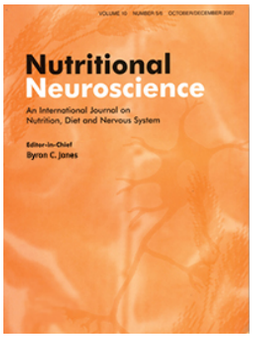

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Undernutrition – thirty years of the Regional Basic Diet: the legacy of Naíde Teodósio in different fields of knowledge

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REVIEW

Undernutrition – thirty years of the Regional Basic Diet: the legacy of Naíde Teodósio in different fields of knowledge

Larissa B. Jannuzzi [a], Amaury Pereira-Acacio [a,b,c], Bruna S. N. Ferreira [a], Debora Silva-Pereira [a], João P. M. Veloso-Santos [a], Danilo S. Alves-Bezerra [a], Jarlene A. Lopes [a,c], Glória Costa-Sarmento [a,c], Lucienne S. Lara [c,d], Leucio D. Vieira [e], Ricardo Abadie-Guedes [e], Rubem C.A. Guedes [f], Adalberto Vieyra [a,b,c,g] and Humberto Muzi-Filho [a,c]

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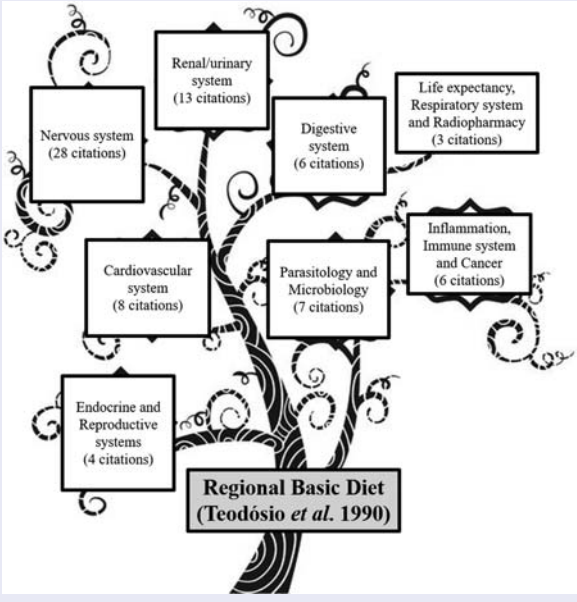
ABSTRACT

Undernutrition is characterized by an imbalance of essential nutrients with an insufficient nutritional intake, a disorder in which the clinical manifestations in most cases are the result of the economic and social context in which the individual lives. In 1990, the study by the medical and humanitarian Naíde Teodósio (1915–2005) and coworkers, which formulated the Regional Basic Diet (RBD) model for inducing undernutrition, was published. This diet model took its origin from the observation of the dietary habits of families that inhabited impoverished areas from the Pernambuco State. RBD mimics an undernutrition framework that extends not only to the Brazilian population, but to populations in different regions worldwide. The studies based on RBD-induced deficiencies provide a better understanding of the impact of undernutrition on the pathophysiological mechanisms underlying the most diverse prevalent diseases. Indexed papers that are analyzed in this review focus on the importance of using RBD in different areas of knowledge. These papers reflect a new paradigm in translational medicine: they show how the study of pathology using the RBD model in animals over the past 30 years has and still can help scientists today, shedding light on the mechanisms of prevalent diseases that affect impoverished populations.



KEYWORDS

Regional Basic Diet; prenatal undernutrition; postnatal undernutrition; prevalent diseases; pathophysiological mechanisms; undernutrition and central nervous system; undernutrition and infectious diseases; undernutrition and cardiorenal alterations

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Introduction

According to the World Health Organization, malnutrition is defined by the deficiency, excess, or imbalance in intake of energy and/or nutrients as a result of the economic and social context in which the individual is inserted. The term malnutrition involves undernutrition, micronutrient-related malnutrition and obesity. In this review, we will highlight undernutrition – which is characterized by wasting (low weight-for-height), stunting (low height-for-age) and underweight (low weight-for-age) – that is generally associated with the distribution of poverty and social inequality [1]. In Brazil, undernutrition is widely encountered in pockets of poverty on the periphery of large cities, in rural areas and in impoverished regions in the North and Northeast regions of the country [2].

Dr. Naíde Teodósio (1915–2005) was a Brazilian, medical and humanitarian researcher in the nutrition and physiology fields. Thirty years have passed since the publication of the study from Dr. Teodósio, in which she proposed using the Regional Basic Diet (RBD) to study the impact of undernutrition [3]. Naíde Teodósio was born in 1915 in Serinhaem, at the coast area of the state of Pernambuco, Northeast Brazil. She graduated in human medicine at the Federal University of Pernambuco, in Recife (the capital of the State of Pernambuco). Her scientific interest for the nutritional aspects of physiological processes appeared soon during the graduate course. The RBD model, which has been extensively tested in the rat, originated from the observation of the nutritional habits of 918 families that inhabited the area of sugar-cane cultivation in the Pernambuco State. She noted that these families consumed 4 staple foods and formulated a multifactorial diet containing (in g%): manioc flour (*Manioc esculenta*) 65, beans (*Phaseolus vulgaris*) 18, sweet potatoes (*Ipomoea batatas*) 13, and jerked meat 4. When compared with the rat control diet, the RBD is characterized by marked deficiencies of protein (8 *vs.* 23% of control diets), lipids (1.7 *vs.* 4.5% of control diets), minerals and vitamins [3]. The importance of the development of RBD is that the nutritional imbalance it provokes in rats is similar to that detected in populations from impoverished regions in different developing countries in the Middle East, Latin America and Africa, and has been used in several studies with different animal and cell models.

The pioneering work of Naíde Teodósio has a social impact, inspiring public policies aimed at preventing childhood undernutrition. In addition, they inspired several scientists from countries around the world in different fields of knowledge. The combination of these deficiencies in an experimental animal model gave support during these 30 years for a better understanding of the impact of undernutrition on the pathophysiological mechanisms underlying several prevalent diseases. Using RBD, their work reflects a new paradigm in translational medicine, showing the studies of pathology that used the RBD model in animals to help scientists today, shedding light on the mechanisms of the prevalent diseases affecting impoverished populations. The present review, in honor of Naíde Teodósio's legacy, is focused on the impact of RBD-induced undernutrition in the etiology of dysfunction from several bodily systems. These studies citing the pioneering paper of 1990 are summarized in Table 1.

Nervous system

There are very many indexed papers citing the pioneering work of Naíde Teodósio et al. [3] focused on the central nervous system (CNS) activity and dysfunctions (36% of the total). In the first, Rocha-de-Melo and Guedes [4] demonstrated that rats undernourished during lactation (perinatal undernutrition model) show disturbed body and brain development, and especially in the increased susceptibility to KCl-induced cortical spreading depression in the offspring, the third week of lactation being the most critical period. In the last 75 years, the model of cortical spreading depression, characterized by waves of cerebral hyperactivity followed by waves of inhibition, with several alterations in neurons and glial cells, became an important and suitable model for the studies of migraine and epilepsy, among other not fully understood dysfunctions of the CNS [5,6] affected by undernutrition, as discovered by the Teodósio's group several years ago [7]. Using the same model of spreading depression used by Rocha-de-Melo and Guedes [4], Santos-Monteiro et al. [8] confirmed that nutritional status influences the cortical spreading depression responses to environmental stimulation, undernourished rats during lactation until 42 days of age being more affected than the normonourished ones. At the same time, Borba et al. [9] showed the relationships between undernutrition (from intrauterine life until 42 days of age) and alterations in NADPH diaphorase (NO synthase)-containing cells in the visual cortex, concluding that undernutrition alters synaptic plasticity and refinement of developmental brain circuits. Almeida et al. [10] investigated whether early undernutrition (intrauterine and during lactation) could affect cells containing γ-aminobutyric acid (GABA) and acetylcholine in the retina. In this ocular structure, the deleterious consequences of amino acid deficiency in the RBD caused a 40% decrease in

Table 1. Citations from Teodósio et al. Arch Latinoam Nutr (1990);40:533–47 [3].

