reddy and Reddy 2011; Zhang et al. 2010). The effects of Pro will be reviewed on some behavioral and neurochemical aspects such as:

Behavior

With regard to Pro, behavioral studies show that animals that bear a mutation in the gene that encodes proline oxidase exhibit high plasma Pro levels and depressed locomotor activity (Hayward et al. 1993; Kanwar and Manaligod 1975; Moreira et al. 1989). Intracerebral administration of Pro produces retrograde amnesia and disrupts the formation of new memories in chickens; the amnesic effect of Pro does not depend on inhibition of brain protein synthesis, but suggests the involvement of glutamate in this process (Cherkin et al. 1976, 1981; Van Harreveld and Fifkova 1974). In addition, using an experimental model of chronic hyperprolinemia in developing rats, it was shown that Pro impairs habituation (Moreira et al. 1989) and spatial memory in adult animals (Bavaresco et al. 2005; Delwing et al. 2006a). Hystological studies showed that rats subjected to same experimental model of hyperprolinemia presented degenerative changes in brain (Shanti et al. 2004).

Glutamatergic system

It is well known that glutamate is the major excitatory neurotransmitter in the brain and is present at millimolar concentrations in the adult CNS. It is released in milliseconds from presynaptic nerve terminals, in a Ca^{2+} dependent manner, into the synaptic cleft where it diffuses to interact with its corresponding receptors on the postsynaptic face of an adjacent neuron. Glutamate receptors are divided into two groups, ionotropic (representing ligand-gated ion channel:

NMDA, AMPA, kainate) and metabotropic (coupled to protein G).

Normal excitatory neurotransmission is essential for plastic processes, which underlie memory and learning (Reis et al. 2009), developmental (Segovia et al. 2001) and environmental adaptation (Ozawa et al. 1998). In contrast, an excessive glutamate excitation caused by enhanced release of glutamate in the synaptic cleft gives rise to prolonged stimulation of its receptors and, via a complex pathomechanism, may induce devastation of the postsynaptic neurons. This process of glutamate toxicity was first described by Lucas and Newhouse (1957), who showed degeneration of the inner layers of the retina following subcutaneous injections of glutamate in infant mice. Approximately one decade after, Olney (1969) coined the term "glutamate excitotoxicity"; from then on this process, which can be thought of as normal physiological response to a CNS insult, has been implicated in the pathogenesis of various acute and chronic disorders (Maragakis and Rothstein 2001; Meldrum 1994).

It has been shown that glutamatergic excitotoxicity may be linked with mitochondrial dysfunction, because energy impairment can lead to partial membrane depolarization, resulting in relief of the magnesium blockage of the N-methyl-D-aspartate (NMDA) channel. Thus, even in physiological concentrations, glutamate via the NMDA receptor increases Ca^{2+} influx, which promotes many normal intracellular signaling pathways; however excessive influx promotes pathological signaling, contributing to cell injury and death via production free radicals such as reactive species of oxygen (ROS) and nitric oxide (NO), as well as other enzymatic processes (Nakamura and Lipton 2010).

The maintenance of below neurotoxic levels of extracellular glutamate concentrations at glutamatergic synapses in the brain is an essential role of glial cells and this is achieved through high-affinity sodium-dependent glutamate transporters, namely GLAST and GLT-1, present mainly in astrocytes (Anderson and Swanson 2000; Attwell 2000; Chen and Swanson 2003; Danbolt 2001). Furthermore, glutamate uptake is inwardly associated with transport of sodium, resulting in an increase in the intracellular sodium concentration (Chatton et al. 2000; Rose and Ransom 1996; Voutsinos-Porche et al. 2003). Such sodium elevations stimulate Na^+,K^+-ATPase and cause increased ATP consumption and glucose uptake by astrocytes (Chatton et al. 2000; Loaiza et al. 2003; Pellerin and Magistretti 1994; Porras et al. 2008). Since free radicals are highly reactive molecules and can modify proteins in many different ways, it has been suggested that they can inhibit glutamate uptake in astrocyte cultures (Piani et al. 1993; Sorg et al. 1997; Volterra et al. 1994).

