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REVIEW

Protein undernutrition during development and oxidative impairment in the central nervous system (CNS): potential factors in the occurrence of metabolic syndrome and CNS disease

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Mitochondria play a regulatory role in several essential cell processes including cell metabolism, calcium balance and cell viability. In recent years, it has been postulated that mitochondria participate in the pathogenesis of a number of chronic diseases, including central nervous system disorders. Thus, the concept of mitochondrial function now extends far beyond the common view of this organelle as the 'powerhouse' of the cell to a new appreciation of the mitochondrion as a transducer of early metabolic insult into chronic disease in later life. In this review, we have attempted to describe some of the associations between nutritional status and mitochondrial function (and dysfunction) during embryonic development with the occurrence of neural oxidative imbalance and neurogenic disease in adulthood.

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Introduction

In most eukaryotic cells, oxidative phosphorylation is the main source of energy, wherein a complex of membrane proteins located in the inner mitochondrial membrane is able to generate large amounts of energy stored in the form of adenosine triphosphate (ATP).[1,2] Mitochondria are dynamic organelles whose roles in cell function originated in part from their prokaryotic ancestor (likely an α-proteobacterium) eons ago. The ability of those prokaryotes to provide energy to eukaryotes in an aerobic environment helped drive the evolution of those early one-celled eukaryotes into the multiplicity of multicellular forms that dominate life on earth today.[3–5]

In addition to their important function as the 'powerhouses' of eukaryotic organisms,[6–8] mitochondria play a role in the pathogenesis of certain chronic non-communicable diseases (NCD). In addition, many clinical and experimental studies have demonstrated a close relationship between nutritional status during embryonic development and the occurrence of metabolic impairment in the adult brain. The close correlation between poor early nutrition and subsequent metabolic dysfunction has led investigators to speculate that early insult to the mitochondrion is a key causative factor in the eventual occurrence of disease. This review focuses in particular on evidence of neural dysfunction associated with developmental undernutrition that results in damage to mitochondrial function. To place these subjects in proper context, we will first describe to the role of the mitochondrion in reactive oxygen species (ROS) production and oxidative stress, and then explore how ROS production (mitochondrial and non-mitochondrial) and nutrition-dependent mitochondrial damage specifically contribute to the development of neurogenic disease.

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Oxidative phosphorylation products: ATP and ROS

Energy production in mitochondria depends mainly upon a proton motive force generated by the electron transport chain (ETC), which transfers electrons through reduced cofactors, NADH and $FADH_2$, derived from either the oxidation of acetyl-CoA derived from the tricarboxylic acid (TCA) cycle or β-oxidation of fatty acids to molecular oxygen (O_2) as a final electron acceptor. The energy generated by the flow of electrons through the ETC is used to transport protons outward across the inner mitochondrial membrane, and the influx of those protons into the matrix through the ATP synthase complex is used to generate ATP from ADP + Pi. When the ETC becomes highly saturated with electrons, excess electrons can be directly transferred to O_2 to generate the superoxide anion ($^{\bullet}O_2^-$), which can be further reduced to a hydroxyl radical ($OH^{\bullet}$), an oxidizing agent even more damaging to cells than $^{\bullet}O_2^-$.[9] In animals living in an aerobic environment,

mitochondria are the major source of ROS, whose production depends essentially on O_2 concentration and the electron flow velocity.[10,11] Due to fluctuations in cellular respiration, the amounts of O_2 available to the ETC also fluctuate and consequently the generation of ROS can vary considerably among different tissues.[12–16]

Mitochondria, on the other hand, also have a high antioxidant capacity residing in both enzymatic and non-enzymatic systems. The role of these antioxidant systems is to convert the ROS into harmless molecules, or at least into less reactive species.[17] The enzymatic antioxidant system employs an enzymatic cascade in which each enzyme uses the product from the prior reaction as a substrate for use by the next enzyme [i.e. $^{\bullet}O_2^-$ conversion to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD); then H_2O_2 to H_2O by either catalase (CAT) or glutathione peroxidase (GPx)], while the non-enzymatic antioxidant system relies on molecules such as reduced glutathione (GSH) that are capable of donating H^+, to stabilize the reactive species.[18–20] Furthermore, H_2O_2 and organic peroxides can be reduced by thioredoxins and peroxiredoxins that use thiol compounds (SH) as their source of electrons.[21,22]

An imbalance between ROS production and removal in favor of retention of the oxidant compounds results in a condition of oxidative stress, characterized by oxidative damage to lipids, proteins, DNA that are causal to several clinical abnormalities.[23–26] In this review, we focus on altered mitochondrial ROS production and oxidative imbalance triggered by protein restriction during fetal development and its relation to the occurrence of specific neural disorders later in life.