Study area	Reference	Undernutrition period
Nervous system	Rocha-de-Melo & Guedes (1997) [4]	Postnatal
	Santos-Monteiro et al. (2001) [8]	Postnatal
	Borba et al. (2000) [9]	Prenatal and postnatal
	Almeida et al. (2001) [10]	Prenatal and postnatal
	Medeiros et al. (2001) [11]	Postnatal
	Guedes et al. (2002) [12]	Prenatal and postnatal
	de Vasconcelos et al. (2004) [13]	Prenatal and postnatal
	Costa-Cruz et al. (2006) [14]	Postnatal
	dos Santos et al. (2006) [17]	Postnatal
	do Monte-Silva et al. (2007) [18]	Postnatal
	Farias-Santos et al. (2009) [19]	Postnatal
	de Aguiar et al. (2011) [22]	Postnatal
	de Aguiar et al. (2011) [23]	Postnatal
	Monte-Guedes et al. (2011) [25]	Postnatal
	Mendes-da-Silva et al. (2014) [26]	Postnatal
	Mendes-da-Silva et al. (2018) [27]	Prenatal and postnatal
	Mendonça et al. (2004) [28]	Prenatal and postnatal
	Vilela et al. (2005) [31]	Prenatal and postnatal
	Almeida et al. (2005) [32]	Prenatal and postnatal
	Anselmo et al. (2006) [33]	Prenatal
	Anselmo et al. (2008) [34]	Prenatal
	Barros et al. (2006) [35]	Postnatal
	Silveira et al. (2007) [36]	Prenatal and postnatal
	Bevilaqua et al. (2015) [37]	Postnatal
	de Souza et al. (2008) [38]	Prenatal and postnatal
	de Souza et al. (2011) [40]	Only citation (review)
	Freitas-Silva et al. (2008) [41]	Postnatal
	Augusto et al. (2017) [42]	Prenatal and postnatal
Parasitology and Microbiology	Ferreira & Coutinho (1999) [44]	Only citation (review)
	Coutinho et al. (2003) [45]	Postnatal
	Coutinho (2004) [46]	Postnatal
	Coutinho et al. (2007) [47]	Postnatal
	Coutinho et al. (2010) [48]	Postnatal (review)
	Barros et al. (2014) [49]	Postnatal
	Moore et al. (2015) [50]	Postnatal
Inflammation, Immune system and Cancer	Ferreira-e-Silva et al. (2009) [51]	Postnatal
	Assis et al. (2011) [52]	Prenatal and postnatal
	Barreto et al. (2012) [53]	Prenatal
	Brown et al. (2015) [54]	Postnatal
	Maier et al. (2013) [55]	Postnatal
	Cantero et al. (2015) [56]	Postnatal
Digestive system	Brigide et al. (2011) [57]	Postnatal
	Ueno et al. (2011) [58]	Postnatal
	Moore et al. (2015) [59]	Postnatal
	Sampaio et al. (2016) [60]	Postnatal
	de Queiroz et al. (2014) [61]	Postnatal
	Salameh et al. (2019) [62]	Only citation (review)
Life expectancy	Lago et al. (1997) [63]	Prenatal and postnatal
Respiratory system	Barbosa et al. (2020) [64]	Prenatal and postnatal
Radiopharmacy	Passos et al. (2000) [65]	Postnatal
Endocrine and Reproductive systems	Anselmo et al. (2009) [66]	Postnatal
	Pessoa et al. (2000) [68]	Prenatal and postnatal
	Muzi-Filho et al. (2015) [69]	Prenatal
	Muzi-Filho et al. (2013) [70]	Postnatal
Cardiovascular system	Monteiro et al. (2001) [72]	Prenatal and postnatal
	Lahlou et al. (2003) [73]	Prenatal
	Lahlou et al. (2004) [74]	Prenatal and postnatal
	Paixão et al. (2005) [75]	Prenatal
	Sant'Helena et al. (2014) [77]	Postnatal
	de Belchior et al. (2012) [78]	Postnatal
	de Belchior et al. (2016) [79]	Prenatal and postnatal
	Mendes et al. (2017) [80]	Postnatal
Renal/urinary system	Silva et al. (2014) [71]	Postnatal
	Paixão et al. (2001) [81]	Prenatal and postnatal
	Paixão et al. (2003) [82]	Postnatal
	Magalhães et al. (2006) [83]	Prenatal
	Vieira-Filho et al. (2009) [84]	Prenatal
	Vieira-Filho et al. (2011) [85]	Prenatal
	Silva et al. (2011) [86]	Prenatal
	Oliveira et al. (2013) [87]	Prenatal and postnatal
	Vieira-Filho et al. (2014) [88]	Prenatal
	Costa-Silva et al. (2009) [89]	Postnatal
	Silva et al. (2014) [90]	Postnatal
	Muzi-Filho et al. (2020) [91]	Postnatal
	Sampaio et al. (2017) [92]	Postnatal

GABAergic neurons on the postnatal day 8. The percentage of cholinergic cells was always higher in undernourished animals than in the control group until postnatal day 30. In both cases, normal levels were restored with age. They concluded that, despite the biochemical and behavioral changes, the neurotransmitter systems were to a certain extent shielded from undernutrition.

Behavioral and related studies also used RBD. Medeiros et al. [11] studied the effect of maternal feeding with RBD during lactation on the aggressiveness of adult rats treated with citalopram, a selective serotonin reuptake inhibitor. Acute or chronic treatment with this antidepressant reduced aggressive response in normonourished rats, but not in undernourished ones. Thus, the authors concluded that undernutrition during the critical period of brain development induced durable alterations in the function of serotoninergic neurotransmission. Guedes et al. [12] recorded a more pronounced antagonistic effect of citalopram on cortical spreading depression in early undernourished rats (intrauterine and during lactation) compared to normonourished rats. In 2004, de Vasconcelos et al. [13] also investigated the combined effects of undernutrition (pregnancy and lactation) and sleep deprivation, demonstrating that the inhibitory effect of a single sub-convulsing dose of pilocarpine on the onset and propagation of spreading depression in undernourished rats was more pronounced than in normonourished rats. Since pilocarpine is a parasympathomimetic drug that binds to muscarinic receptors, their results indicated an important cholinergic influence on spreading depression *via* these receptors, which is differentially modulated by sleep deprivation and multifactorial undernutrition.

Costa-Cruz et al. [14] reported interesting results regarding spreading depression and diabetes, a metabolic condition frequently programmed by undernutrition [15,16]. They treated normonourished and RBD-undernourished rats with streptozotocin, a type-I diabetes inducer. Normonourished rats treated with pilocarpine or streptozotocin had reduction in the propagation rate of spreading depression. In contrast, streptozotocin – but not pilocarpine – decreased spreading depression in undernourished rats during lactation (Figure 1). This difference probably reflects the mutual influence of multifactorial nutritional deprivation and hyperglycemia on the circuits that are sensitive to pilocarpine. Since such effects occurred in adulthood, the authors concluded that early undernutrition-induced cortical changes responsible for these effects are long-lasting.

The model of spreading depression associated with RBD-induced undernutrition has been extensively investigated in other neuropharmacological studies. dos Santos et al. [17] showed that maternal undernutrition during lactation did not affect the antagonistic effect of fluoxetine – a selective serotonin reuptake inhibitor – on cortical spreading depression. This antagonistic serotoninergic influence on spreading depression is similar to that with citalopram, another serotoninergic drug used in the previous studies mentioned above [11,12]. In the following year, do Monte-Silva et al. [18] investigated the effects of repeated episodes of peripheral electro-stimulation (between 2nd and 4th week of age), associated with undernutrition during lactation on cortical spreading depression propagation induced by KCl. Their results indicated the influence of RBD feeding provoking changes in brain plasticity as a consequence of an interaction between sensory input activation and undernutrition. The importance of the specificity of the sensorial input activation and nutritional status emerged when Farias-Santos et al. [19] investigated the lasting effects of moderate heat exposure on the propagation of cortical spreading depression in normonourished rats, and rats that had been undernourished during lactation. In contrast to that found by do Monte-Silva et al. [18] with the use of electric stimulus, the response of spreading depression to heat exposure was similar in both groups, indicating that undernutrition may have effects on the cortical cerebral activity, probably depending on the type of physical stimulus.

Caffeine and lithium are well known as the most effective drugs against headache and migraine [20,21]. Their effects in association with RBD-induced undernutrition during lactation were pioneered by de Aguiar et al. [22,23], who found that an amino acid imbalance modulates the subcortical effects of caffeine in attention process, but not on cortical spreading depression, a difference that has implications for the learning process. In RBD undernourished rats, lithium decreased the rate of propagation of spreading depression – not seen in normonourished animals – an effect that disappeared when protein levels (8%) were restored to control (23%) in the artisanal RBD, a clear demonstration of the interaction of nutritional status and pharmacological effects on the CNS. RBD-provoked undernutrition also did not alter modulation of dopaminergic subcortical receptors, which are involved in the attention processes. The authors proposed that these receptors do not interact with caffeine at the cortical level; for this reason, the cortical spreading depression is unmodified [22]. These studies using a combination of widely used drugs and RBD helped to detect how undernutrition can affect differentially regions of the CNS.

Due to its high lipid content and the intense O_2 supply in the brain, the production of harmful O_2

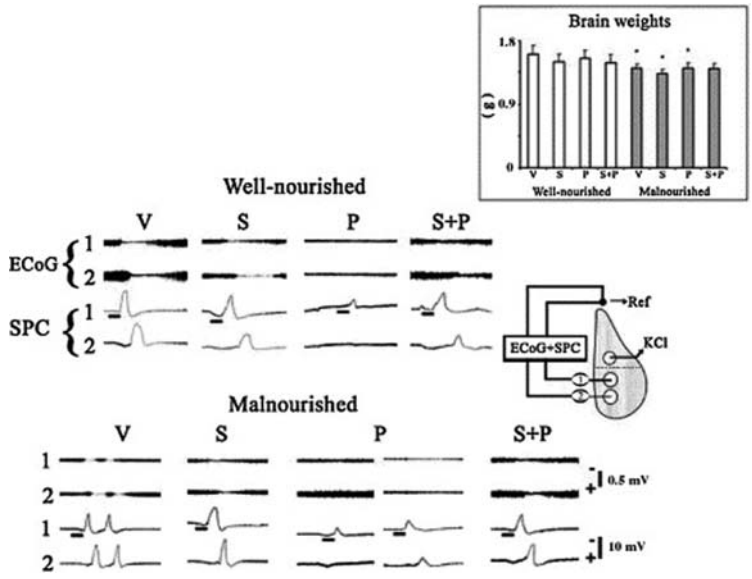

Figure 1. Recordings of electrocorticogram (ECoG) and slow potential change (SPC) during induced cortical spreading depression (CSD) in well-nourished and malnourished rats. The animals received injections (i.p.) of streptozotocin (S), pilocarpine (P) or both drugs (S + P). Well-nourished groups received only vehicle (V). The right-hand skull diagram shows the register positions 1 and 2 as well as the reference electrode (Ref). CSD was stimulated by KCl. Malnourished-V rats presented 2 CSD episodes (see peaks) after 1 KCl stimulation, which indicates an increased cortical susceptibility. Note the blockade of CSD due to pilocarpine. The inset shows the brain weights after the CSD recording session. Results are expressed as means ± SD. *Mean value significantly different compared to well-nourished controls ($p < 0.05$; one-way ANOVA followed by Tukey test). Taken from Costa-Cruz et al. [14], with permission.

reactive species (ROS) and oxidative damage are also high, which has an impact on cerebral function and the pathogenesis of diseases, such as Alzheimer and Parkinson diseases [24]. Failure or impairment of the antioxidant defenses aggravate the injury. One of these defenses is ascorbic acid, which is also highly concentrated in the brain and produces anticonvulsant or proconvulsant effects, depending on the model of seizures. Monte-Guedes et al. [25] investigated the effects of high doses of ascorbic acid in undernourished rats fed with RBD during lactation; they demonstrated that this vitamin in high dose accelerates cortical spreading depression regardless of the nutritional condition. The same approach was used in another paper by Mendes-da-Silva et al. [26], in which they demonstrated that pro-oxidant and antioxidant effects of the vitamin, as well as those related with spreading depression, are dose-dependent and once again were unaffected by undernutrition. They also investigated the effects of chronic pilocarpine administration at a sub-convulsive dose, with or without ascorbic acid, on the cortical spreading depression and lipid peroxidation in normonourished and undernourished rats during intrauterine life and lactation [27]. Their data supported the conclusion that, even though undernutrition accelerates spreading depression, it does not modify pilocarpine/ascorbic acid interactions in the immature rat brain that could otherwise influence neuronal electrical activity and damage due to oxidative stress.