Excitotoxic properties have been also demonstrated for Pro, which at higher concentrations activates NMDA and AMPA receptors, suggesting that Pro might potentiate glutamate transmission (Cohen and Nadler 1997b; Fremeau et al. 1992; Nadler 1987; Nadler et al. 1992). It has also been shown that Pro, in vitro (added to assay), decreases glutamate uptake in the cerebral cortex and hippocampus slices of rats. On the other hand, Pro administration at high concentrations to plasma (similar to those found in hyperprolinemia) reduced glutamate uptake in the cerebral cortex slices of rats, but did not alter this parameter in the hippocampus slices (Delwing et al. 2007d). Knowing that glutamate uptake by astrocytes is the main process involved in pathophysiological neuroprotection against glutamatergic excitotoxicity, by reducing the extracellular glutamate concentrations below toxic levels, this inhibitory effect caused by Pro corroborates with previous studies that suggest that this amino acid has excitotoxic properties (Cohen and Nadler 1997b; Fremeau et al. 1992; Nadler 1987; Nadler et al. 1992). In addition, it is possible that the reduction in glutamate uptake is mediated by the reduction in Na^+,K^+-ATPase activity caused by Pro, leading to increased extracellular glutamate concentrations and promoting excitotoxicity. Thus, a reduction in glutamate uptake and Na^+,K^+-ATPase activity may act synergistically and cooperate to provoke the brain damage that is characteristic of hyperprolinemia.

Energy metabolism

Mitochondria are responsible for the energy supply of cells; besides playing crucial roles in other cell processes such as signaling, calcium homeostasis, cell cycle regulation processes, apoptosis, free radical production and thermogenesis, which are crucial to cell development. In performing the primary metabolic pathways for ATP production, these organelles consume the greatest amount (85–95%) of oxygen in cells to allow oxidative phosphorylation, which depends on the electron transport chain through the action of various respiratory enzyme complexes located in the inner mitochondrial membrane. Impaired electron transport, in turn, leads to decreased ATP production, increased formation of toxic free radicals, and altered Ca^{2+} homeostasis. These toxic consequences of transport chain dysfunction may sustain further mitochondrial damage, including oxidation of mitochondria, DNA, protein and lipids, and may open of the mitochondrial permeability transition pore that, together, can lead to cell death by both apoptotic and necrotic pathways (Dumont et al. 2010; Mancuso et al. 2010; Reddy et al. 2008; Solaini et al. 2010; Wallace 2005). In this context, increasing evidence sustains the hypothesis that mitochondria energy metabolism underlies the pathogenesis of neurodegenerative, psychiatric and others (Beal 2000; Beal 2007; Dumont et al. 2010; Lin and Beal 2006; Reddy and Reddy 2011; Rezin et al. 2009;

Solaini et al. 2010; Sullivan and Brown 2005; Zeviani and Carelli 2007).

Although Pro can be considered a direct substrate for ATP production via proline oxidase/P5C dehydrogenase and/or participate in a metabolic interlock with glucose-6-phosphate (pentose phosphate pathways) via P5C redutase and/or via anaplerotic reactions (alpha-ketoglutarate/Krebs cycle) (Phang et al. 2008a, b), high levels of Pro lead to alterations in the cell redox state, resulting in decreased oxygen consumption and lower oxidation of the NADH formed by the cell (Phang et al. 2001). In addition, previous findings have demonstrated that acute and chronic Pro administration decrease cytochrome c oxidase activity in the cerebral cortex of rats, indicating that Pro also compromises the respiratory chain (Delwing et al. 2007a). Interestingly, more recently we have shown that a single administration of high Pro increases the activity of brain succinate dehydrogenase (Ferreira et al. 2010). This phenomenon could have occurred to compensate for the decrease in mitochondrial electron transport generated by the inhibition of cytochrome c oxidase, which could result in the production of free radicals.