Superoxide production sources

Superoxide, in most cases, is the first ROS produced, and it can be formed by auto-oxidizable reactions of non-radical molecules, both in mitochondrial enzymatic sites and non-mitochondrial enzymatic reactions.[27]

Two non-mitochondrial enzymatic reactions involve NADPH oxidase and xanthine oxidases. The first of these is a protein complex composed of membrane-associated cytochrome (b_{558}) containing the subunits ($gp91^{phox}$ and $p22^{phox}$), plus regulatory subunits localized in cytosol ($p47^{phox}$, $p40^{phox}$ e $p67^{phox}$) and a small G protein (Rac1 or Rac2). Although this enzyme complex is best recognized in phagocytic cells such as neutrophils, other cell types also produce $^{\bullet}O_2^-$ through NADPH oxidase activity.[28] Xanthine oxidase also results in the non-mitochondrial production of superoxide, and is often activated following ischemia reperfusion, wherein hypoxanthine and xanthine components are oxidized to urate with concomitant $^{\bullet}O_2^-$ production.[29] For more information about those sources of ROS, see the reviews by Cantu-Medellin and Kelly and Bedard and Krause.[30,31]

The mitochondrial monovalent reduction of O_2 to $^{\bullet}O_2^-$ is thermodynamically favored and is regulated by two factors. The first is the concentration of electron carrier in proteins in a redox form and the second is the proportion of these proteins that are able to react with O_2.[32] Although complexes I and III are the major sources of mitochondrial ROS,[13] there are additional mitochondrial sites that are able to produce ROS[32–34] (see Fig. 1). Some of these are described below:

(1) Pyruvate dehydrogenase (PDH) is a mitochondrial enzymatic complex with three main catalytic components[35] responsible for catalyzing the conversion of pyruvate to acetyl-CoA. It is proposed that the rate of ROS production from the PDH complex increased as the NAD(P)H/NAD(P)$^+$ pool reduce.[36,37]
(2) 2-oxoglutarate dehydrogenase is another important mitochondrial enzymatic complex present in the Krebs (TCA) cycle that is able to produce ROS through NADH oxidation.[38] The mechanism relies on a third enzymatic element, in which the flavin from dihydrolipoamide dehydrogenase can generate large amounts of ROS in the mitochondrial matrix as consequence of NADPH/NAD$^+$ ratio.[39]
(3) Mitochondrial glycerol 3-phosphate dehydrogenase (mGPDH) is a coenzyme located in the outer surface of the inner mitochondrial membrane that is able to transfer reduced cytosolic factors to the mitochondrial ETC.[40] In addition to the ROS generated from mGPDH, oxidation of glycerol 3-phosphate can drive electrons both to complex IV and to complex I, leading to additional ROS production from these mitochondrial sources/sites.[41]
(4) Electron transferring flavoprotein Q oxidoreductase (ETF-QOR). During fatty acid oxidation mitochondrial acyl-CoA dehydrogenase transfers electrons to ETF, which is then oxidized by ETF-QOR by donating electrons to the ubiquinone (UQ) pool.[42] Once the ratio of reduced ubiquinone (UQH_2) and UQ becomes elevated, the electron leak increases ROS generation.[43]
(5) Monoamine oxidase (MAO) is a flavoenzyme located in the outer mitochondrial membrane that deaminates biogenic amines in the central and peripheral nervous systems and blood[44,45] in two-step reactions. In the first reaction, the flavin prosthetic group is reduced and produces aldehyde and ammonium. In the second, the reduced flavin is oxidized to form H_2O_2.[46,47]
(6) Flavin site in complex II. Although the estimated $^{\bullet}O_2^-$ generation by this complex is ordinarily low, in a condition of low levels of succinate and diminished activities of complexes I and III, the flavin site complex can produce both superoxide and H_2O_2 at high rates.[13] The mechanism proposed for this is based on the electron leak achieved by flavin in the semi- or fully reduced state.[34]
(7) Flavin prosthetic group in complex I. This process relies on the flavin mononucleotide (FMN) binding site, whose full reduction during forward electron flow from NADH induces electron leak to O_2, producing $^{\bullet}O_2^-$.[48]
(8) Ubiquinone site in complex I. This source of $^{\bullet}O_2^-$ is associated with the reduction of UQ to UQH_2 by a substrate such as succinate, glycerol 3-phosphate or acyl-CoA. However, the electrons can also be driven