Besides neurons, it became clear in the late nineties that glial cells could be affected by undernutrition and that RBD might again be useful. Mendonça et al. [28] investigated the effects of RBD-provoked undernutrition in young rats (*in utero* and during lactation) on the astrocyte distribution in 2 hypothalamic regions, the circadian pacemaker suprachiasmatic nucleus (SCN) and the medial preoptic area (MPA), which control the formation and physiology of astrocytes. Glial fibrillary acidic protein (GFAP) expression is reduced in SCN and MPA from undernourished rats, which suggests that undernutrition in the 2 development periods led to alterations in gliogenesis or glial cell proliferation in both nuclei, with an influence on neuronal development and function as a whole [29]. Furthermore, compensatory plasticity mechanisms in GFAP expression seem to be developed in astrocyte differentiation in the SCN, especially when undernutrition occurred during lactation [28], demonstrating that cellular loss induced by undernutrition stimulates these compensatory mechanisms, thereby unveiling one of the most important defenses ensuring survival under adverse conditions.

Biological rhythms, such as the sleep-wake rhythm, are associated with mental diseases [30], and the use

of RBD shed light on this field 20 years ago. Vilela et al. [31] investigated the effects of RBD administration to young rats on the main structures of the circadian timing system: retina, hypothalamic suprachiasmatic nuclei (SCN), thalamic intergeniculate leaflet, retinohypothalamic and geniculohypothalamic tracts. Compared to controls, the total retinal surface was reduced and the topographical distribution of retinal ganglion cells was altered in undernourished rats during gestation and lactation, with an increase in their density and reduction in the SCN dimensions. The data anticipated changes of structures involved in the regulation of circadian timing induced by undernutrition – possibly as the result of intracellular molecular mechanisms [30] – with potential behavioral implications. As a further demonstration that multifactorial undernutrition by RBD during gestation can alter molecular events at the CNS, Almeida et al. [32] reported that myelination of the optic nerve was significantly smaller in undernourished rats compared to normonourished rats (Figure 2), and a high percentage of large non-myelinated fibers. The authors, therefore, concluded that RBD-undernutrition affected permanently optic nerve organization and myelination, impairing nerve transmission and probable dysfunction in visual acuity.

The use of RBD also helped us understand how undernutrition affects the evolution of nervous reflexes. Anselmo et al. [33] investigated whether the exposure of pregnant rats to an electromagnetic field (EMF) in association with RBD feeding influenced reflex maturation in the offspring. The authors demonstrated that the evolution of all the reflex responses investigated was delayed by the association of the EMF with undernutrition during pregnancy. Two years later, the same group investigated the influence of these experimental conditions on somatic maturation, and found that the association between EMF and prenatally administered RBD caused a delay in all somatic maturation indexes: eye-opening, auricle opening, auditory canal opening, lower incisor eruption and upper incisor eruption [34]. Using the same experimental approach, Barros et al. [35] investigated postpartum undernutrition effects on motor development, confirming that RBD-induced undernutrition caused deleterious effects on the somatic development and maturation of the nervous system, with delay in reflex maturation and locomotor activity evolution.

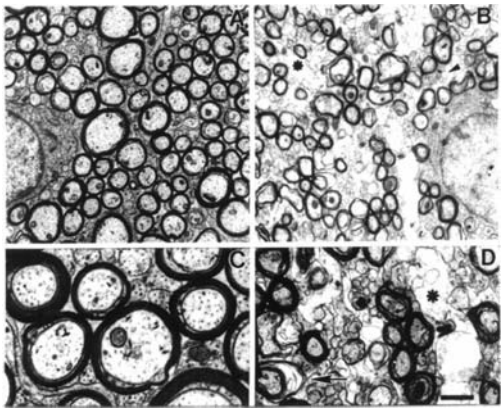

Figure 2. Electron micrographs of optic nerves of rats aged 21 days. (A) Control rat showing a very compact tissue at a more advanced stage of development. (B) Undernourished rat displaying a less compact tissue with empty spaces (*) and some fibers in the process of myelinization, and the presence of a few unmyelinated axon of small caliber. (C) High magnification of A. (D) High magnification of B, showing a large number of unmyelinated axons, empty spaces (*), and fibers with anomalous myelin alterations (arrow). Scale bars: 1.5 µm in A; 1.7 µm in B; 0.5 µm in C; and 0.8 µm in D. Taken from Almeida et al. [32], with permission.

The influence of undernutrition on the development of visual sense was also studied using RBD. Silveira et al. [36] investigated how maternal RBD-feeding during the prenatal and suckling periods might affect the neurogenesis of GABAergic cells in the retina. There was a delay in GABAergic cell generation in the undernourished rats that might have resulted in significant functional consequences in the developing retina and the vision of the offspring. Bevilaqua et al. [37] subsequently investigated the effects of postpartum undernutrition on CNS development, including retinal development. They confirmed that undernutrition with RBD delays important events, such as neurotransmitter expression and neurogenesis; they also demonstrated that the adult retina shows degenerative changes induced by long-term undernutrition during postnatal development.

The correlation between biochemical changes in brain fatty acids caused by multifactorial malnutrition and learning and memory performance was investigated by de Souza et al. [38], focusing on two periods of development (pregnancy and lactation). They found a decrease in unsaturated and polyunsaturated fatty acids accompanied by an increase in saturated fatty acids from the frontal cortex of the offspring, the cerebral region that controls cognitive skills, including memory [39]. Nutritional rehabilitation resulted in partial normalization of fatty acid profiles and of cognitive performance (latency to escape from water). The same group reviewed [40] the role of long-chain polyunsaturated fatty acids on brain development and function, and the RBD effects on spatial cognitive learning ability. They concluded that alterations in lipid composition would change the synthesis of prostaglandins, leukotrienes, and thromboxanes with implications in hormone production, fertility, immunity and

inflammatory responses. In this same field, Freitas-Silva et al. [41] compared the maturation of the monosynaptic stretch reflex in rats submitted to RBD-induced neonatal undernutrition and normal controls. Undernourished rats had long-term decrease in reflex and nervous conduction velocity, normal reflex excitability being rapidly recovered after nutritional rehabilitation, which points to the severe impact of RBD on the plasticity of the reflex pathway. The structural/functional modifications induced by RBD were later investigated by Augusto et al. [42], who found increased ROS production, lipid peroxidation, decreased NO formation and decreased glutathione (GSH) in the offspring. Once astrocytes become the more important resources of GSH [43], they also demonstrated – in addition to the above observations by Mendonça et al. [28] – that the use of RBD during pregnancy and lactation programs disruption of the functional relationships between neurons and glia in the adulthood.

Parasitology and microbiology

Socioeconomic factors, lack of sanitation and access to treated water are often linked to undernutrition in developing countries, contributing to parasite proliferation. However, RBD showed puzzling aspects not yet fully understood between undernutrition and infections. Some studies [44–48] demonstrated an association between undernutrition effects and parasitic diseases, including schistosomiasis, which will be our central example in this review. Ferreira and Coutinho [44] summarized their facts and ideas, proving that host undernutrition directly favors the biological development of *Schistosoma mansoni,* and worsens the clinical manifestations of the disease, which include the aggravating factors caused by the depression of the immune system. The Coutinho group [45] focused on the association between this disease and undernutrition. They showed that chronically undernourished mice by RBD feeding lost weight after infection with *S. mansoni* cercariae. After acute alterations of the disease, 'early undernutrition' (beginning at weaning – 21 days of age) followed by a control diet did not affect the liver, as commonly demonstrated in schistosomiasis. In the following year, Coutinho [46] found that mice subjected to 'late undernutrition' (receiving RBD after a 16-week normal feeding period) developed schistosomal liver fibrosis (Symmers' fibrosis) and large fibrotic granulomas, characteristic of schistosomiasis. This would indicate that these lesions appeared during the normal feeding period, triggered by changes in the production of inflammatory cytokines IFN-γ and IL-5. These data, taken together, suggest that the host nutritional status interferes with connective tissue changes that occur in hepatic schistosomiasis [46]. Coutinho et al. [47] showed that the Symmers' fibrosis model induced by repeated cercaria infections did not occur in RBD-undernourished mice. Deregulation of fibrogenic cytokine production and hypersensitivity of anti-*S. mansoni* T lymphocytes could explain the unexpected and puzzling difference between normonourished mice and those receiving RBD [47]. In a review, Coutinho et al. [48] summarized the previous findings from their group regarding the transitions between normonutrition and RBD-induced undernutrition in the onset and progression of schistosomiasis [44–47]. Barros et al. [49] showed that decreased release of immunogenic agents from the parasite eggs and reduced expression of fibrogenic and inflammatory cytokines in chronic undernourished mice [48] were associated with reduced viability and maturation of eggs and low protein synthesis. This would promote a decrease in collagen synthesis and expression of transforming growth factor (TGF-β1), key elements for the development of schistosomal liver fibrosis [49] (Figure 3).