Oxidative stress

Oxidative stress is defined as an imbalance between formation and scavenging (neutralizing) of free radicals and it is presumed to be involved in the physiopathology of many diseases that affect CNS, including ischemia, epilepsy, and neurodegenerative and metabolic diseases (Allen and Bayraktutan 2009; Beal 1995; Droge 2002; Halliwell and Gutteridge 1985; Matte et al. 2006; Matte et al. 2009; Peker et al. 2009; Wajner et al. 2007; Waldbaum and Patel 2010; Wyse et al. 2002; Zhang et al. 2007). It has been shown that the brain is highly susceptible to oxidative stress due to the elevated rate of oxygen consumption, presence of high levels of polyunsaturated fatty acids and low cerebral antioxidant defenses compared to other tissues (Floyd 1999; Halliwell 2006), a fact that makes it more vulnerable to reactive oxygen species. Inherently, it has been shown that, during the Pro oxidation by proline oxidase, the electrons from Pro can reduce oxygen to yield superoxide (Liu et al. 2005). It has also been suggested that when the activity of P5C dehydrogenase is decreased, P5C-Pro cycle can transfer more electrons to the mitochondria electron transport chain and produce reactive oxygen species (Szabados and Savoure 2010). This phenomenon may be explained by the increase in Pro. Interestingly, we have shown that high Pro concentrations, similar to those found in hyperprolinemia, induce lipoperoxidation and reduce non-enzymatic and enzymatic antioxidant defenses in rat brain, suggesting that Pro elicits oxidative stress (Delwing et al. 2003).

Na^+,K^+-ATPase activity

Na^+,K^+-ATPase is a plasma membrane-embedded enzyme responsible for the active transport of sodium and potassium ions in the nervous system, maintaining and re-establishing, after each depolarization, the electrochemical gradient necessary for neuronal excitability and regulation of neuronal cell volume. Because of the frequent perturbation of ion homeostasis, resulting from constant neural activity, the workload of Na^+,K^+-ATPase is high, consuming about 40–50% of the ATP generated in brain (Erecinska and Silver 1994). Decreased Na^+,K^+-ATPase is found in various neuropathological conditions, including cerebral ischemia (Wyse et al. 2000) epilepsy (Grisar 1984), and neurodegenerative disorders (Hattori et al. 1998; Lees 1993; Pisani et al. 2006; Vignini et al. 2007). Additionally, some psychiatric disorders are believed to be associated with perturbation of ion homeostasis, and earlier studies have shown that Na^+,K^+-ATPase activity is decreased in depression and other psychiatric disorders (Goldstein et al. 2006; Zugno et al. 2009). Exciting new findings have revealed additional fundamental roles for Na^+,K^+-ATPase as a signal transducer and modulator of growth, apoptosis, cell adhesion and motility (Aperia 2007). We have shown that Pro in vitro and in vivo (acute and chronic) decreases Na^+,K^+-ATPase activity in cerebral cortex and hippocampus of rats (Pontes et al. 2001). This inhibition may be explained by free radical production by Pro in the brain, which damages the membrane lipid bilayer containing Na^+,K^+-ATPase. Moreover, this enzyme is known to be highly susceptible to changes in the composition of membrane lipids (Jamme et al. 1995; Murali et al. 2008; Rauchova et al. 1999; Zhang et al. 2007). Besides, reduction of energy metabolism caused by Pro with consequent decrease of ATP levels may impair the activity of Na^+,K^+-ATPase and consequently the electrochemical gradient necessary for maintain neuronal excitability.

More recently, we have shown that hyperprolinemia increases ganglioside content in the cortex and hippocampus of rats, while this membrane lipid content was not altered in the hypothalamus and cerebellum. In addition, phospholipid and cholesterol contents were not modified in any of the structures studied, suggesting that Pro affects in a distinct manner different cerebral regions concerning the lipid composition of the cell membranes, reflecting on its distribution in the cortex membrane microdomains. Among the consequences of these phenomena, distinct modulations in enzymes such as Na^+,K^+-ATPase and synaptic transmission may be suggested (Vianna et al. 2008).