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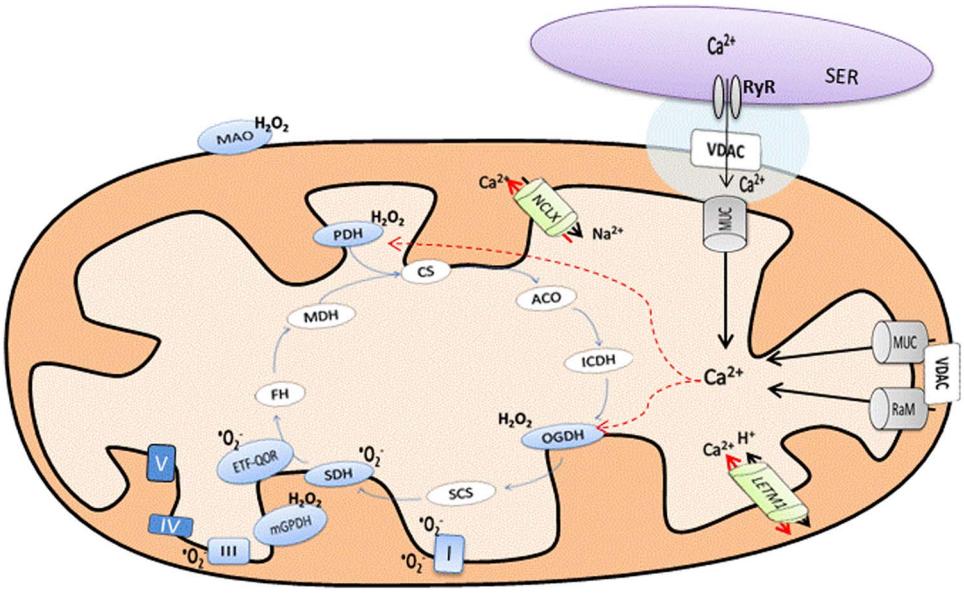

Fig. 1. Schematic representation of the mitochondrial sites of reactive oxygen species (ROS) production and Ca^{2+}-related ROS increase. In light blue, sites of ROS production: MAO, monoamine oxidase; PDH, pyruvate dehydrogenase; OGDH, oxoglutarate dehydrogenase; SDH, succinate dehydrogenase; ETF-QOR, electron transferring flavoprotein Q oxidoreductase; mGPDH, mitochondrial glycerol 3-phosphate dehydrogenase; electron transport chain complexes I and III. In gray, the proteins responsible for Ca^{2+} influx: RyR, ryanodine receptor; MCU, mitochondrial Ca^{2+} uniporter and RaM, rapid mode of calcium uptake. Dashed red lines indicate what enzymes have their ROS production stimulated by Ca^{2+} overload: OGDH and PDH. In light green, the proteins responsible for Ca^{2+} efflux: NCLX, Ca^{2+}/Na^{+} exchanger and LETM1, Ca^{2+}/H^{+} antiporter. Dark blue represents the other mitochondrial complexes; white ellipse; other enzymes from Krebs cycle; white rectangle, Voltage-dependent channels, VDAC; and purple, the sarcoplasmic reticulum.

reversely from UQH_2 to NAD^+, thereby generating $^{\bullet}O_2^-$ at high rates.[33,49]

(9) Outer ubiquinone site in complex III. The $^{\bullet}O_2^-$ production in this complex is based upon the electron transfer mechanism called Q cycle. Electron carriers into this complex gather the electrons from UQH_2 to water-soluble cytochrome *c* in a sequential process that results in the formation of an unstable semiquinone UQ^- that can reduce O_2 to superoxide.[14]

Calcium (Ca^{2+}) signaling and mitochondrial ROS overproduction

A compelling body of evidence shows that Ca^{2+} regulates numerous cellular functions, and that differences in Ca^{2+} concentration are controlled by complex membrane transport systems moving the cation between the extracellular environment, the cytosol and membrane de-limited intracellular organelles.[50] The mitochondrion stands out as a critically important organelle in Ca^{2+} homeostasis as this organelle can internalize cytoplasmic calcium derived from the extracellular environment as well as Ca^{2+} released from the smooth endoplasmic reticulum (SER) (syn. in muscle: 'sarcoplasmic' reticulum) (SR).[50,51]

Calcium crosstalk between mitochondria and the SER employs a ryanodine receptor (RyR)-mediated mechanism. Although recent evidences have described the expression of mitochondrial inner membrane RyR in cardiomyocytes and striatal neurons,[52] the RyR is better described as a channel protein located on the SER membrane that is sensitive to small changes in cytosolic Ca^{2+} concentration and to Ca^{2+} overload in the SER lumen.[53] In either situation, the RyR allows Ca^{2+} release from storage in the SER (or SR) into the cytosolic mitochondrial microdomains that facilitate Ca^{2+} uptake.[54,55] Voltage-dependent channels located in outer mitochondrial membrane allow the entry of Ca^{2+} into the intermembrane space, and then either of two different processes can mediate its influx into the mitochondrial matrix:

