Pathology - Research and Practice 214 (2018) 1940–1951

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

Melatonin treatment in fetal and neonatal diseases

Fernanda Rodrigues Helmo[a], Renata Margarida Etchebehere[b], Natália Bernardes[a], Maria Flávia Meirelles[a], Caetano Galvão Petrini[c], Laura Penna Rocha[a], Maria Luíza Gonçalves dos Reis Monteiro[a], Camila Souza de Oliveira Guimarães[d], Vicente de Paula Antunes Teixeira[a], Marlene Antônia dos Reis[a], Juliana Reis Machado[a], Rosana Rosa Miranda Corrêa[a,*]

[a] Discipline of General Pathology, Institute of Biological and Natural Sciences, Federal University of Triângulo Mineiro, Uberaba, Minas Gerais, Brazil
[b] Surgical Pathology Service, Clinical Hospital, Federal University of Triângulo Mineiro, Uberaba, Minas Gerais, Brazil
[c] Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil
[d] Department of Health Sciences, Discipline of General Pathology, Federal University of Lavras, Lavras, Minas Gerais, Brazil

ARTICLE INFO

Keywords:
Melatonin
Oxidative stress
Fetal disease
Neonatal disease

ABSTRACT

This literature review aims to address the main scientific findings on oxidative stress activity in different gestational disorders, as well as the function and application of melatonin in the treatment of fetal and neonatal changes. Oxidative stress has been associated with the etiopathogenesis of recurrent miscarriages, preeclampsia, intrauterine growth restriction, and stillbirth. Both, the exacerbated consumption of the antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase, and the increased synthesis of reactive oxygen species, such as superoxide, peroxynitrite, and hydrogen peroxide, induce phospholipid peroxidation and endothelial dysfunction, impaired invasion and death of trophoblast cells, impaired decidualization, and remodeling of maternal spiral arteries. It has been postulated that melatonin induces specific biochemical responses that regulate cell proliferation in fetuses, and that its antioxidant action promotes bioavailability of nitric oxide and, thus, placental perfusion and also fetal nutrition and oxygenation. Therefore, the therapeutic action of melatonin has been the subject of major studies that aim to minimize or prevent different injuries affecting this pediatric age group, such as intrauterine growth restriction, encephalopathy, chronic lung diseases, retinopathy of prematurity Conclusion: the results antioxidant and indicate that melatonin is an important therapy for the clinical treatment of these diseases.

1. Introduction

In pregnancy, there is increased oxidative stress (OS) due to the higher metabolic rate and also an increasing demand for oxygen by the organs and tissues. Thus, increased levels of OS and reduction of antioxidant activity during pregnancy may contribute to the etiopathogenesis of maternal and perinatal pathological conditions such as preeclampsia, intrauterine growth restriction (IUGR) and perinatal asphyxia [1].

The human placenta is responsible for approximately 1% of basal metabolic rate during pregnancy. Being a highly vascularized organ exposed to high oxygen partial pressure and rich in mitochondria, it is the main site for ROS synthesis, lipid peroxidation and consequently, peroxidation markers (e.g. malondialdehyde and lipid hydroperoxide) synthesis [1–3]. In healthy pregnancies, the increased placental blood flow favors oxygen supply and greater expression and activity of the

Abbreviations: AANAT, arilalkilamina N-acetiltransferase; 6-BH4, 6-tetrahidropterina; Clock, circadian locomotor output cycles kaput; GDM, gestational diabetes mellitus; HIF-1α, factor induced by hypoxia-1α; HIOMT, hidroxindol-O-methyltransferase enzyme; IUGR, intrauterine fetal growth restriction; NADPH, nicotinamide adenine dinucleotide phosphate; NAT, arylamine N-acetyltransferase; NEC, necrotizing enterocolitis; NF-κB, nuclear factor kappa B; NO, nitric oxide; NOS2, nitric oxide synthase-2; NOS3, nitric oxide synthase-3; $O^{\cdot}-$, superoxide; 8-OHdG, 8-hydroxy-20-deoxyguanosine; ONOO–, peroxynitrite; OS, oxidative stress; PE, preeclampsia; RDS, respiratory distress syndrome; ref-1, redox factor-1; ROP, retinopathy of prematurity; ROR, retinoid orphan receptor; ROS, reactive oxygen species; RZR, retinoid Z receptor; sFlt-1, soluble fms-like tyrosine kinase-1; SCN, suprachiasmatic nucleus; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; TPH, tryptophan hodroxilase; VEGF, vascular endothelial growth factor

* Corresponding author at: Instituto de Ciências Biológicas e Naturais/Disciplina de Patologia Geral/Universidade Federal do Triângulo Mineiro, Rua Frei Paulino nº 30, Bairro Nossa Senhora da Abadia, CEP: 38025-180, Uberaba, Minas Gerais, Brazil.
E-mail address: rosana.correa@uftm.edu.br (R.R. Miranda Corrêa).

https://doi.org/10.1016/j.prp.2018.10.016
Received 10 July 2018; Received in revised form 19 September 2018; Accepted 19 October 2018

antioxidant enzymes (e.g. catalase and glutathione reductase), which are essential for the control of ROS and OS [1].

Melatonin has an important role in the elimination of free radicals and reduction of oxidative damage since it stimulates higher production of antioxidant enzymes, reduction of lipid peroxidation and apoptosis of placental cells [4], demonstrating that this hormone regulates important placental functions. According to studies, pregnant women with preeclampsia present reduced melatonin levels compared to healthy pregnant women, reflecting on a poor antioxidant response in the placenta [1,5].

Literature shows that the therapeutic use of melatonin during the perinatal period may reduce materno-fetal complications [1,6]. According to studies, the administration of melatonin reduces blood pressure levels and ischemia / reperfusion injury in placentas of hypertensive pregnant women [1,5,7]. Experimental studies on IUGR and intrauterine asphyxia emphazise that the offspring of matrices treated with melatonin had a significant increase in the umbilical artery blood flow, great reduction of ROS, lipid peroxidation, apoptosis and cerebral inflammatory response [1,6,8–11].