RBD was not only used in parasitology studies involving *Schistosoma mansoni*. Moore et al. [50] investigated the influence of undernutrition on diarrhea caused by the anaerobic gram-positive *Clostridium difficile* bacteria. The study showed that the RBD-like low protein diet increased survival of the infected mice, with delayed onset of disease and initially a decreased pathogen shedding and fecal toxin production compared with a normal diet. They concluded that undernutrition-induced alterations in intestinal microbiota from mice that received this similar RBD could impair colonization and clostridial toxin production compared to normonourished mice [50].

Inflammation, immune system and cancer

Inflammatory mediators and the immune system are modified by intrauterine or chronic undernutrition; RBD is an appropriate model of diet for studying these modifications. Ferreira-e-Silva et al. [51] showed that during lactation RBD administration to rats reduced the number of macrophages in alveolar cells and augmented the release of NO by these cells after stimulus by an agonist of serotonin transporters, proving that serotonergic signaling pathways are affected by undernutrition (Figure 4). RBD given to mothers during pregnancy and lactation attenuated the chronic inflammatory response in adult rats by reducing and plasma levels of albumin and C-reactive protein, without altering leukocyte and lymphocyte counts [52]. However, the RBD feeding attenuated the anti-

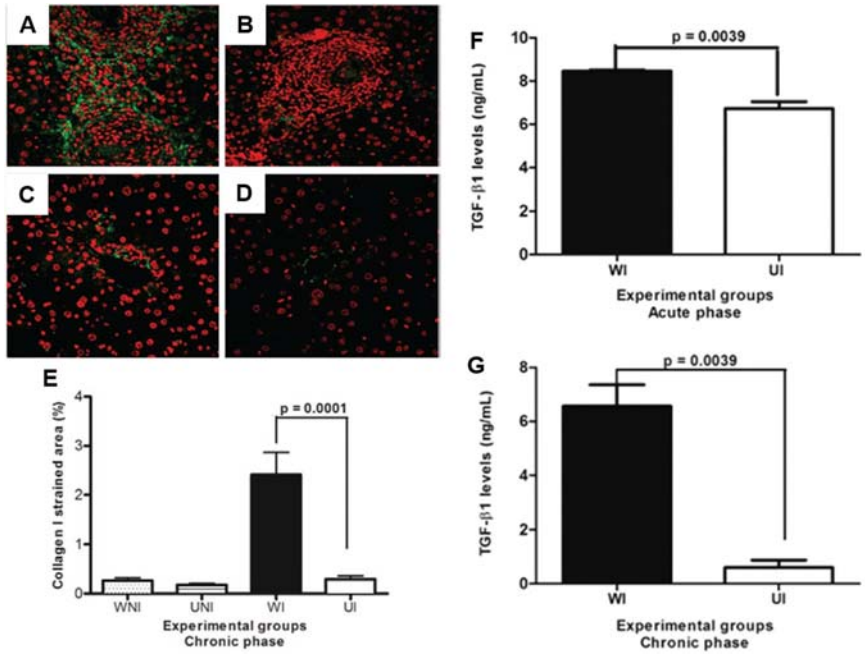

Figure 3. Collagen synthesis and TGF-β1 expression in the liver of normonourished and undernourished (RBD) mice infected or not with *Schistosoma mansoni*. (A–D) Immunolabelling by Alexa-Fluor 488 of collagen I (green) in the liver of mice chronically infected with *Schistosoma mansoni*. Hepatic cells nuclei were stained with TO-PRO 3 (red). (A) Normonourished infected mice (WI). (B) Undernourished-infected mice (UI). (C) Normonourished non-infected mice (WNI). (D) Undernourished non-infected mice (UNI) (magnification 400×). (E) Graphical representation of the data shown in the A–D panels. Results are expressed as means ± SEM. Significance was considered when $p < 0.05$ (non-parametric Mann-Whitney U test). (F and G) TGF-β1 levels in the supernatant of splenic cells (24 h culture) in UI and WI mice, in the acute (F) and chronic (G) phases of infection. Results are expressed as means ± SEM. Significance was considered when $p < 0.05$ (Student's *t*-test). Taken from Barros et al. [49], under the terms of the Creative Commons Attribution Non-Commercial License.

inflammatory effect of indomethacin in reducing hind paw swelling [52]. Using the undernutrition model, Barreto et al. [53] showed that the acute, but not the subchronic inflammatory response induced by granulomatous injury, was mitigated by intrauterine undernutrition. In addition, TNF-α and IL-6 plasma levels were reduced in the offspring subjected to intrauterine undernutrition. As in the previous study [52], indomethacin was less effective in its anti-inflammatory response in acute processes. Finally, Brown et al. [54] sought to establish a model of environmental enteropathy, which is a chronic subclinical inflammatory disease of the small intestine aggravated by the childhood undernutrition. They administered the same RBD-like low protein diet used by Moore et al. [50], in combination with commensal *Bacteroidales spp.* and *Escherichia coli*. The study showed that chronic undernutrition affects the structure of the small intestinal epithelium and intraepithelial lymphocyte composition; PCR analyses also demonstrated modifications in several species of the intestinal microbiota, thus increasing susceptibility to enteric infection.

Interestingly, the use of RBD demonstrated that important immunologic events are not modified by undernutrition. Maier et al. [55] showed that the rotavirus vaccine protected equally the normonourished and undernourished mice against rotavirus infection, with induction of serum anti-rotavirus IgA antibodies. Moreover, vaccination protected equally undernourished and normonourished mice. Regarding gastrointestinal cancers, Cantero et al. [56] showed that RBD administered to mice between 60 and 180 days of age increased DNA lesions in lymphocytes, but did not increase the predisposition to colorectal cancer. They reached this conclusion because RBD did not modify the levels of the biomarker for 1,2-dimethylhydrazine-induced colorectal cancer.

Digestive system, life expectancy, respiratory system and radiopharmacy

RBD has also been used for the study of undernutrition effects on the structure and function of the digestive system. Brigide et al. [57] evaluated the bioavailability of radioactive iron ([59] Fe) in Wistar rats by using RBD depleted or non-depleted of Fe and supplemented with multimixture (the cheap mixture of rice or wheat bran plus powdered eggshells and cornmeal) given to

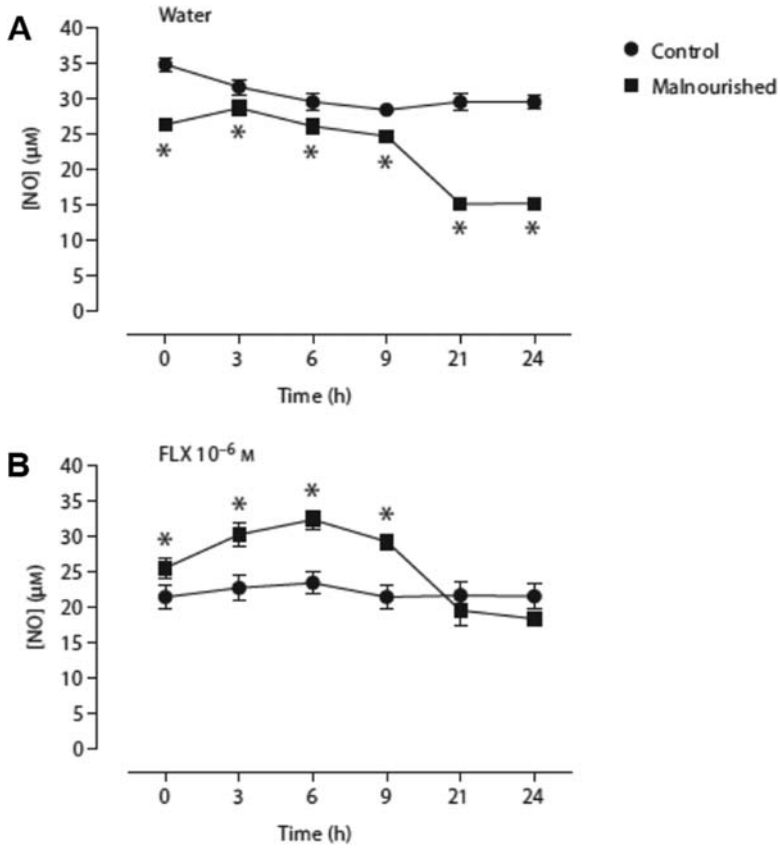

Figure 4. Time-course of NO release in the supernatants of alveolar macrophages exposed to 10^{-6} M fluoxetine (FLX). Normonourished and post-weaning undernourished rats had serum samples collected at 90 days of age. Results are expressed as means ± SEM. *$p < 0.05$ *vs*. control group (2-way ANOVA for repeated measures followed by Holm–Sidak post-test). Panels selected from Figure 5 by Ferreira-e-Silva et al. [51], with permission.

Brazilian children a few years ago. They found that RBD – depleted or not of Fe – did not change Fe bioavailability compared to controls. RBD with or without Fe, and with or without multimixture, did not affect hemoglobin levels. It was concluded that the low Fe content in RBD (3.5 mg/100 g diet) can maintain normal Fe bioavailability, and that 'supplementation with multimixture was innocuous' [57].