Creatine kinase activity

Creatine kinase (CK), also known as creatine phosphokinase, plays a key role in energy metabolism (Eppenberger

et al. 1967). This enzyme catalyzes the reversible transfer of the phosphoryl group from phosphocreatine to ADP, to regenerate ATP. CK is especially fundamental in tissues with high and fluctuating ATP consumption such as skeletal and cardiac muscle, brain and retina, where phophocreatine serves as an energy reservoir for the rapid regeneration of ATP. The CK enzyme consists of two subunits, B (brain type) and M (muscle type), which are compartmentalized specifically in the places where energy is produced or utilized (Wallimann et al. 1992). Different cells can contain several different CK isoforms, and the isoenzyme patterns differ among organs. Two isoforms, M-CK and ubiquitous B-CK, are cytosolic, and two others, Mi b-CK and ubiquitous Mi a-CK, are mitochondrial (Wallimann et al. 1998). CK is inhibited by oxidative stress (Delwing et al. 2007b; Ferreira et al. 2007; Zugno et al. 2007) and its activity is decreased in neurodegenerative, metabolic and psychiatric diseases (Aksenov et al. 2000; David et al. 1998; Delwing et al. 2007b; Zugno et al. 2007). It has been shown that in vitro Pro and acute hyperprolinemia administration decrease CK in the cerebral cortex of rats (Kessler et al. 2003) and this inhibitory effect on the enzyme may potentially impair energy homeostasis, since it is known that inhibition in this enzyme can contribute to cell death (Tomimoto et al. 1993).

Acetylcholinesterase and NTPDases activities

ATP and acetylcholine serve as extracellular signaling substances in the nervous system and in other tissues. They can even be co-stored within synaptic vesicles and co-released from cholinergic nerves. Neither ACh nor ATP can be directly recycled. They must first be degraded to either choline or adenosine and those substances are transported back into cells. Acetylcholine is specifically hydrolyzed by acetylcholinesterase (AChE). This enzyme contributes to the integrity and permeability of the synaptic membrane that occurs during neurotransmission and conduction (Grafius et al. 1971). In addition to the classic enzymatic role, AChE also has some non-classical properties concerning CNS development. For instance, it is accepted that AChE has functions associated with adhesion, neurite growth, circuit formation and apoptosis (Johnson and Moore 2000; Layer and Willbold 1995; Sharma and Bigbee 1998; Silman and Sussman 2005; Soreq and Seidman 2001; Zhang et al. 2002). In this context, it has been shown that AChE forms a complex with amyloid precursor protein and perlecan that seems to be involved in substratum adhesion and polarized migration of adherent cells (Anderson et al. 2008). This enzyme is inhibited by free radical and/or oxidative stress and its cholinergic and non-cholinergic actions may play a role in schizophrenia, neurodegenerative and neurometabolic diseases (Arendt et al. 1992; Cummings 2000; Henderson et al. 1996). Importantly, Pro has been demonstrated to act as an AChE inhibitor, which results in higher synaptic levels of acetylcholine (Delwing et al. 2005b).