According to a study, serum malondialdehyde (MDA) and nitrite/nitrate levels in newborns with intrauterine asphyxia presented a significant decrease 12 and 24 h after the administration of melatonin [6,12]. Literature also emphazises that the administration of 4 mg/kg of melatonin favors the prevention of alveolar lesions and interstitial fibrosis in chronic lung disease, which are prevalent in newborns requiring oxygen therapy [13]. In necrotizing enterocolitis and retinopathy of prematurity, melatonin has an important cytoprotective effect promoting lipid peroxidation, synthesis of ROS, activation of p38 mitogen-activated protein kinase (p38 MAPK), production of nitrite and action of hypoxia inducible factor-1α, for example [14,15].

Thus, the use of melatonin as an antioxidant therapy is promising in the prevention of different lesions during the perinatal period, since it is able to cross physiological barriers and reach intracellular compartments [6].

Therefore, this literature review aims to address the main scientific findings on oxidative stress activity in different gestational disorders, as well as the function and application of melatonin in the treatment of fetal and neonatal conditions.

2. Materials and methods

This study is a major review of the therapeutic use of melatonin and its protective action against some of the main perinatal conditions. Extensive research was conducted on Pubmed database, in search of scientific manuscripts discussing potential associations between melatonin treatment and OS in fetal and neonatal diseases.

Initially, about 500 articles were identified through main keywords and cross-referencing of terms such as preeclampsia, necrotizing enterocolitis, retinopathy of prematurity, intrauterine growth restriction, encephalopathy and chronic lung diseases. Subsequently, abstracts were analyzed aiming a previous selection of the main studies; in this stage, there were 210 remaining articles.

After reading and analyzing each research, those meeting the proposed objectives were prioritized and 66 articles were excluded. Thus, 144 papers were included in this study.

2.1. Oxidative stress

Oxidative Stress (OS) results from an imbalance between the synthesis of ROS and the action of antioxidant mechanisms of the body [16–19]. According to Srivastava & Kumar (2015), this dysfunction may result from exogenous stressors such as UV rays, environmental pollutants and radiation; from a decrease of non-enzymatic antioxidants such as ferritin, ceruloplasmin, transferrin, uric acid, α-tocopherol and ascorbic acid; from the reduction in the enzymatic activity of glutathione peroxidase, glutathione reductase, superoxide dismutase (SOD) and catalase; and from changes in electron transport [18,20]. In oxidative phosphorylation, for example, oxygen is an essential component in the electron transport chain and production of adenosine 5′-triphosphate (ATP). However, free radicals and other harmful substances resulting from this reaction act as harmful agents for several cellular components such as proteins, lipids and DNA, among others [18].

Superoxide anion ($O^{\cdot-}$) is the main ROS synthesized under physiological conditions in the mitochondrial electron transport chain, and also through the action of enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and cytochrome P450.

It should also be noted that the excessive synthesis of $O^{\cdot-}$ is responsible for the production of peroxynitrite ($ONOO^{-}$), a powerful oxidizing agent. On the other hand, hydrogen peroxide ($OH^{\cdot}$) is the result of the activity of catalase and glutathione peroxidase enzymes in the water molecule, and of changes in the levels of $O^{\cdot-}$ and OH in the body [18].

ROS plays different roles in cellular function, including the activation of redox-sensitive transcription factors and protein kinases, opening of ion channels, lipid peroxidation, and DNA oxidation [18,21], whose rate of injuries is regulated by cellular repair mechanisms. Nonetheless, changes in the mitochondrial redox potential and deficiencies in the repair mechanisms lead to increased and persistent DNA damage, interfering with both, transcription and replication process [22].

For instance, the offspring of heterozygous mice for the dysfunction of endothelial nitric oxide synthase gene (NOS3) present higher expression of inducible nitric oxide synthase (NOS2) enzymes, SOD-1, heat shock proteins, and peroxiredoxin-3 in the kidney; the latter alone presented a 20-fold increase. These enzymes act as mediators of oxidative stress, since they favor inflammatory and hemodynamic changes, denaturation of proteins, mitochondrial peroxide and superoxide reduction, and synthesis of $O^{\cdot-}$ and $ONOO^{-}$; consequently, higher incidence of systemic hypertension in adult life is observed [23].

Therefore, repetitive oxidative damage in the cell DNA is considered triggering factor of mutagenesis, loss of homeostasis and, consequently, of the etiopathogenesis of several entities, such as Diabetes Mellitus (DM), systemic hypertension, neoplasias, reproductive disorders, and also cardiovascular, neurodegenerative and autoimmune diseases [16,20,22,23].

3. Pregnancy and oxidative stress

3.1. Oxidative stress and adverse pregnancy outcomes

The ROS syntheses have important physiological functions in different signaling transduction pathways in the development of ovarian follicles, ovulation, fertilization, regression and steroidogenesis of the corpus luteum, endometrium changes, embryogenesis, and placental implantation, growth and development [24]. However, strong evidence suggests that OS is associated with the etiopathogenesis of several pathological changes in pregnancy, such as recurrent miscarriages, PE, IUGR, and fetal death [21,24,25].

The exacerbated consumption of antioxidant factors, for instance, leads to the following disorders in PE: peroxidation of phospholipids and endothelial dysfunction, trophoblast invasion injury caused by maternal-fetal immune system disorders, impaired decidualization and remodeling of maternal spiral arteries [24,26]. The OS is believed to stimulate the synthesis of specific antiphospholipid antibodies, responsible for lipid oxidation, and also changes in the prostacyclin-thromboxane ratio that contributes to endothelial cell injury [21].

The impairment of placental perfusion contributes to a permanent state of hypoxia, which then promotes a higher expression of soluble fms-like tyrosine kinase-1 (sFlt-1), an antiangiogenic factor which acts as a receptor in the defective regulation of vascular endothelial growth factor (VEGF) and of placental growth factor in the cytotrophoblast

[27–29]. Tumor necrosis factor-α (TNF-α) is one of the inflammatory mediators that stimulate sFlt-1 expression. In an experimental study, there was a significant increase in TNF-α serum levels and consequently, an increase in sFlt-1 serum levels in response to acute placental hypoxia [28]. Therefore, these changes are considered triggering factors of vascular complications present in this entity.