(1) The mitochondrial calcium uniporter (MCU), which relies on the negative mitochondrial membrane potential to take up Ca^{2+} into the matrix.[51]

(2) A rapid mode of calcium uptake (known as RaM), which is thought to respond to rapid changes in cytosolic Ca^{2+}.[56]

Calcium efflux, on the other hand, depends upon the Ca^{2+}/Na^{+} exchanger (NCLX), which is also able to switch the ion exchange flow (either forward or reverse) depending on cytosolic Na^{+} concentration and mitochondrial membrane potential.[57] Efflux is also dependent on the Ca^{2+}/H^{+} antiporter, which appears to be especially important in tissues that have low NCLX activity, such as liver, kidney and lung.[58]

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Several reports have shown that Ca^{2+} can stimulate ROS production by different mechanisms:

(1) *Krebs cycle stimulation*. It has been proposed that Ca^{2+} can allosterically activate enzymes, such as PDH, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase in order to supply the ETC with reduced cofactors.[59] As discussed previously some of these enzymes can also produce ROS.[33]
(2) *A change in lipid organization in the inner mitochondrial membrane*. Studies in model membranes suggest that Ca^{2+} sequesters the cardiolipin attached to membrane carrier proteins, and that this membrane rearrangement in some way increases ROS production.[60]
(3) *Mobilization of intramitochondrial ferrous iron* (Fe^{2+}). Studies using isolated mitochondria have indicated that mitochondrial Ca^{2+} overload is associated with an increase in hydroxyl radical formation and oxidative damage. However, when the mitochondria were treated with a Fe^{2+} chelator, the oxidative damage was abolished.[61]
(4) *Opening of the mitochondrial permeability transition pore (MPTP)*. The outer mitochondrial membrane allows essentially a 'free' translocation of small molecules from the cytosol into the mitochondrion. However, selective transporters in the inner mitochondrial membrane are needed to assure homeostasis between cytosolic and matrix environments.[62] Mitochondrial Ca^{2+} overload combined with oxidative imbalance leads to the opening of the MPTP in the inner membrane, thereby allowing bi-directional traffic of small metabolites through the mitochondrial membrane[63] and a disruption of the normal electrolytic equilibrium. This disruption leads to mitochondrial swelling, a decrease in proton motive force, an increase of ROS production, and may also rupture the outer mitochondrial membrane with the consequent release of pro-apoptotic factors (e.g. cytochrome *c*, Smac/DIABLO, Omi/HtrA2 and others) into the cytosol.[64,65]

Oxidative impairment in the central nervous system (CNS): the mitochondrion as a trigger of neurogenic disease

Oxidative damage is innate to all eukaryotic cells. However, tissue types vary in their sensitivity to that damage, and by that measure the brain stands out as being particularly vulnerable to oxidative damage due to its morphologic and physiologic characteristics.[16] In normal resting conditions, the adult brain is responsible for over 15% of total O_2 consumption, an exceptionally large rate of oxygen use per unit mass compared with others tissues.[16] In addition to its heavy consumption of O_2, the brain is also vulnerable to oxidative damage due to the specialized characteristics of neural tissue as described below:

(1) The presence of excitotoxic amino acids, such as glutamate. Glutamate levels are tightly controlled in the brain, however, under conditions of stress, neurons undergoing apoptosis release a large amount of glutamate into the surrounding tissue. Furthermore, Mailly *et al.*[66] showed that neurons in the presence of excess hydrogen peroxide enter a prolonged excitatory state triggered by the continuous activation of *n*-methyl-D-aspartate (NMDA) receptors by glutamate.
(2) A high content of biologically important amines that are oxidized in the presence of O_2. Neurotransmitters such as dopamine, serotonin, adrenalin and noradrenalin react slowly with oxygen to produce superoxide, which in turn reacts with those neurotransmitters to form other ROS in a chain reaction.[67] Furthermore, several oxygenases possess tetrahydropteridine as a co-factor, which in elevated levels is able to induce ROS-dependent neuronal apoptosis.[68]
(3) SOD-independent H_2O_2 generation. Most ROS production occurs downstream from the dismutation of $^{\bullet}O_2^-$. However, the brain can generate large quantities of H_2O_2 independently of SOD activity. During the recycling of biogenic amines (e.g. serotonin, epinephrine, norepinephrine, dopamine), enzymes located in outer mitochondrial membranes of neurons and glia can form H_2O_2 through oxidative deamination of those amines.[69,70]
(4) Prevalence of polyunsaturated fatty acids (PUFA) in the CNS. PUFA are widespread in the CNS, and if antioxidant systems are not adequate to inhibit ROS formation, the ROS can remove hydrogen from PUFA or attach to it to initiate lipid peroxidation.[25] Once lipid peroxidation has been initiated, intermediate compounds react with oxygen to form lipid proxy radicals, which then react with PUFA in a cyclic reaction to generate isoprostanes as well as multiple α,β-unsaturated aldehyde products, such as acrolein, 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA).[71]