Despite the lack of effect on Fe absorption, RBD highlighted the serious damage that undernutrition causes to the digestive tract. Ueno et al. [58] demonstrated in mice that a RBD-like low protein diet [50,54] given after lactation induced intestinal epithelial injury characterized by hyperpermeability, which is blunted by food supplementation with alanine-glutamine (Ala-Gln) dipeptide. This beneficial effect occurs in the recovery of the intestinal barrier function from children with postnatal undernutrition-associated enteropathy. Using this same diet and the window of administration, Moore et al. [59] found that RBD compromises intestinal epithelium and crypts in mice and that these effects were reverted by Gln or Ala-Gln. They clearly showed that the beneficial effects are related to intestinal stem cell expansion by the mTOR signaling pathway activation. Sampaio et al. [60] showed in mice that postnatal RBD-feeding reduces the intestinal crypt depth (Figure 5) and modifies the expression of intestinal transporters. Since villi morphology and abundance of transporters were not modified, one can suggest that translation of these molecules is preserved. Despite the apparently light intestinal damage, RBD-provoked post-weaning undernutrition caused diarrhea and intestinal inflammation that could be reversed by Zn^{2+} supplementation, possibly as the result of Zn^{2+}-induced upregulation of anti-inflammatory cytokines and transporters [61]. The different facts and ideas regarding the influence of RBD-induced undernutrition on the intestinal tract have been reviewed by Salameh et al. [62], who highlighted the importance of jejunal and ileal hyperpermeability [58] underlying the physiopathogenesis of diarrhea during lactation.

This section finally reviews a small, though important ensemble of data demonstrating raising the questions about RBD over a wide range of scientific fields. Teodósio's group [63] addressed the simple question as to how long a rodent that was undernourished during all its life

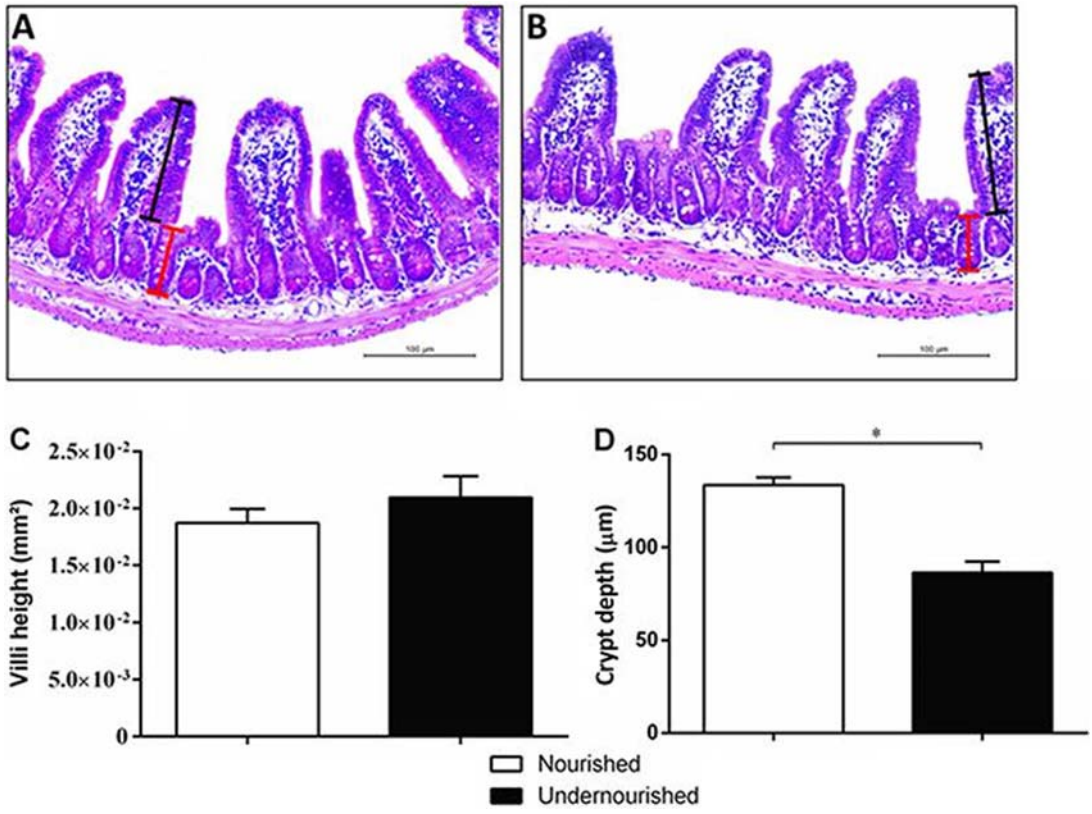

Figure 5. Undernutrition after weaning decreases crypt depth (represented by a red line) but not villi area (black line) in the intestine of mice (A, B). Hematoxylin and eosin staining; scale bar 100 µm. (A) Representative histology from a well-nourished mouse (~30 g body mass), 7 days after feeding a standard diet. (B) Representative image from a mouse (~25 g body mass) given RBD during 7 days. (C, D) Villi area and crypt depth from normonourished (empty bars) and RBD-undernourished mice (black bars), respectively. Results are expressed as means ± SEM; *$p < 0.01$ (Mann–Whitney nonparametric test). Taken from Sampaio et al. [60], under the terms of the Creative Commons Attribution Non-Commercial License.

can live. Besides programming specific morbidities, they demonstrated that RBD-induced intrauterine undernutrition reduced the life expectancy of adult rats, which had remained an unanswered question by the end of the last century. One might propose that the same applies to human beings. Focusing on the respiratory system, Barbosa et al. [64] showed that rats exposed to perinatal undernutrition (intrauterine and during lactation), followed by consumption of a high-fat diet after weaning to 90 days of age resulted in a higher volume of air displaced in each normal respiratory cycle; therefore, there was an increased risk of pulmonary barotrauma and impairment of cardiac function. Since the rats normonourished during the entire perinatal window had normal respiratory function after exposure to the high-fat diet, it became clear that perinatal programming by RBD might lead to changes in lungs after induction of overweight by a high-fat diet after weaning, with altered respiratory function. Finally, Passos et al. [65] using a radiopharmaceutical drug showed that undernutrition during the young adult life of Wistar rats specifically decreased thyroid accumulation of sodium pertechnetate ($Na^{99}Tc^{m}O_4$), a medicinal radiocompound used in thyroid scintigraphy and other nuclear medicine procedures.

Endocrine and reproductive systems

The legacy of Naíde Teodósio is also encountered in the endocrine and reproductive systems. Anselmo et al. [66] showed that exposure to an electromagnetic field (EMF; 60 Hz, 3 µT) reduced the thyroid hormones T3 and T4 serum levels in RBD-undernourished pregnant rats, but not in normonourished rats. Furthermore, there was a 3-fold increase in the T4:T3 ratio in the undernourished group of dams not exposed to EMF, and an 8-fold increase when the same undernourished females were exposed to EMF. Plasma levels of insulin, glucose and cortisol were lower. These changes indicate severe impairment in basal metabolism and severe hypothyroidism caused by the multifactorial undernutrition, especially when the hypothalamic-pituitary-gonad-thyroid-adrenal axis [67] was perturbed by electromagnetic radiation [66]. This study provided a unified view

between undernutrition and an increased risk of cancer induced by radiation.

Regarding the reproductive system, the RBD feeding in pregnant rats decreased the number of pups per litter, with low weight gain during gestation. In addition, RBD caused a low body weight at birth, together with marked post-weaning immaturity and high mortality rates, occurring in 3 consecutive rat generations [68]. This gave important proof of the idea that metabolic imprinting during gestation can be passed on from generation to generation.

The decreased number of pups per litter and the lower weight at birth is a clear indication that multifactorial undernutrition using RBD affects the reproductive performance of females [68]. Later Muzi-Filho et al. demonstrated that undernutrition also impairs fertility in male rats, either as the result of maternal programming [69] or chronic administration of RBD after weaning [70], indicating several underlying molecular mechanisms. Male fertility and fecundity decreased by 50% and 70%, respectively, due to RBD acting on the contractility of the *vas deferens* from adult males (Figure 6) due to alterations in intracellular Ca^{2+} handling. RBD increased Ca^{2+} extrusion through sarcoplasmic reticulum Ca^{2+} channels, and increased Ca^{2+}-ATPase activities in the plasma membrane and sarco/endoplasmic reticulum, i.e. a totally disrupted ensemble of Ca^{2+}-transporting proteins and their regulatory kinases. Carbonylation of these proteins and peroxidation of the membranous surrounding lipids are – at least in part – the underlying mechanisms, possibly as a consequence of amino acids imbalance and racemization that RDB induces in male rats [71].

Cardiovascular system

In the cardiovascular system, Monteiro et al. [72] showed that RBD administration for a prolonged *in utero* or postnatal undernutrition period culminates in hypertension and decreased baroreflex sensitivity, which were restored to control values after standard feeding, with differences, however, depending on the undernutrition period. Post-natal undernutrition, even when followed by standard feeding, reduced body weight and a tendency of tachycardia reflex, indicating persistent cardiovascular impairment compared to the intrauterine restriction. Focusing on dopaminergic signaling, Lahlou et al. [73] showed that RBD is selective in terms of alterations of reactivity phenomena in the cardiovascular system. Intrauterine undernutrition reduced tachycardia induced by bromocriptine, a dopamine D_2 receptor agonist, an effect that might be related to central D_2 receptor desensitization, but not to the heart autonomic regulation or the cardiac β_1-adrenoceptor desensitization, which seems to be unaffected by RBD. In 2004, the same group investigated the effect of undernutrition during intrauterine life and lactation on the pressure response to quinpirole, another dopamine D_2 receptor agonist [74]. RBD administration reduced the pressure response by the same mechanism, indicating that early undernutrition modifies the effects of several dopamine D_2 agonist drugs and, therefore heart autonomic regulation. Selectivity emerged again from these data: this mechanism is unrelated to vascular hyporesponsiveness due to α_1-adrenoceptor or vasopressin receptor stimulation [74].