On the other hand, in pregnancies with IUGR, these disorders culminate in the death of trophoblast cells caused by the utero-placental insufficiency observed during pregnancy [24]. According to data in the literature, the action of ROS damages the DNA chain components through cross-links between DNA and proteins and structural changes in purines and pyrimidines, among other factors. Studies demonstrate that the increased expression of 8-hydroxy-20-deoxyguanosine (8-OHdG) and of repair enzyme redox factor-1 (Ref-1) are important markers of OS, not only in the placenta of pregnant women with PE or IUGR, but also in women with PE accompanied by IUGR [30,31]. Therefore, there is a significant increase in the maternal serum levels of derivatives of reactive oxygen metabolites [30–32], 8-isoprostane [33], creatinine, and aspartate aminotransferase [34].

Maternal obesity is another factor that may lead to OS during pregnancy, since lipotoxicity causes endothelial dysfunction, and compromises trophoblast invasion, as well as its metabolism and function. It is assumed that the intracellular accumulation of triacylglycerol compromises the efficient electron transport in the mitochondria, promotes the syntheses of $O^{\cdot-}$ and of non-esterified fatty acids, such as lipid peroxides, oxidized lipoproteins, and oxysterols. The plasma concentration of non-esterified fatty acids favors the synthesis of ROS in smooth and endothelial muscle cells, the increase in oxygen uptake by the cells of the immune system, and the oxidation of other lipids, such as the low density lipoprotein [35]. Therefore, these metabolic disorders are associated with the development of gestational diabetes mellitus (GDM), gestational hypertension, PE, and increased incidence of obesity in the descendants [35,36].

According to a study, obese pregnant women present high serum and placental MDA levels, protein carbonyl, and nitrites, as well as low levels of reduced glutathione and decreased activity of the enzymes SOD and catalase. Moreover, an intense maternal-placental-fetal interaction was observed, since the newborns also had increased levels of MDA and nitrites, hypertriglyceridemia, and lower antioxidant activity [37]. A similar result was found in another study, in which newborns of pre-gestational overweight and obese mothers showed a significant increase in the serum levels of MDA and nitric oxide, compared to newborns of eutrophic mothers [38]. Multivariate regression analysis showed that either maternal overweight or obesity was significantly associated with high F2-IsoPs levels in small-for-gestational-age newborns [39].

It is important to note that the fetuses of obese mothers show increased production of proinflammatory adipocytokines, such as leptin (which circulates in the cord blood and is synthesized and secreted in breast milk, especially in colostrum) and adiponectin (which is released in breast milk), increased insulin resistance and OS susceptibility [35,36,38].

The serious impact of GDM is also associated with OS. Increased protein glycation and glucose oxidation favor the production of free radicals and, hence, lipid peroxidation and cell membrane damage. Literature shows decreased antioxidant capacity, increased plasma levels of the inflammatory marker myeloperoxidase, advanced oxidation protein products, and lipid peroxidation in GDM and PE cases [40].

Experimental studies have reported that on GDM associated with obesity, ROS can damage the artery branch of the placenta and increase the synthesis of MDA by up to 84.4%. It may also increase the synthesis of mRNA and of the protein factor induced by hypoxia-1α (HIF-1α), both important markers of hypoxia in GDM. Consequently, the reduction of oxygen concentration results in an increase in the mRNA synthesis of VEGF, increased phosphorylation of the nuclear factor kappa B (NF-κB), and exacerbated synthesis of the pro-inflammatory interleukins IL-1β, IL-1 and TNF-α [41].

According to Dennery (2010) and Ornoy *et al.* (2015), the oxidative state triggered by DM during pregnancy leads to uncontrolled apoptosis, mainly in the first trimester, culminating in the incidence of congenital malformations, miscarriages, premature birth and other gestational complications [25,42].

Therefore, researches show that pregnant women with PE, DM and preterm births have a lower antioxidant response and, hence, a higher pro-oxidant activity [43].

3.2. Normal fetal and neonatal antioxidant enzyme maturation

The effective synthesis of the antioxidant enzymes SOD, catalase and glutathione peroxidase occurs in late pregnancy. Analysis carried out on lungs of rat and rabbit fetuses showed that the expression of these three enzymes is reduced at the beginning of the third trimester of pregnancy; but it is increased at the end of gestation [26,27].

SOD is responsible for catalyzing the conversion of the $O^{\cdot-}$ radicals into H_2O_2 and water, and it has three main isoforms: CuZnSOD (SOD1), located in the cytoplasm and in the cell nucleus; MnSOD (SOD2), located in the mitochondria; and extracellular (EC)-SOD (SOD3), which contains copper and zinc in its active sites, and is located in the matrix and extracellular fluids in adults, and in the intracellular environment of the lung epithelium in newborns [44–46]. As regards catalase, glutathione peroxidase and glutathione reductase, they are responsible for the conversion of H_2O_2 into water [26,27].

The progressive maturation of this antioxidant system promotes the transition from the intrauterine environment – in which the fetus develops in the presence of relative hypoxia (arterial PaO2 3.3 kPa, alveolar PaO2 0.7 kPa) – to an extrauterine hyperoxic environment (arterial PaO2 8e11 kPa, alveolar PaO2 19 kPa at room temperature), consequently with a higher intracellular synthesis of ROS after birth [26–28,30,31]. According to data in the literature, not only does the increase of > 150% in the synthesis of antioxidant enzymes at the end of the third quarter correlate with an increased protection of fetal and neonatal lung cells against OS [46,47], but also with the maturation of the lung surfactant, since the latter presents SOD and catalase enzymes in its constitution [46,48].