Due to the brain's particular vulnerability to oxidative stress, many studies have been designed to assess how varying relationships among mitochondria, oxidative imbalance and lipid peroxidation can predispose an individual to neurodegenerative diseases such as Alzheimer's (AD), Huntington's, Parkinson's diseases, multiple sclerosis and neurogenic hypertension.

In the case of AD, it was shown that oxidative stress as well as lipid peroxidation in the cerebral cortex and hippocampus exert a positive influence on disease progression by inducing amyloid-beta peptide (Aβ) accumulation,[72] wherein products of lipid oxidation impair energy production in the brain.[73] Moreover, AD patients exhibit lower cerebral activity of mitochondrial enzymes in the Krebs cycle[74] as well as an impairment in oxygen consumption via a decrease in complex I and III activities.[75] Such metabolic dysfunctions in neural tissue lead to an increase in ROS generation and a decrease in energy supply, thus enhancing the damage promoted by Aβ accumulation[75] and impairing many higher level brain functions, including judgment, memory and orientation.

Similarly a dysfunction in complex II may represent an important factor in Huntington's disease (HD), a disorder associated with cognitive deficits, psychiatric illness and

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involuntary movements. Striatal degeneration induced by defective mitochondrial complex II function has been used as a common animal model of HD[76] and may reflect the disease process in humans Furthermore, disruptions in hippocampal calcium signaling, mitochondrial membrane potential, sensitivity of the MPTP, pyruvate dehydrogenase and complex IV activities, and an increase in lipid peroxidation have also been described in brains of patients with HD.[71,77]

Systemic inhibition of complex I has been used as an experimental model of Parkinson's disease (PD).[78] Complex I disruption in dopaminergic neurons, present mainly in the striate nucleus, results in decreased ATP production and increased mitochondrial ROS production, thereby stimulating pathways involved in MPTP activation as well as initiating the release of inflammatory and pro-apoptotic molecules to induce neuronal cell death.[79] Increased products from lipid peroxidation, such as F2-isoprostanes and 4-HNE can also contribute to neuronal death[25,80] in PD, which culminates in bradykinesia, rigidity and tremors induced by the striatal dopamine deficiency.[80]

Mitochondrial dysfunction has also been related to neuropathology of multiple sclerosis (MS). A decrease in the complexes I and III activities of 50% or more impairs the capacity of mitochondria to produce ATP.[81,82] The mismatch between energy requirements and ATP production in turn, contributes to axonal degeneration in upper motor neurons in MS patients.[81,83] The energy deficit is further enhanced by damage to mitochondrial DNA caused by nitric oxide or its products.[84] In amyotrophic lateral sclerosis (ALS), a neurologic disease characterized by motor neuron and neuromuscular junction degradation, oxidative stress is a major contributor to the etiology of the disease by impairing the machinery of transmitter release in the pre-synaptic motor nerve terminal of the neuromuscular junction.[85] In fact, a mutation in the gene coding for cytosolic SOD (SOD1) is responsible for 20% of ALS cases.[86] In addition, ALS patients exhibit decreased mitochondrial function and impairment in Ca^{2+} homeostasis, both of which contribute to oxidative damage in the lumbar and thoracic spinal cord.[87] It is proposed that the downstream oxidative damage in ALS patients depends largely on the capacity of the defective SOD1 to increase ROS production both in mitochondria and in plasma membrane bound NADPH oxidase.[88,89]

Central redox balance also plays a key role in cardiac diseases arising from CNS defects.[90] Nuclei located in the brainstem, including the rostral ventrolateral medulla (RVLM) and the nucleus tractus solitaries (NTS) play key roles in neurogenic hypertension,[91] wherein the imbalance of ROS and nitric oxide in neurons within these nuclei can alter the peripheral vascular system by increasing sympathetic vasomotor tone.[23,92] Chan *et al.* demonstrated that in spontaneously hypertensive rats, the increase in blood pressure is directly related to lower expression and activity of mitochondrial superoxide dismutase and catalase in the RVLM.[93] Additional studies found that the elevation of $^{\bullet}O_2^-$ and H_2O_2 in brainstem sites such as RVLM and NTS originate from activation of NADPH oxidase via protein kinase C and phosphatidylinositol 3-kinase, as well as via an increase in intracellular Ca^{2+}, and down regulation of mitochondrial uncoupling protein 2 (UCP2) and reduction in ETC capacity[94–97] contributes to the increase in arterial blood pressure.