Using a cell culture model, Paixão et al. [75] showed that the serum of adult male and female offspring from dams that received RBD during gestation increased aortic and renal vascular smooth muscle cells, a key element in the development of atherosclerotic plaque. This suggests that RBD elicits responses mediated by circulating factors, which modulates cell growth, as demonstrated by Umeda et al. [76] in the case of diabetes, a morbidity frequently induced by undernutrition [16]. Sant'Helena et al. [77] showed that RBD-induced alterations in heart rate varied as a function of age, as well as to changes in sympathetic tonus, suggesting autonomic cardiac dysfunction. These 2 studies indicate that RBD simultaneously causes structural and regulatory alterations that might facilitate severe cardiovascular disturbances in later life.

With the use of RBD, de Belchior et al. [78] showed that post-weaning undernutrition also increased blood pressure and heart rate in rats, together with alterations in the responses to phenylephrine and acetylcholine in the caudal artery. *In vitro*, the authors evaluated the contractile response of aortic rings to phenylephrine. L-NAME treatment increased the response to phenylephrine in aortic rings in normonourished rats, but the effect was more pronounced in chronically undernourished rats. Apocynin depressed increased contractility induced by phenylephrine, being more accentuated in rats fed with RBD. The authors suggested that the underlying mechanism is a more accentuated apocynin-induced increase in superoxide anion ($O_2^{\bullet -}$) release in undernourished rats. They found increased both phenylephrine-induced contraction and acetylcholine-provoked relaxation in the caudal artery of post-weaning undernourished rats, clear evidence of vascular dysfunction.

Finally, RBD was also used in studies involving Ca^{2+} handling and signaling in heart. de Belchior et al. [79] demonstrated that myocardial contractility is compromised in the offspring of rats that were given RBD during gestation and lactation, which could be ascribed

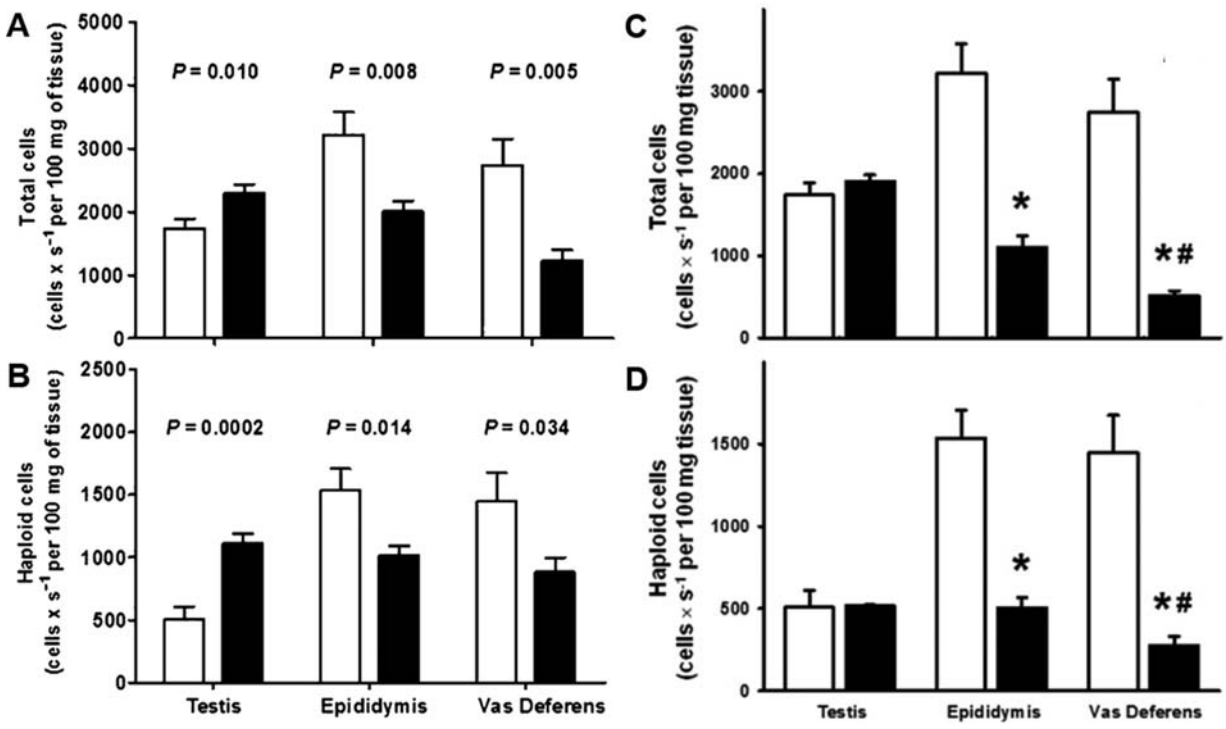

Figure 6. Germ cell counts in testis, epididymis and *vas deferens*. Total (A and C) and haploid (B and D) cells were counted in testis, epididymis, and *vas deferens* from normonourished (empty bars) and undernourished rats (filled bars). (A and B) Normonourished *vs*. prenatally undernourished rats. Results are expressed as means ± SEM. Significance was considered when $p < 0.05$ (Student's *t*-test). Taken from Muzi-Filho et al. [69], under the terms of the Creative Commons Attribution Non-Commercial License. (C and D) Normonourished *vs*. chronically undernourished rats. Results are expressed as means ± SEM. *$p < 0.05$ *vs*. the respective normonourished control; $^{\#}p < 0.05$ *vs*. cell counts in epididymis from chronically undernourished rats ($p < 0.05$; Student's *t*-test). Taken from Muzi-Filho et al. [70], under the terms of the Creative Commons Attribution Non-Commercial License.

to alterations in intracellular Ca^{2+} handling. There was a reduction in the myocardial content of SERCA2a and phosphorylated phospholamban, in addition to an increase in the Na^{+}/Ca^{2+}-exchanger protein content. These data indicate that hypertension associated with altered sympathetic and parasympathetic responses in the heart is potentiated by alterations in the abundance of Ca^{2+}-handling proteins. Similar data emerged from Mendes et al. [80] using the post-weaning undernutrition model. Their study demonstrated that RBD induced profound changes in physiological, morphometrical and functional parameters of the heart. Cardiac output, ejection fraction, stroke volume, left ventricle diameter and muscular area were reduced in rats given RBD. Furthermore, recently infarcted areas were evident, indicating that chronically undernourished rats develop heart failure (Figure 7). They also found changes in cardiac contractility, isoproterenol (β_1-adrenoceptor agonist)-induced inotropism, and intracellular Ca^{2+} handling and signaling. Since PMCA activity increased, SERCA activity decreased, non-phosphorylated phospholamban content was augmented, Na^{+}/Ca^{2+} exchanger content was decreased, and calphostin C-sensitive protein kinase (PKC)-mediated phosphorylations were increased. The authors demonstrated that RBD after weaning completely deregulated the complex machinery by which Ca^{2+} regulates cardiac function [80].

Renal/urinary system

The RBD-induced undernutrition model has relevance in the field of renal physiology and pathophysiology. Regarding *in utero* and lactation periods, Paixão et al. [81] showed that intrauterine and postpartum undernutrition reduced the number of nephrons, triggering glomerular hypertrophy, thereby increasing renal vascular resistance and hypertension. The data indicate that undernutrition in the early stages of development alters renal hemodynamics and glomerular morphometry, leading to chronic renal injury in adulthood. As with the heart, some renal alterations are also reversed, depending on the time-window of RBD administration. Paixão et al. [82] gave RBD after weaning with or without NaCl supplementation. Without salt supplementation, the rats had low renal vascular resistance, high renal blood flow, and high urinary Na^{+} excretion, which

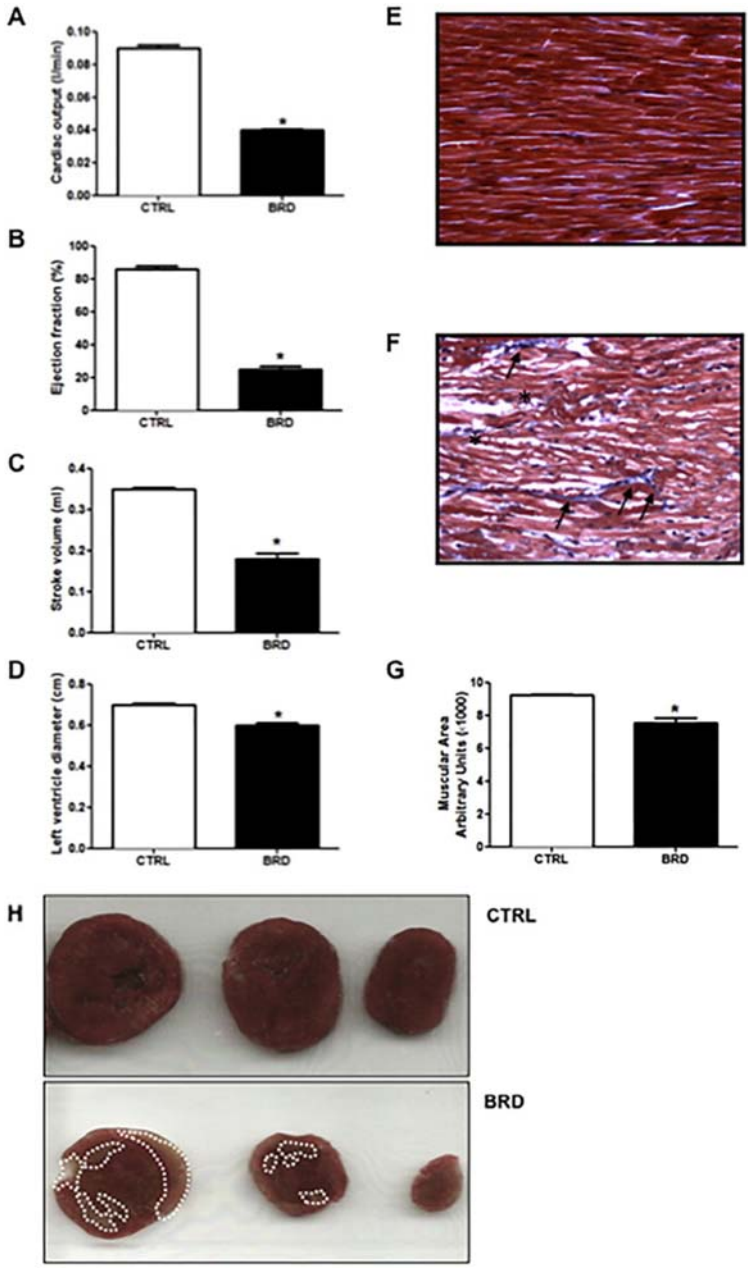

Figure 7. (A) Cardiac output, (B) ejection fraction, (C) stroke volume, and (D) left ventricle diameter in control normonourished (CTRL) and RBD-undernourished (BRD) rats. (E–G) Left ventricle slices from normonourished and undernourished rats stained with Masson trichrome. (F) Arrows indicate collagen formation (blue-stained); asterisks indicate fat deposits. (G) Left ventricle muscular areas from CTRL and BRD rats. (H) Infarcted areas are marked with dotted lines in BRD hearts. Where correspondence exists, results are expressed as means ± SEM. *Significantly different in comparison to the CTRL group ($p < 0.05$; Student's *t*-test). Modified from Mendes et al. [80], with permission.