The association of antioxidant enzymes with a complex composition of phospholipids and proteins is responsible for the specific properties of the pulmonary surfactant, such as the changes in surface tension during lung expansion and deflation, as well as for promoting alveolar stability and minimal breathing effort in each respiratory cycle. Therefore, this substance protects the pulmonary epithelium from the action of extracellular ROS synthesized mainly by neutrophils, macrophages and parenchyma cells [49].

An experimental study showed that hyperoxia impairs both alveolar and bronchiolar epithelial proliferation until the seventh day of postnatal life, and these changes are mainly associated with type II pneumocytes, which behave as progenitor cells of type I pneumocytes [45,50]. In contrast, proliferation was preserved in the lungs with higher expression of EC-SOD [45], which is correlated with its modulating action in the synthesis of $ONOO^{-}$ from the reaction of nitric oxide (NO) and $O^{\cdot-}$ in the vascular endothelium and pulmonary airways [44].

Thus, the perfect development of this system enables the interaction of the uterine-placental-fetal redox signaling pathways during embryogenesis [46], since the expression of antioxidant enzymes changes in different fetal organs as gestational age increases. The placenta, for example, is a fetal organ responsible for maternal-fetal gas exchange. Therefore, there is a higher expression of the enzymes SOD, catalase, glutathione reductase and peroxidase, concomitantly with a decrease in lipid peroxidation, as well as prevalence of the EC-SOD synthesis in the villi from the second trimester on, and change in its expression (which was intracytoplasmic in the cytotrophoblast and syncytiotrophoblast) to the extracellular matrix of fetal villous vessels [46].

3.3. Preterm birth and oxidative stress

The prevalence of an immune and antioxidant system in continuous process of maturation during the first year of life, a highly aerobic metabolism and a deficit in homeostasis mechanisms, contribute to the increased susceptibility of newborns to ROS. Hence, prematurity aggravates OS [34,35], and the antioxidant enzyme activity [27,36] is reduced in this age group.

Fetal disorders resulting from infections, IUGR and GDM, for example, may impair the regulation of the antioxidant system in premature infants [46,51]. In response to hypoxia due to the impairment of the fetal-placental blood flow, there is an increased synthesis of ROS changing the structure and function of the collagen fibers (strength and elasticity) and causing premature rupture of the placental membranes. On the other hand, the greater exposure to ROS in postnatal life is associated with bronchopulmonary dysplasia, retinopathy of prematurity (ROP), necrotizing enterocolitis, renal failure, neuronal injury, and intraventricular hemorrhage, which are diseases associated with free radicals [51–53].

According to a study, premature newborns that developed free radical-related diseases (FRD) had increased serum levels of hydroperoxides, advanced oxidation protein products and non-protein-bound iron. Furthermore, there was a high risk of intraventricular bleeding in children with concentrations higher than 910,000 UCARR/L hydroperoxide, 90.70 μmol/L of advanced oxidation protein products and 10.07 μmol/L of non-protein-bound iron [54]. This change could be associated with the reduced activity of the enzymes Na^+ and K^+-ATPase, which are highly dependent on ATP and are responsible for the regulation of the ion channels and the maintenance of membrane potential. It may also correlate with the changes in phosphorylation/dephosphorylation cycles of N-methyl-D-aspartate receptor, which favors the increase of intracellular Ca^{2+} influx; and, consequently, with the activation of different reactions that promote the synthesis of ROS and the expression of apoptotic genes and endonuclease enzymes in the brain during hypoxia [55]. Thus, these substances may act as markers of diseases associated with free radicals in this age group. [35,40].

Studies carried out by Sakata et al. (2008) and Menon (2014) indicate that OS promotes the overexpression of metalloproteinase enzymes (MMP-3 and MMP-8), as well as cyclooxygenase-2, prostaglandins, IL-1β and TNF-α through the NF-κB pathway; up-regulation of apoptotic genes p53, bax, and of pro-apoptotic cytokine IL-18 in the placenta; higher expression of intercellular adhesion molecule and connexin 4; and insufficient expression of antioxidant heme oxygenase enzyme, which is responsible for the degradation of the heme portion of hemoglobin, for instance. Therefore, in decidual bleeding, not only is there increased synthesis of ROS derived from intracellular free iron via the Fenton reaction, but also of cyclooxygenase-2 and prostaglandin F2α. The increased production and activation of these substances is associated with the pathogenesis of premature rupture of membranes, and the induction of premature labor [56,57].

Research shows that premature infants with severe bronchopulmonary presented high potential of glutathione redox reactions, represented by changes in the serum levels of its reduced form, L-glutathione, and of its oxidized form, glutathione disulfide. Moreover, the total serum concentration of this antioxidant was reduced in preterm infants who had received a fraction of inspired oxygen (FiO_2) ≥ 25% [58]. In premature infants with low birth weight (< 1500 g and < 2000 g) there were also increased serum levels of malondialdehyde and protein carbonyl, hence, a higher rate of lipid and protein peroxidation, whereas the levels of vitamins A, C and E were reduced in preterm infants with low birth weight (< 2500 g). It should be noted that the total antioxidant capacity among premature infants considered small for gestational age was lower in these individuals [59].

3.4. Oxidative stress and the inflammatory response

Similarly to OS, the inflammatory response is associated with both the maintenance of normal pregnancy and the pathogenesis of different gestational changes. According to a literature [60] review, in HELLP syndrome and in PE, for example, the systemic maternal endothelial dysfunction promotes the recruitment of circulating inflammatory cells (e.g.: granulocytes, monocytes and lymphocytes) to the tissues through the activation of the vascular endothelium, disseminated intravascular coagulation due to the increased expression of tissue factor, and impaired regulation of anticoagulant of the protein C pathways and fibrinolytic proteins. Concomitantly, inflammatory mediators TNF-α, IL-6 and IL-8 are increased in the maternal plasma.

Therefore, it is believed that ROS may act as secondary messengers in the signaling synthesis of inflammatory and immune response such as NF-κB factor, as well as in the signaling pathways of apoptosis and necrosis of syncytiotrophoblast, thus favoring the increase of debris in maternal circulation, and behaving as an important pro-inflammatory agent [60]. In GDM, for example, increased ROS synthesis triggers a higher expression of cytokines IL-1β, macrophage inflammatory protein, and TNF-α [61] in the placenta.