Since ATP is an unstable molecule that cannot cross biological membranes by diffusion or active transport, its breakdown is carried out by specific enzymes located on the outer surface of cells, called ecto-enzymes (Plesner 1995). ATP and the other extracellular nucleoside tri- and diphosphates can be hydrolyzed by ectonucleotidases, including ecto-nucleoside triphosphate diphosphohydrolase (NTPDases), which are enzymes that hydrolyze ATP and ADP, and are present in many tissues, including the vascular system (Ralevic and Burnstock 2003) and CNS of several species (Sarkis et al. 1995). The AMP produced is subsequently hydrolyzed to adenosine by an ecto-5′-nucleotidase (CD73, EC 3.1.3.5), which constitutes the rate-limiting step in this pathway (Battastini et al. 1995; Zimmermann 1992). Although the extracellular concentrations of ATP are considerably lower than its intracellular concentrations (3–10 mM), the extracellular ATP and its breakdown products, ADP and adenosine, have pronounced effects in a variety of biological processes, including neurotransmission, muscle contraction, cardiac and platelet function, and vasodilatation (Agteresch et al. 1999). In addition, adenosine is an important endogenous neuromodulator and an inhibitor of platelet aggregation (Cristalli et al. 1995). On the other hand, extracellular nucleotides may be related to the development of several pathologies including disorders of the immune system, epilepsy and neurodegenerative, vascular and neurometabolic diseases (Bohmer et al. 2004; Bonan et al. 2000; Bours et al. 2006; Delwing et al. 2006b, 2007c; Seye et al. 2003; Wyse et al. 1994, 1995). In regard to Pro, it has been shown that this amino acid does not alter nucleotide hydrolysis when added to enzyme assays, but when administered acutely or chronically, it decreases ATP hydrolysis in rat cerebral cortex synaptosomes; ADP and AMP hydrolysis are not altered by Pro administration (Delwing et al. 2007e). Chronic hyperprolinemia decreased ATP and ADP hydrolysis that may result in high levels of extracellular ATP, suggesting that this inhibition in ATP hydrolysis can disturb a number of processes related to brain excitability. Pro (in vitro) significantly increased ATP, ADP and AMP hydrolysis in rat serum (Delwing et al. 2006b). It seems reasonable to postulate that Pro could alter, at least in part, the responses mediated by adenine nucleotides in the central nervous and peripheral systems of hyperprolinemic patients.

The neurochemical effects of Pro are summarized in Fig. 2.