Early oxidative stress as a developmental determinant of health and disease in later life

It is well known that environmental influences can alter numerous internal body functions and as a result can trigger such NCD as diabetes, metabolic syndrome, and cardiac disorders.[98] An increase in NCD risk is not limited to physiologic changes occurring in adulthood but may also result from adverse events that occur much earlier in life. Thus, endogenous and exogenous signals[99] if occurring within certain critical developmental windows within the embryonic period can permanently affect physiologic processes within the mature individual.[100]

The first suggestion that this phenomenon exists came from observations of the occurrence of impaired glucose tolerance and the development non-insulin-dependent diabetes in a 64-year old who had exhibited a significantly reduced growth rate in early life.[101] The data suggested that poor nutrition during periods of fetal life and infancy induced diabetes via changes in B-cell function. The researchers further hypothesized that permanent adaptations to the early nutritional deficit provided survival benefits by shunting glucose to critical organs and away from those organs considered as secondary for survival.[101] Ironically the permanent adaptations so necessary for survival in fetal life/infancy may be the same physiologic alterations that predispose and individual to chronic disease in later life.

The ability to express different phenotypes following a physiologic challenge is known as phenotypic plasticity, and in development is dependent upon specific temporal windows during which the organism is especially prone to change its developmental pattern in order to survive.[102] Further investigation has shown that the post-developmental environment helps to determine whether the initial exposure will or will not be harmful.[103,104] This suggested that the early influences acted as environmental cues that led to adaptive responses providing survival advantages to the individual in later life. However, if the postnatal environment does not 'match' or coordinate with the prenatal environment, the adaptations that occurred during development would no longer be advantageous to the individual and would predispose him or her to the occurrence of adult diseases.[105]

As human mothers are able to quench small environmental perturbations of short duration,[106] it would be expected that environmental changes during life generate a mother's phenotype and this phenotype will shape the offspring's adaptations, by generating a variability in metabolic capacity.[107,108] Wells[107], suggested that the maternal phenotype is responsible for the adaptations in her offspring, and that her phenotype might depend, in turn, on the environmental history of close ancestors, as has been reviewed in detail.[109]

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Martin-Gronert and Ozanne[110] highlighted three proposed mechanisms of how events in the perinatal period of development can produce life-long effects in the individual. The first mechanism involves the occurrence of permanent structural changes in key organs such as the brain, pancreas and kidney. The second mechanism involves changes in gene expression resulting from epigenetic modification, as has been described elsewhere[111,112] (e.g. DNA methylation, histone modification and microRNA action on mRNA).[111] The third mechanism for the long-lasting effects of a developmental insult is dependent upon the process of cellular ageing. An example of this is the induction of cellular senescence secondary to mitochondrial dysfunction and increased oxidative stress, as suggested by Luo *et al.*[113]

In the past several years, oxidative stress has been studied as a molecular trigger for the effect of maternal nutritional deficiency on NCD occurring later in life in her offspring. In animal models of protein restriction, researchers have found mitochondrial dysfunction in the early mouse embryo[114] and heart; oxidative stress in pancreatic islets as a consequence of a mismatch among antioxidant enzymes (i.e. increase in SOD with concomitant decrease in CAT and GPx);[115] an increase in pancreatic oxidative stress and heart rate associated with aging[116] and an increase in the protein expression of enzymes related to ROS production as well as oxidative stress and DNA damage.[117]

Early low-protein diet and cerebral oxidative impairment:

Nutrition is often considered as the greatest exogenous influence in early life. Classified as the main non-genetic contributor to changes in brain development, nutritional inadequacy has been known to have several deleterious effects on the fetal brain.[118–122] Early studies of restrictive diets on offspring had described oxidative impairment, such as decreased GSH levels in the forebrain;[123] lower mRNA expression of SOD and CAT in the brain;[124] increased vascular $^{\bullet}O_2^-$ production[125] and a decrease in SOD activity,[126] and in newborn infants, an increase in oxidative damage as a consequence of the reduction in serum antioxidant capacity.[127,128]

Although all categories of nutrient are important in brain development, protein has the greatest effect on neural function.[129] Early protein deficiency affects the brain in several ways that vary with the period of exposure, the type of protein deficiency and its severity, and also with the specific cerebral region.[130] The critical period for brain development is marked by several specific temporal windows in which the processes of neurogenesis, neuron migration, and neuron alignment and orientation are quickly increased then either decreased or ceased.[131]