Studies demonstrate that the villous macrophages (Hofbauer cells) of pregnant women with type 1 DM changed from an M2 (anti-inflammatory) profile to an M1 (pro-inflammatory) profile. The expression of CD68, IL-1β and CCR7 (M1 profile) was higher, whereas the expression of CD209, CD163 and IL-10 (M2 profile) was lower in the placentas of these women; similar results were observed in the placenta of rats with GDM, with increased expression of CD68 and decreased expression of CD163. The expression of Toll-like receptors 2 and 4, of the adapter molecule myeloid differentiation primary response 88 (MyD88), interleukin-1 receptor-associated kinase 4, TNF-receptor-associated factor-6, interferon regulatory factor 5, and NFκB was also increased. The latter comprise a complex pathway of receptors that promote the synthesis of pro-inflammatory mediators; hence, there was an increase in gene expression of TNF-α, IL-12, IL-1β, HIF1-α, NOS2 and NO [62].

The predominance of Th1 immune response is another factor that may be cause and/or consequence of the OS in PE. Literature suggests that there is a higher percentage of Th1 cells in this entity, as well as a higher proportion of Th1:Th2, whereas the Th2 response prevails in normal pregnancies [48,49]. The increased expression of Th1, in turn, is reflected on the higher synthesis of pro-inflammatory cytokines IL-2, IFN-γ and TNF-α [63,64], and on the existence of a positive correlation between the increased concentration of these mediators in peripheral blood, and the increase of maternal blood pressure [64].

Changes in the inflammatory response also appear to be associated with embryo implantation defects and recurrent abortions. The highest concentration of $CD56^+$ natural killer cells [65–68] and $CD16^+$ uterine killer cells in the endometrium appears to be associated with impaired expression of VEGF and IL-6 [68,69], and with increased cytotoxic activity in women with infertility of unknown cause and failure in embryo implantation [51,54].

Studies also demonstrated that the combination of maternal infections and perinatal anoxia promotes the synthesis of pro-inflammatory mediators IL-1, IL-4, TNF-α [70] and C-reactive protein [71,72], as well as increased exposure to the activity of ROS [70,71] and SOD [70]. These changes are associated with severe brain injury in premature infants and other diseases in adulthood.

Nonetheless, it is important to note that the literature states that even pregnancies without complications are associated with an inherent pro-oxidative and inflammatory state, since studies show increased serum levels of advanced oxidation protein products, C-reactive protein, and anticardiolipin IgG antibody during the first and second trimesters of gestation [73]. Furthermore, there is also an activation of the immune system similar to PE in the last trimester, however, more moderate [60].

4. Melatonin treatment to target oxidative stress in fetal and neonatal period

4.1. Melatonin: synthesis and its receptors

Melatonin or *N-acetyl-5-methoxytryptamine* is an indolamine synthesized and secreted by the pineal gland through a complex metabolic pathway driven by the suprachiasmatic nucleus (SCN) according to the circadian rhythm [74,75], as well as in different extrapineal sites [76,77]. This neurohormone was first isolated from bovine pineal glands and it was found to have an antagonist action against the α-melanocyte stimulating hormone (α-MSH) [78–80].

The retinohypothalamic tract in the central nervous system receives direct photic input which is then converted into a monosynaptic reflex in the SCN via retinal ganglion cells. Later, this reflex reaches the paraventricular nucleus and the ganglion of the intermediolateral column through a GABAergic input via polysynaptic neural pathways. Then, preganglionic adrenergic fibers transmit the stimulus from the ganglion of the intermediolateral column to the superior cervical ganglion and to the pineal gland via postganglionic noradrenergic fibers [60,65].

The synthesis of melatonin, in turn, consists of biochemical reactions synchronized via α1 and β-adrenergic receptors in the pinealocytes, which culminate in a higher concentration of cyclic adenosine monophosphate [81]. Thus, the first stage of this reaction is the hydroxylation of aromatic amino acid L-tryptophan, which is catalyzed by tryptophan hodroxilase (TPH) and its cofactor 6-tetrahydropterin (6-BH4) to 5-hydroxytryptophan, is the first stage of this reaction. Subsequently, this compound is decarboxylated by the aromatic amino acid decarboxylase enzyme [82] to serotonin or 5-hydroxytryptamine which by the action of arylalkilamine N-acetyltransferase (AANAT) is converted into N-acetylserotonin. Finally, hidroxindol-O-methyltransferase enzyme (HIOMT) is responsible for the methylation of N-acetylserotonin to melatonin [79,80].

The synthesis mechanisms in extrapineal sites are not fully understood. However, molecular studies performed on thymus of rats [69,70] and humans [83] showed the expression of arylamine N-acetyltransferase (NAT), which performs the same function as AANAT, as well as the expression of HIOMT in fetal and postnatal thymocytes. A similar finding was observed in human cytotrophoblast cells [84], since they expressed both AANAT and HIOMT enzymes. The skin also appears to be a local metabolic pathway, as it is able to express THP and its cofactors 6-BH4, AAD, NAT or AANAT, and HIOMT [85,86] for the synthesis of this neurohormone.

Literature emphazises that, mainly in humans, the interaction of this neurohormone occurs through two transmembrane receptors, MT1 and MT2, coupled to the G protein. In mammals, the MT1 receptor was first identified in sheep and humans; its molecular structure consists of 350 amino acids, and proteins Giα2, Giα3 and Gq/11 and their main couplers [66,74]. Moreover, MT1 is expressed in the retina [76], heart, aorta, periphery blood vessels [80,87], mast cells, lymphocytes, macrophages [62,63,70], skin [72,73], mammary glands, liver, gall bladder, kidneys, adrenal glands, pancreas, spleen, testicles, ovaries [66,75], placenta [84,88], and the brain [80,89]. In the brain, it is prevalent in the hypothalamus, cerebellum, hippocampus, *substantia nigra*, and ventral tegmental area [66,74,75].