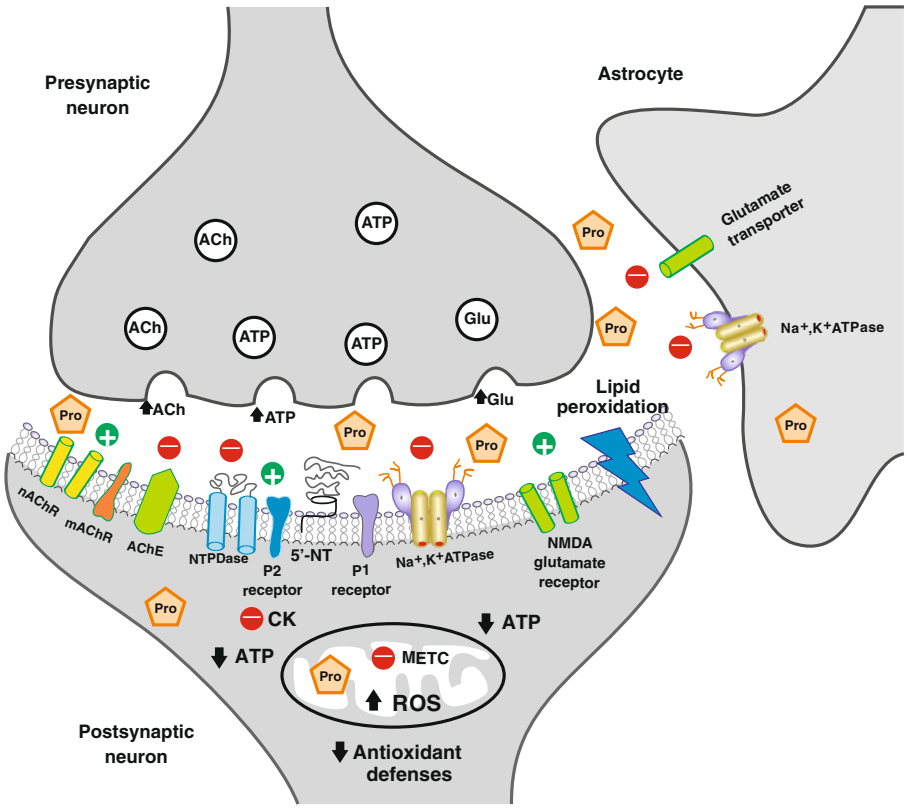

Fig. 2 Suggested mechanisms of neurochemical effects in hyperprolinemia. Accumulating proline may exert their actions mainly by three possible pathomechanisms, namely oxidative stress, energy deficit and excitotoxicity. This amino acid may induce generation of reactive oxygen species (ROS) and reduce tissue antioxidant defences (oxidative stress). Proline is also able to inhibit key enzymatic activities of energy metabolism, such as Na^+,K^+-ATPase, creatine kinase and enzymes of mitochondrial electron transfer chain (METC), leading to diminished ATP levels (energy failure) and increased ROS which might cause lipid oxidation, and protein and DNA damage. Proline may also decrease glutamate (Glu) uptake in presynaptic neurons, causing excitotoxic cell death by overstimulation of NMDA receptors. *NMDA* N-methyl-D-aspartate

Possibilities for neuroprotection

The investigation of neuroprotection is one of the main focuses of neuroscientists, since understanding the control mechanisms of neuronal damage, caused by a neurotoxin that is accumulated in a disorder, allows the development of new tools for preventing it. Oxidative stress plays a critical role in the physiopathology of most of the important neural pathologies, including stroke, epilepsy, Parkinson's disease, Alzheimer's disease and more recently neurometabolic disease (Behl 2005; Halliwell 1996; Zarkovic 2003). It is known that, in order to defend themselves against oxidative damage, cells develop antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione-peroxidase (GPx). Cells also utilize non-enzymatic antioxidants defenses such as vitamin E (alpha-tocopherol), vitamin C (ascorbic acid) and gluthatione (GSH) (Halliwell 2006).

Since oxidative stress is an imbalance between formation and removal of free radicals by scavengers and Pro increases lipoperoxidation and decreases enzymatic and non-enzymatic antioxidant defenses, strategies to prevent brain oxidative damage seem to be adequate. In this context, both water-soluble (vitamin C) and lipid soluble (vitamin E) nutrients comprise an important characteristic of the antioxidant defense system, particularly in brain cells (Zaidi and Banu 2004). Based on this, we investigated the effect of administration of classical antioxidants, vitamins E and C, on the alterations in biochemical parameters namely energy metabolism, Na^+,K^+-ATPase, glutamate uptake, enzymes of cholinergic and purinergic systems, as well as on memory deficit caused by hyperprolinemia in rats. It is amply described in the literature that these factors seem to be associated with the physiopathology of various diseases, affecting CNS, at least in part, by the involvement of free radical and/or oxidative stress.

Vitamin E, a generic term for all tocopherols and its derivatives, is essential for normal neurological function (Muller and Goss-Sampson 1989; Sen et al. 2004; Takada and Suzuki 2010). Eight isomers have been found to have vitamin E activity: alpha-, beta-, gamma- and delta-tocopherol and alpha-, beta-, gamma- and delta-tocotrienol, which are amply distributed in nature. Although tocopherols are predominantly found in corn, soybean, and olive oils, tocotrienols are found in palm, rice bran and barley oils (Sen et al. 2004; Traber and Packer 1995; Traber and Sies 1996). In contrast to plants, mammalian tissues contain almost exclusively alpha-tocopherols, where the highest content of this compound is found in adipose tissue, while erythrocytes have a relatively low content (Azzi and Stocker 2000). Because of its hydrophobicity, alpha-tocopherol is mainly transported in association with lipoproteins in the plasma compartment. It has been shown that liver, prostate and brain tissue express a cytosolic tocopherol binding protein (Stocker 1999). Often the term, vitamin E, is synonymously used as alpha-tocopherol.