unexpectedly decreased after NaCl supplementation. This demonstrated that RBD *per se* can disturb intrarenal Na^+ handling and corporal Na^+ balance in a manner that is independent of the salt intake. In intrauterine undernourished rats, Magalhães et al. [83] showed that RBD increased plasma volume and renal lipid peroxidation in parallel to the elevation of blood pressure, without changes in renal hemodynamics and proteinuria. In these rats, post-weaning supplementation with 1% NaCl (w/v) did not aggravate hypertension or provoke further increase in plasma volume, but increased lipid peroxidation in renal membranes. However, urinary protein, glomerular filtration rate (GFR) and filtration fraction (GFR/renal plasma flow ratio) increased [83]. Clearly, these data together indicate that RBD programmed, in association with high salt, hemodynamic changes compatible with late kidney disease development.

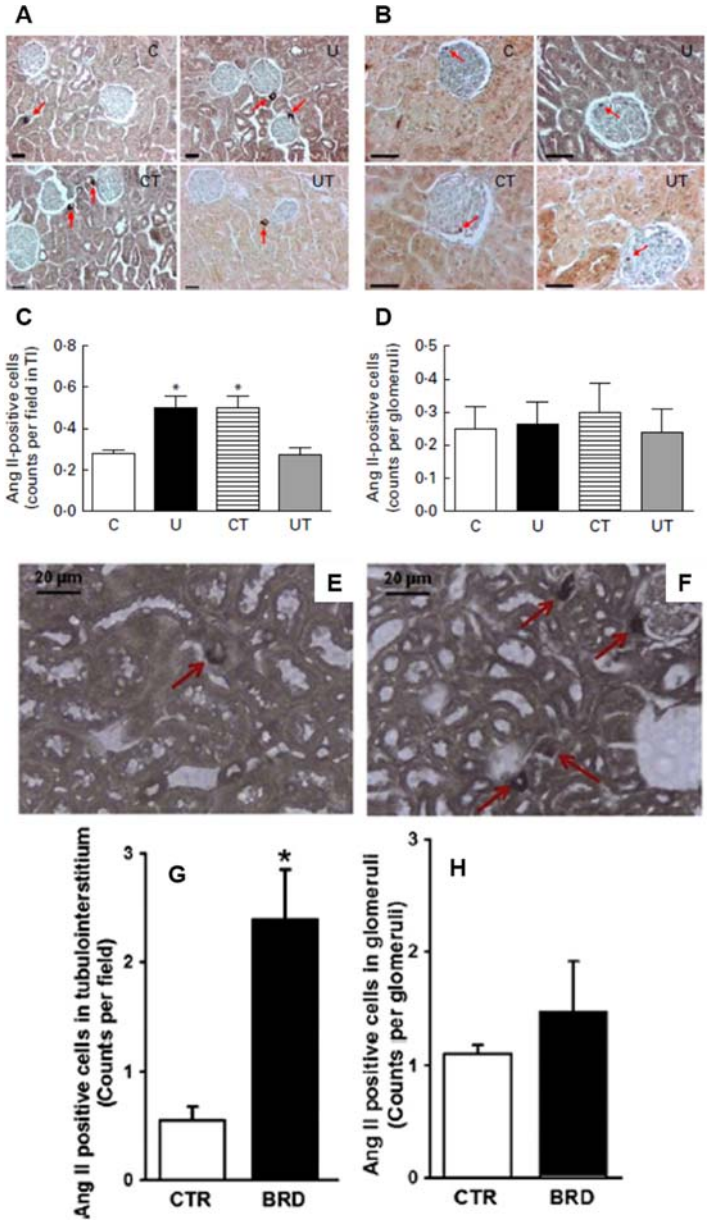

Figure 8. Ang II-positive cells in renal tubulointerstitium and glomerulus. (A) Ang II-positive cells (red arrows) in renal tubulointerstitium (magnification 200×), and (B) in glomerulus (magnification 400×). Rats aged 150 days. Groups: control (C), undernourished from mothers that received RBD (U), control with α-tocopherol during lactation (CT), and undernourished with α-tocopherol (UT). (C and D) Cell count in tubulointerstitium and glomeruli, respectively. (E) Ang II-positive cells (red arrows) in renal tubulointerstitium from normonourished rats; (F) from chronically undernourished rats (magnification 400×). Rats aged 90 days. (G and H) Cell count in tubulointerstitium and glomeruli, respectively. Results are expressed as means ± SEM. *Mean values were significantly different from C or CTR groups. $p < 0.05$; 2-way ANOVA followed by Bonferroni test (C and D) and Student's *t*-test (G and H). Modified from Vieira-Filho et al. [88] and Silva et al. [90], with permission.

Increased oxidative stress as the result of RBD administration has also been demonstrated by Vieira-Filho et al. [84], who showed that RBD induced placental and hepatic oxidative stress in pregnant rats, indicating the possibility of vertical transmission to the offspring of the maternal increased $O_2^{\bullet-}$ provoked by RBD in pregnant mothers. Two years later, this group [85] showed that maternal treatment with the antioxidant, α-tocopherol, prevents the increase in renal lipid peroxidation of the adult offspring from dams fed with RBD. Simultaneously, and possibly as the result of the maternal oxidative stress, RBD led to alterations in the regulation of Na^+-transporting pumps, especially those mediated by renin-angiotensin-aldosterone system (RAAS) signaling. All these effects,

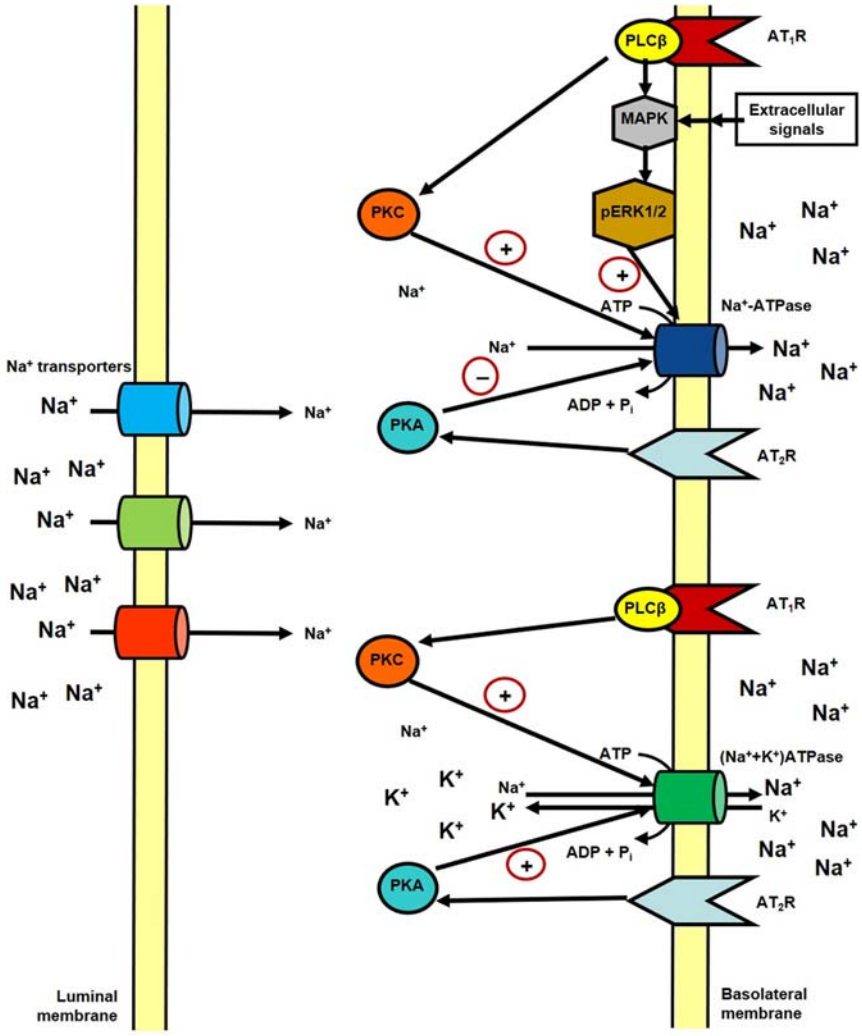

Figure 9. Proposed interactions between Ang II receptors, protein kinases A and C (PKA and PKC), and MAPK/ERK1/2, which target Na^+-transporting ATPases in proximal tubule cells from chronically undernourished rats. Stress – by a multideficient diet such as RBD and altered local Ang II levels – can induce alterations in signaling pathways coupled to AT_1R and AT_2R. Stimulation of MAPK/ERK1/2 signaling pathway can upregulate PKC. AT_1R signaling is coupled to activation of the PLCβ→PKC and MAPK→pERK1/2 pathways, thereby stimulating Na^+-transporting ATPases. AT_2R signaling is coupled to activation of the adenylate cyclase→cAMP→PKA pathway, inhibiting Na^+-ATPase and stimulating $(Na^+ + K^+)$ATPase. These regulatory mechanisms are responsible for the fine-tuning of the regulation of Na^+ extrusion and can be altered by AT_1R blockers, e.g. losartan.