On the other hand, MT2 was observed in the human brain, pituitary gland, and retina. It consists of 363 amino acids, of which 60% are homologous to the MT1 receptor, and also has Gi protein as the main coupler [66,74] Similarly, it is expressed in the retina [76], pituitary gland, adipose tissue [80,87], mast cells, lymphocytes, macrophages [62,63,70], skin [72,73], kidneys, gastrointestinal tract, testicles, mammary glands, placenta [84], and in the brain, particularly in the hypothalamus and in the SCN [66,74].

In addition to these usual pathways, it is believed that a cytosolic enzyme called quinone reductase 2 could be a third site of action of melatonin, since this enzyme has been observed in several animal tissues, such as rabbit retinas. Studies show that this intracytoplasmic site appears to interfere with electron transfer reactions and, therefore, protect the body against the harmful effects of the oxidative stress [66,75]. Some nuclear receptors of the subfamily of retinoid Z (RZR) or retinoid orphan receptor (ROR), such as RZRβ, RORα and RORα1 [90–92], are also mentioned as hormonal signal transduction pathways in the brain and the placenta [84], for instance.

During the perinatal period, these receptors are identified in the fetal SCN from the 18th week of intrauterine development on. It is believed that maternal melatonin, which is able to cross the placental barrier, is primarily responsible for the stimulation of the circadian rhythm of fetuses and newborns [80,81] until the efferent connections among the SCN, the superior cervical ganglion (SCG) and the pineal gland are mature for autonomous secretion, which is observed from the second week [74] of life. Nonetheless, the regulation of the circadian rhythm only occurs between the sixth and eighth weeks [82,83] of postpartum.

This hypothesis is based on the expression of the Circadian Locomotor Output Cycles Kaput (CLOCK) genes, responsible for the regulation of the circadian rhythm in the cellular level in adults. A study on capuchin monkey fetuses, whose mothers were kept in cycles of 14 h of light and 10 h in the absence of light during pregnancy, found that Bmal-1, Per-2, Cry-2 and Clock genes are expressed in the SCN, in the adrenal, pituitary, and thyroid glands, and in brown fat, whereas Bmal-1, Cry-2 and CLOCK were expressed in the pineal gland. Furthermore, the study demonstrated that the expression of Bmal-1, Per-2 and MT1 in the offpring SCN is dependent on maternal melatonin [81]: and that in the adrenal gland, for example, the expression of the respective CLOCK genes may respond to other still unknown fetal and maternal metabolic stimuli [81,93,94].

4.2. Physiological functions of melatonin

Melatonin is a pleiotropic neurohormone, as it plays multiple roles in different cell types not only in adults but also during the perinatal period. Among these roles, its antioxidant action should be highlighted, since it can be metabolized to cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxy-kynuramine, and N1-acetyl-5-methoxy-kynuramine [95], which are potent suppressors of peroxide, hydroxyl and carbonate radicals. Concomitantly, melatonin favors the regulation of important enzymes that also act controlling these substances, as follows: glutathione peroxidase, glutathione reductase, γ-glutamylcysteine synthase, glucose 6-phosphate dehydrogenase, Mn, Zn, and Cu-superoxide dismutase and catalase [84,85].

In addition, this neurohormone and its metabolites appear to favor the synthesis of anti-apoptotic proteins Bcl-2 and Bcl-xL, and ATP by maintaining glutathione [96] levels, and also to inhibit the activation of caspase-3, the synthesis of cytochrome c, and lipid peroxidation in the inner membrane of the mitochondria [95] and of the plasmatic membrane [96]. Accordingly, literature reports that melatonin has a neuroprotective activity in the etiopathogenesis of neurological disorders such as epilepsy, amyotrophic lateral sclerosis, Alzheimer's disease, and ischemic injury, since the synthesis of these cytotoxic substances leads to neuronal injury and mitochondrial dysfunction [95] in these entities.

Melatonin is mainly responsible for regulating energy consumption in mammals. An experimental study found that in obesity and aging, melatonin supplementation promoted a reduction in body mass, and an increase in insulin sensitivity in the hypothalamus, skeletal muscle and liver. These findings appear to be related to the increased phosphorylation of proteins in the insulin intracellular signaling pathway [97,98], since melatonin induces tyrosine phosphorylation of the insulin receptor substrate-1 and consequently, of p42MAP and AKT kinase proteins in the rat hypothalamus in vivo [99].

In addition, literature suggests a possible interaction between the neuro-hormone and the leptin secreted by adypocites. It is believed that

melatonin plays a regulatory role in the plasma levels of leptin, since the adipose tissue expresses the respective receptors MT1 and MT2 [95]. Therefore, although not fully understood, these molecular mechanisms seem to contribute to the control of body weight and daily energy balance in individuals, since the lack of secretion of this neurohormone leads to increased insulin resistance and hepatic gluconeogenesis [100], impaired regulation of the expression of glucose transporter 4 [82,101], glucose intolerance, and impaired response of pancreatic β cells to glucose levels [82].

The immune response is also influenced by the action of melatonin, since T cells and mast cells, for example, express this neurohormone receptors, or an increased sensitivity to chemical mediators of the inflammatory response is observed. Thus, studies demonstrate the relationship between the seasonal variations of melatonin secretion and the proliferation of granulocyte-monocyte colony-forming units (CFU-GM) [102–104], eosinophils, basophils, and mast cells, as well as the proliferation of dendritic cell progenitors and natural killer cells [103].

When building the immune response against infections caused by different etiological agents, this interaction appears to be relevant due to its influence on the proliferation of inflammatory cells such as lymphocytes; its contribution to the synthesis of pro-inflammatory cytokines, such as IL-1 and TNF-α, which are responsible for stimulating phagocytosis and apoptosis; its modulation of the inflammatory response by inhibiting enzymes such as phospholipase A, lipoxygenase and cyclooxygenase [104]; and its regulation of mast cell degranulation [103]. Therefore, it is postulated that the biochemical signaling triggered by the initial processing of antigens acts as a stimulus for the pineal gland to synthesize and secrete melatonin, as observed under the stimulation of IL-12 and the granulocyte-macrophage colony-stimulating factor [103], for instance.