Vitamin E is the major lipid-soluble vitamin; its protection against lipid peroxidation is well described, and includes scavenging of lipid peroxyl radicals to break membrane-damaging chain reactions (Burton et al. 1990; Sandy et al. 1988). Lipid peroxyl radicals present in the plasma membrane interact with alpha-tocopherol, resulting in the formation of a lipid peroxide and the alpha-tocopheroxyl radical. Ascorbic acid (vitamin C) plays an important role together with the lipophilic antioxidant, alpha-tocopherol, in protecting the membrane from oxidative stress. This is, in part, because ascorbic acid can regenerate reduced alpha-tocopherol present in the cell membrane. During this process, alpha-tocopherol is converted to the tocopheryl radical, requiring ascorbic acid for its regeneration back to reduced alpha-tocopherol (Buettner 1993; Carr and Frei 1999; Frei et al. 1990; McCay 1985), thus increasing its antioxidant activity. Ascorbic acid traps hydroxyl and superoxide radicals (Halliwell and Gutteridge 2007). This combination of alpha-tocopherol and ascorbic acid has proven to be effective in preventing biochemical and behavioral deficits produced in animal models of metabolic diseases (Wyse et al. 2002; Delwing et al. 2007a), as well as in age-related motor and memory deficit of rats (Bickford et al. 2000).

It has been shown that the pretreatment with alpha-tocopherol and ascorbic acid, at ineffective doses per se, completely prevents the spatial memory impairment caused by Pro, supporting the notion that oxidative stress is probably involved in this mechanism. This is in agreement with previous studies from our laboratory reporting that the administration of these vitamins prevents memory impairment in human and animal models (Delwing et al. 2005a; Engelhart et al. 2002; Monteiro et al. 2005; Reis et al. 2002; Wengreen et al. 2007). Therefore, the imbalance between free radical production and antioxidant defenses caused by Pro administration could have also contributed to the spatial navigation deficits found in rats. These findings are in agreement with evidence that oxidative stress and reactive oxygen species might be involved in memory modulation mechanisms (Abidin et al. 2004; Bickford et al. 2000; Cantuti-Castelvetri et al. 2000; Silva et al. 2004). Another line of evidence supporting the role of oxidative stress in behavior emerges from studies showing that alpha-tocopherol improves cognitive function of patients with temporal lobe radionecrosis (Chan et al. 2004) and may be beneficial in lowering the cognitive impairment in patients with Alzheimer's disease (Mecocci 2004). Orally supplemented vitamin E reaches the cerebrospinal fluid and brain and may be an interesting approach (Vatassery 1998).

Studies also show that alpha-tocopherol provides protection to cells exposed to oxidative stress damage by scavenging free radicals, stabilizing membranes and blocking the cascade of biochemical routes involved in cell death (Kelly 1998). Interestingly, pretreatment with alpha-tocopherol plus ascorbic acid prevents the reduction of lipoperoxidation, antioxidant defenses, Na^+,K^+-ATPase, acetylcholinesterase, as well as cytochrome c oxidase in the rat brain, caused by Pro administration (Bavaresco et al. 2003; Delwing et al. 2005a, 2006a, 2007a; Franzon et al. 2003). However, pretreatment with alpha-tocopherol and/or ascorbic acid did not prevent the effect of Pro administration on glutamate uptake. Alpha-tocopherol per se reduced glutamate uptake in the cerebral cortex slices of hyperprolinemic rats. These results reinforce the theory that the reduction in glutamate uptake is probably not caused by free radicals or, at least, by those scavenged by alpha-tocopherol and ascorbic acid. Regarding the inhibitory effect of alpha-tocopherol on glutamate uptake, no studies are available to demonstrate such effects and new studies should be performed to elucidate such mechanisms.

In summary, it is evident that high Pro concentrations provoke memory deficit and/or other neurochemical effects, which seem to be associated with the imbalance between free radical production and antioxidant defenses caused by this amino acid. Thus, it is possible that oxidative stress could contribute to the effects of Pro on energy metabolism, excitotoxicity, and cholinergic and purinergic systems, which may act synergistically and cooperate, at least in part, with the brain dysfunction that is characteristic of hyperprolinemia. In support of this hypothesis, pretreatment with classical antioxidants (alpha-tocopherol and ascorbic acid) prevented various actions of Pro. We argue that advances in the understanding of the effects of Pro in the brain may represent a promising goal for neuroprotective strategies for diseases that present hyperprolinemia such as inborn errors of metabolism, schizophrenia and others.

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