As proteins do not readily cross the placenta into the fetal circulation, nutritional deficits in the mother are generally transmitted to the fetus the level of the amino acid composition of the ingested protein. Consequently, the lack of any one of the essential amino acids in the maternal protein diet can lead to a complete protein deficiency in the fetus.[131] Nutritional protein restriction may reduce antioxidant capacity by inhibiting the synthesis of antioxidant enzymes,[132] and the resulting oxidative stress on fetal cells could alter gene expression and further damage the cells with oxidized proteins and lipids.[113]

Several studies have demonstrated the effects of protein restriction in oxidative balance and mitochondrial function in the CNS (see Fig. 2). Bonatto *et al.*[133] evaluated these parameters in the hippocampus of rats exposed to moderate protein restriction from the 1st day of the gestational period until 75 days of postnatal life and found an increase in protein oxidation but a decrease in lipid oxidation. The investigators suggested that the opposing effects of a protein-restricted diet on proteins *v.* lipids resulted from an overall increase in SOD activity in the protein-restricted group, wherein the elevated SOD protected lipid, but not protein, from oxidation. As the activity of CAT did not change with restricted protein, it was suggested that the higher activity of SOD without a concomitant up-regulation of CAT drives the accumulation of H_2O_2, followed by formation of the hydroxyl radical ($^{\bullet}OH$),[134] considered among the most reactive of ROS. Thus hydroxyl radical formation could be the responsible for the increased protein oxidation observed in the face of increased SOD activity.[135,136] As evidence of this, when the protein-restricted animals were supplemented with methionine, SOD activity was reduced and the animals exhibited increased oxidative damage to their lipids.

Further investigations in 21-day-old rats,[133,137] showed that low-protein diet increases oxidative damage to lipids in the cerebellum and hippocampus but has no influence on oxidation, in the cortex. Evaluation of SOD and CAT activities in those brain regions, moreover, showed that SOD activity was reduced only in cerebellum with low-protein diet, and not in either the cortex or hippocampus. A possible explanation for the cerebellar damage, is that low-protein induced decrease in SOD activity enhances interaction between $^{\bullet}O_2^-$ and $NO^{\bullet}$ to form peroxynitrite, which is capable of oxidizing lipids, proteins and thiol compounds as well as DNA.[138]

Feoli *et al.*,[139] on the other hand, showed no difference in ROS production in either cerebellum, cortex or hippocampus of animals fed a low-protein diet (casein 7%) from the first gestational day until 60 days of life. Although ROS levels did not change, an increase in lipid peroxidation in the cerebellum and cortex occurred due to a decrease in SOD activity in the cerebellum, and the reduction in total antioxidant reactivity in the cortex. When the authors evaluated the content of tryptophan and tyrosine, (important neurotransmitter precursors) as a measure of damage, all three brain regions were negatively affected by low-protein diet, and the damage was closely related to the lower serotoninergic and catecholaminergic neurotransmitter concentrations.[140]

Tatli *et al.*,[141] by evaluating three types of induced CNS damage: (1) intrauterine growth restriction (IUGR), (2) moderate and (3) severe protein restriction in five different CNS regions (cortex, cerebellum, cervical, thoracic and lumbar cord) showed that only severe undernutrition triggered lipid