Literature also shows that melatonin and its metabolites play important roles during the intrauterine development. The former is responsible for stimulating the synthesis of progesterone, which inhibits early stimulation of uterine muscle contraction [76,95] and immune rejection of trophoblast [88], despite inhibiting the synthesis of prostaglandins [76,95]. Thus, the increased plasma levels observed in maternal circulation contribute to the maintenance of pregnancy.

Accordingly, it is possible to infer that gestational disorders such as placental insufficiency exhibit changes in the maternal melatonin synthesis. A study carried out on human placentas reported a significant reduction in mRNA expression, not only in AANAT and HIOMT enzymes, but also in the MT1 and MT2 receptors in placentas of women with pre-eclampsia in comparison with normotensive women [105]. These findings are complementary to experiments on pregnant rats subjected to ischemia and placental reperfusion flow, which showed that the oral administration of melatonin solution inhibited IUGR in the offspring, since weight loss in the evaluated offspring was reduced. Moreover, a significant reduction in the concentration of 8-hidroxi-2′-deoxiguanosina compound in the placental tissue was observed. This compound is an important biomarker of DNA oxidative damage in IUGR and PE [106].

Hence, it is assumed that melatonin induces specific biochemical responses that regulate cell proliferation in the fetus, and that its antioxidant action favors the nitric oxide (NO) bioavailability, leading to placental perfusion, nutrition and oxygenation of the fetus [107].

4.3. Therapeutic use of melatonin

Prematurity, infections and placental dysfunction involve complex physiological disorders, and are accompanied by serious changes in cellular biochemical metabolism, which leads to perinatal stress. The therapeutic action of melatonin is the subject of major studies aiming to minimize or prevent different conditions that affect this pediatric age group.

In respiratory distress syndrome (RDS), for instance, excessive ROS synthesis is observed, but the use of supportive oxygen therapies, pro-oxidant drugs, and pulmonary or extrapulmonary infection favor the depletion of antioxidants and, thus, the retention of ROS [14]. Research shows that the treatment with melatonin in grades III and IV of RDS leads to a lower synthesis of proinflammatory cytokines such as IL-6, IL-8, TNF-α, resulting in greater efficacy of clinical treatment [99,98] in newborns.

Moreover, the antioxidant and anti-inflammatory properties of melatonin are indicated as a possible treatment to control the neurological damage caused by hypoxia and ischemia, as well as by neonatal sepsis [14], respectively. These views are based on their ability to regulate the formation of free radicals and promote the expression of enzymes such as glutathione; to reduce the recruitment of polymorphonuclear leukocytes [38,100]; and to inhibit the expression of adhesion molecules and of the nuclear factor NF-κB [54] during the inflammatory response. In sepsis, for instance, it is acknowledged that not only do elastase, cathepsin and hypochlorous acid act as bactericides, but also as proteolytic substances that produce ROS and NOS [108], hence triggering multiple organ failure.

Regarding hypoxic and ischemic damage, experimental studies on rat brains concluded that melatonin reduces the expression of the oxidative stress biomarkers, such as isoprostanes, neuroprostanes and neurofurans, the recruitment of inflammatory cells, the expression of glial fibrillary acidic protein [101,102] associated with the formation of new astrocytic processes and reactive gliosis, and also the impaired expression of the basic myelin protein [109].

These findings, thus, reinforce the neuroprotective action of melatonin, and demonstrate that either the prophylactic or post-injury administration of melatonin in the perinatal period may reduce the extent of the infarction area, the neuronal injury, and the lipid and protein peroxidation, and in addition, it may inactivate apoptotic pathways [109–111], minimizing possible neonatal complications.

Prematurity, for instance, is a condition that exposes the child to several physiological disorders, such as temperature control, susceptibility to infections, severe inflammatory response, and impaired gas exchange. Melatonin also appears to be a treatment with multiple possibilities of intervention [112], since especially in chronic perinatal stress [113], there is a greater expression of its receptors on fetal and placental tissues.

Another use of melatonin is pain control during clinical procedures in the intensive care unit. According to evaluation, the intensity of pain was significantly lower in newborns treated with this compound up to seven days after endotracheal intubation. Furthermore, the dosage of pro-inflammatory interleukins IL-6, IL-8 and IL-12 in the plasma of these children was reduced compared to those who did not receive melatonin treatment [108]. It is believed that this property may be related to the modulation of GABA and μ-opioid receptors, reducing the concentration of cAMP as a second intracellular messenger [114]. Therefore, these findings are of great importance, since this age group is exposed to painful stimuli in neonatal intensive care units [100,108].

5. Protective role of melatonin in fetal diseases

5.1. Intrauterine growth restriction

Placental dysfunction is the main triggering factor of IUGR, which may cause premature birth, perinatal death and severe cardiovascular and neurological injuries such as cerebral palsy. It is believed that fetal-placental hypoxia and oxidative stress are the main conditions responsible for triggering brain damage, since the inadequate oxygen supply compromises the maintenance of different metabolic pathways and, as a result, increased synthesis of ROS [109,110].

According to experimental data, maternal treatment with melatonin after an episode of ischemia/placental reperfusion contributed to reverse the changes in the mitochondrial respiratory activity in the brain and placenta of rats. Melatonin is quickly transferred to both organs after its administration and, due to the increase in the activity of the

antioxidant enzymes, it prevents lipid peroxidation, changes in the respiratory chain, and impaired ATP synthesis [97,109–111]; moreover, lower variation in offspring weight is observed [97,110].