including those that involve modifications in protein levels, were reversed by α-tocopherol, indicating that the antioxidant triggers non-oxidizing effects on gene transcription and protein synthesis that had been altered by RBD. Silva et al. [86] observed that RBD induced medullar renovascular changes, decreasing the capacity of urine concentration and water saving. Since these alterations were worsened by inhibition of the key enzyme involved in prostaglandin synthesis, cyclooxygenase-2 (COX-2), it became clear that the diet effect on water balance is modulated by lipid signaling. This idea was supported by the observation of Oliveira et al. [87], who showed that rats continuously undernourished from intrauterine life to adulthood had reduced cholesterol and phospholipids in the kidney, together with increased lipid peroxidation, reduced cortical Na^+ reabsorption and increased fractional Na^+ excretion. They also detected simultaneous loss of the capacity to concentrate urine, thus confirming the RBD-induced damage of the renal medulla noted by Silva et al. [86]. In another study focusing on prenatal undernutrition related to renal physiology, Vieira-Filho et al. [88] showed that maternal α-tocopherol administration reversed hypertension in the undernourished offspring, and in the alterations in RAAS and the upregulation in proximal tubules of a key enzyme that catalyzes $O_2^{\bullet-}$ formation: the $p47^{phox}$ regulatory

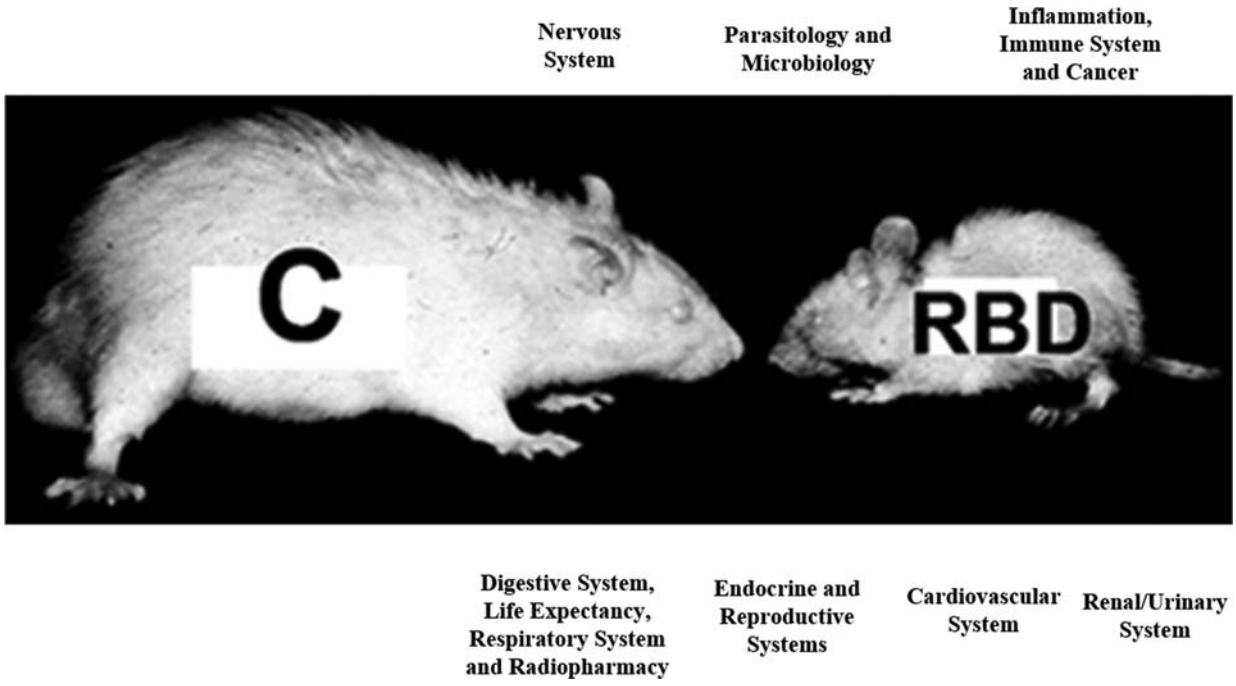

Figure 10. Rats aged 120 days and fields of knowledge, in which the use of RBD help us to understand over the last 30 years some of the physiopathological mechanisms of diseases aggravated by undernutrition. Modified from Teodósio et al. [3], under the terms of the Creative Commons Attribution Non-Commercial License.

subunit of NADPH oxidase. This study shed light on the complex network that involves RBD-induced $O_2^{\bullet-}$ levels and RBD-induced upregulation of renal RAAS (Figure 8(A–D)).

In relation to post-weaning RBD-induced chronic undernutrition, Costa-Silva et al. [89] showed that rats given RBD presented with increased proximal Na^+ reabsorption, with concomitant reduction in the Na^+ distal delivery. Urinary Na^+ excretion also increased in chronically undernourished animals. These findings indicate deregulation of Na^+-transporting ATPases, and decreased Na^+ distal delivery possibly elicits incorrect signals from the macula densa that activates the RAAS (systemic and intrarenal) and leads to hypertension. Silva et al. [71] investigated the molecular mechanisms related to these changes in kidney and heart. They showed that post-weaning rats given RBD presented with reduced essential amino acids plasma levels, as well as amino acid racemization, with simultaneous cardiac electric remodeling and generation of cardiac arrhythmias, indicative of an increased risk of sudden death. As in the case of the renal alterations described by Costa-Silva et al. [89], the primary molecular mechanisms involve alterations in active Na^+-transporting ATPases, and in the RAAS, because most of these alterations were reversed with losartan, the type 1 angiotensin II (Ang II) receptor (AT_1R) blocker. Modifications in abundance/activity of several protein kinases indicate that a cascade of phosphorylations that is triggered from the chronic undernutrition-induced RAAS upregulation stimulate Na^+ proximal reabsorption and renal and cardiac dysfunctions, culminating in hypertension and cardiorenal syndrome (Figure 9). The same group [90] investigated the mechanisms linking RBD-provoked RAAS upregulation with increased Na^+ reabsorption and hypertension. They found that one Na^+-transporting ATPase is activated as a result of abnormal phosphorylations in specific serine and threonine residues, which are phosphorylatable for PKC and cyclic AMP-dependent protein kinase (PKA). These effects are related to an RBD-triggered increase of Ang II-positive cells in the tubulointerstitial space, as happens in the intrauterine undernutrition model (Figure 8(E–H)). Muzi-Filho et al. [91] continued to investigate the molecular mechanisms altered by post-weaning undernutrition that underly renal and cardiac dysfunctions. Post-weaning undernutrition-induced inhibition of histone deacetylase (HDAC) activity in proximal tubule cells and left ventricular cardiomyocytes was reversed by administration of losartan and valproate (an inhibitor of all histone deacetylase isoforms), suggesting a crosstalk between RAAS and HDAC. The study also showed that HDAC downregulation is associated with PKC and PKA stimulation in the kidney –

but not in heart – indicating the involvement of kinase-mediated phosphorylations in tissue-specific manner. Both kinases were inhibited by losartan and valproate, an evidence of their participation in the cross-signaling between RAAS and HDAC. Furthermore, post-weaning undernutrition induced different effects in renal and cardiac Na^+-transporting ATPases. Taken together, the complementary effects of both drugs open new vistas in the treatment of alterations of Na^+ transport, hypertension and cardiorenal lesions associated with chronic undernutrition [71].

Finally, Sampaio et al. [92] investigated whether chronic undernutrition provoked physiological alterations in the bioactive lipids from kidney tissue, which could culminate in progressive chronic kidney disease. The results point to significant changes in the function of renal epithelium as a consequence of altered production and distribution of the bioactive lipids cholesterol, phosphatidylinositol, diacylglycerol, arachidonic acid and ceramide. This approach – as that used by Oliveira et al. [87] – showed that RBD modifies signaling pathways that affect ion transporters and kidney function, thus contributing to the establishment of chronic kidney disease.

Conclusion and perspectives

When all the studies, in different fields of knowledge that were performed using the RBD, are combined, it is possible to gain a complete view of the effects of the diet in each system, as summarized in Figure 10. Furthermore, with the 1990 study as a basis [3], several findings by many Brazilian researchers and from other countries – France [41,62,75], USA [50,55,58–61] and Canada [54] – have been expanded the field related to the physiopathological aspects of undernutrition and several diseases in the last 30 years. These studies show that RBD is an excellent model, providing valuable information for a better understanding of the undernutrition effects in countries with similar socio-economic conditions and social inequality as found in Brazil. Additionally, with these situations persisting in several countries worldwide, RBD remains an interesting model for studying undernutrition, not only focusing on a single nutrient, but on a multifactorial model closer to reality. Finally, it is important to mention again that all this information was followed from the pioneering work of Naíde Teodósio, a prominent name in Nutrition and Physiology research; she inspired students, coworkers and several research groups. Several MSc dissertations and PhD theses were carried out using RBD as an experimental model, evidence of a wonderful legacy for at least the next 30 years.

> Farewell is a term of spurious meddling in my affective world, in which our University appears in a plane only surpassed by the love for my family, but in a level equal to that occupied by our suffering people, whom I learned to love, feeling the imperative need to serve, to donate myself, since my life as a child (Naíde Teodósio, speaking on the day of her retirement).

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