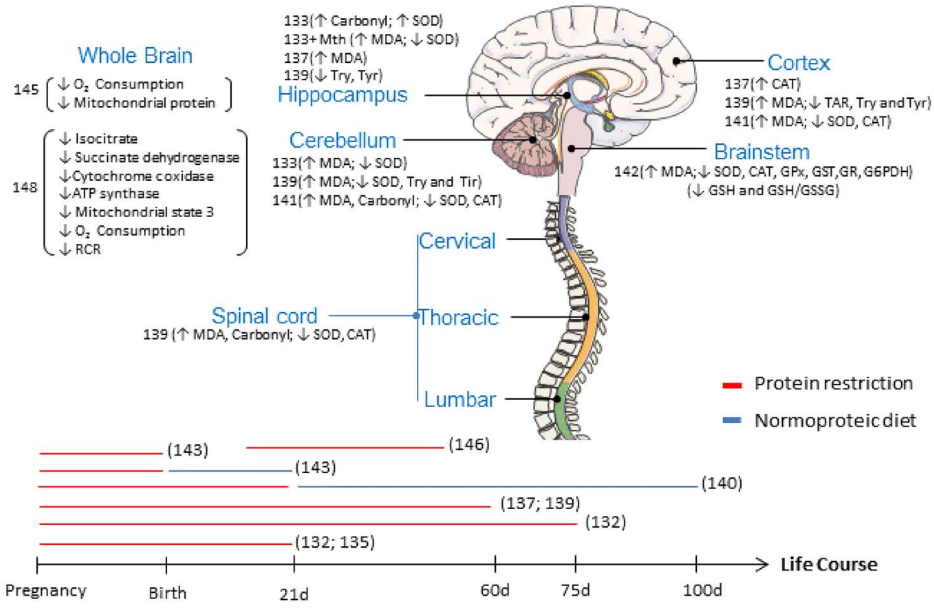

Fig. 2. Main findings on early protein restriction and central nervous system oxidative balance. Red lines represent protein restriction, blue lines, normoprotein diet, and the length of each approximates the time during which either feeding state was applied for each study referred to in the text. Numbers in parentheses refer to the references cited in the text. MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GST, glutathione-*S*-transferase; GR, glutathione reductase; G6PDH, glucose-6-phosphate dehydrogenase; GSH, reduced glutathione; GSSG, oxidized glutathione; TAR, total antioxidant reactivity; Try, tryptophan; Tyr, tyrosine; and RCR respiratory control ratio.

oxidation in all five CNS structures at 60 days of life. Protein oxidation was shown to vary in proportion to the degree of undernutrition, with the cerebellum showing greater sensitivity to protein oxidation than the other CNS regions. In addition to increasing oxidative biomarkers, early nutritional adversity also decreased the activity of SOD and CAT in all regions analyzed.

In our laboratory, we have evaluated offspring through 100 days of age from mothers fed a low-protein diet throughout the perinatal period (gestation and lactation) and found that low-protein animals had increased oxidative damage in the brainstem. The data showed a marked decrease in antioxidant capacity, wherein enzymatic activities of SOD, CAT, GPx and glutathione-*S*-transferase were decreased by over 15%. The redox state was also affected by the maternal low-protein diet through a reduction in glutathione concentrations as a consequence of lower glutathione resynthesis and a decrease in NADPH supply.[142] Oxidative imbalance in certain brain regions is directly related to the occurrence of cardiovascular impairments,[143] mainly hypertension.[23,90,91,144] Thus, it is feasible that early nutritional insult is a central trigger for the development of hypertension in adulthood.

Assessing brain O_2 consumption, Muzzo *et al.*[145] found that newborns from mothers fed throughout the gestational period with a diet containing only 4% protein, exhibited decreases in both brain mitochondrial protein and in O_2 consumption. Animals that were reefed from the 1st until 16th postnatal day also showed a reduction in O_2 consumption and phosphorylation capacity. Although the gestational period encompasses most of the period during which neurogenesis occurs,[146] in rats, the duration of maternal lactation represents the most important period for brain development.[131] Thus, several studies have described effects of protein restriction during other periods of brain development that may lead to lasting changes even after refeeding due to the impairment in the metabolic activity.[118,147]

In rats experiencing severe protein restriction during a period of 30 days (from the 18th to the 48th postnatal day),[148] brain mitochondria were shown to have alterations in Krebs cycle, isocitrate and succinate dehydrogenase, as well as in ETC enzymes, cytochrome *c* oxidase and ATP synthase. In addition, the mitochondrial ETC exhibited an impairment in function, such that low-protein animals were less responsive to ADP stimulation by complexes I and II substrates.

Despite the important role of the mitochondrion in several neurogenic diseases (i.e. PD, AD, ALS, etc.), very few studies have investigated the role of mitochondrial dysfunction in the central oxidative imbalance induced in protein restriction models. The antioxidant system, however, has been shown to be significantly affected by a low-protein diet, which also contributes to the disruption of mitochondrial capacity and may compromise the overall brain function.

Conclusion

In this review, we discuss the importance of mitochondrial dysfunction and oxidative stress in the development of neural disorders, and show how such diseases could be induced by nutritional insult during development. Although decreases in mitochondrial content and/or activity have been demonstrated

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in several studies employing nutritional manipulation either during the gestational and/or locational period, further investigations will be necessary to determine the specific mechanism causing mitochondrial dysfunction due to a protein-poor diet within a restricted developmental window. Compelling evidence has already shown that several neurogenic diseases are associated with mitochondrial disruption accompanying high-fat intake. Therefore it seems likely that a diet low in protein could also disrupt mitochondrial function sufficiently to induce neurogenic disease. Many studies to date have shown that protein restriction deeply affects central oxidative balance by decreasing antioxidant capacity. Further studies must be conducted, however, to assess the contribution of ROS generators in this oxidative disruption.

The underlying mechanisms responsible for impaired mitochondrial function in metabolic disorders induced by low-protein diet during embryonic development have not yet been elucidated. It is hoped, however, that prospective clinical investigations of mitochondrial function in healthy and diseased humans will begin to provide insight into precisely how early nutritional deficit and the occurrence of metabolic disease in adulthood are linked.

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