In infections, for instance, melatonin also attenuates the damage caused by bacterial toxins. Experimental studies demonstrated that both groups, the pregnant rats treated with melatonin after lipopolysaccharide administration, and those that received melatonin doses before and after the toxin, showed a significant reduction in the number of intrauterine deaths, improved cephalocaudal growth and fetal weight, bone growth retardation recovering ossification centers (e.g.: supraoccipital) in fetuses, as well as attenuation in lipid peroxidation and glutathione depletion in the maternal liver [115], thus confirming the beneficial action of melatonin against OS.

5.2. Preeclampsia

Even though there are several gaps regarding the etiopathogenesis of PE, it is known that the dysfunction during the process of remodeling of the uterine arteries appears to be triggered mainly by an imbalance between the synthesis of angiogenic and antiangiogenic factors. Consequently, hypertension, OS, and changes in maternal-fetal metabolism are increased [116].

Experimental studies suggest that melatonin may exert a protective role in the control of systemic arterial hypertension in preeclamsia, since it regulates the expression of components of the renin-angiotensin system, modulates the expression of class I histone diacetylase enzyme (highly expressed in precursor nephrons), then becoming able to contribute to the restoration of the amount of nephrons [117].

In addition, melatonin is believed to be a powerful antioxidant in placental hypoxia. Experimental studies argue that oxygen depletion leads to a reduction in the mitochondrial respiratory control ratio and in the rate of adenosine diphosphate-5 level/oxygen consumption, and also increases lipid oxidation in placental cells [111,113]. Melatonin, in turn, prevents these mitochondrial dysfunctions by inhibiting the synthesis of ROS and of other OS markers (e.g. 8-OHdG, MDA, and ref-1) in the placenta [97,110].

5.3. Gestational diabetes

Gestacional Diabetes Mellitus (GDM) is a complication caused by the increase of the blood glucose levels during pregnancy. Maternal hyperglycemia, which is an important teratogenic factor, is responsible for major congenital malformations, intense ROS formation and lipid peroxidation through protein glycosylation and self-oxidation of glucose [118,119].

Experimental research showed that rats with GDM presented an increae in blood glucose levels, increased serum level of sMDA, impaired action of catalase, SOD and glutathione peroxidase, as well as reduced maternal weight and number of viable fetuses. However, the rats treated with melatonin had a significant decrease in serum MDA concentrations, increased antioxidant activity, and consequently, decreased lipid peroxidation [115,116]. So, confirming that melatonin is able to minimize the dysfunctions triggered by GDM.

5.4. Maternal malnutrition

Maternal malnutrition may have significant effects on the offspring. Literature shows impaired folliculogenesis, since there are fewer ovarian follicles and increased OS in the ovary, which promotes granulosa cell apoptosis and subsequently, follicle atresia [120]. IUGR is also associated with the consequences of malnutrition in pregnancy [95,117,118].

According to experimental studies, the offspring weight of calorie-restricted mothers during pregnancy only and during pregnancy *and* lactation was lower not only after birth, but also later in life. By quantifying the mRNA of spliced and unspliced X-box binding protein 1, PIK3CA, and NFκB, a progression of OS was observed, as well as severe follicular apoptosis, and reduced expression of Beclin-1 (a component of the autophagy pathway), of LC3 (an autophagosome marker), of VEGF, of VEGFR2 and of vessel density in the ovaries of both groups' offspring [120].

The changes in the inflammatory response were also significant since there was higher mRNA expression of IL-6 and lower expression of IL-1β (which plays a role in the suppression of apoptosis) in the offspring. In contrast, the treatment with melatonin contributes to a lower mRNA expression of the HIOMT enzyme [120]. Other studies have even emphasized the increased expression of Mn-SOD and catalase in the placenta, as well as a decrease in the expression of xanthine oxidase in placentas of undernourished mothers after treatment [107].

In IUGR, dietary supplementation with melatonin led to an increase of up to 20% in umbilical artery blood flow, 9% in fetal biparietal distance, 12% in length, and 19% in the kidney width, as well as an increase in mean placental diameter, in abdominal circumference, and in the weight of fetuses whose mothers received an adequate diet in relation to those subjected to a restricted diet [8].

5.5. Maternal stress

Different comorbidities are responsible for triggering OS during pregnancy, such as hypertension, smoking, DM, dyslipidemias, inborn errors of metabolism, among others.

Hyperphenylalaninemia, for instance, favors the accumulation of toxic products of metabolism and, hence, an increased synthesis of ROS, lipid peroxidation, and DNA damage. Increased syntheses of MDA and 4-HNE were observed in the cerebral cortex and in the liver, thus confirming the presence of OS in the organs. Nonetheless, the treatment with melatonin and vitamins C or E prevents the accumulation of lipid peroxidation-derived products [121].

Toxic cigarette substances such as nicotine can cross the placental barrier and reach fetal circulation, causing changes during embryonic development. An experimental study found that serum and tissue levels of MDA were particularly higher in rats that received small and high doses of nicotine than in the control group; furthermore, fetal myocyte injury was also significantly higher in both cases. Similarly, NO levels were significantly reduced in the animals that received a small dose of nicotine associated with melatonin, in comparison with those that received only nicotine. Regarding the levels of glutathione peroxidase and SOD, they were higher in the animals that were given small and high doses of nicotine and melatonin in comparison with those that only received nicotine [122].

Maternal hyperthermia may cause miscarriages in the pre-implantation period due to OS. Studies show that mothers exposed to hyperthermia presented higher levels of thiobarbituric acid-reactive substances, which were related to lipid peroxidation. Furthermore, the percentages of embryos that remained a longer period in a single 2-cell stage, then needing a longer time to reach the morula stage were significantly higher in this group. Nevertheless, these disorders were less severe in the rats treated with melatonin, due to the increased maternal antioxidant activity [123].

The use of melatonin has also showed positive results in intrahepatic cholestasis disorders of pregnancy. The changes associated with hepatocyte injury (increase in the level of bilirubin, in the activity of alkaline phosphatase, in GGT, and in transaminase enzymes, and decrease in the level of albumin); the action of pro-apoptotic enzymes caspase-3 and Bax-α: as well as the increased lipid peroxidation in maternal and fetal liver and in the placenta were minimized by the action of melatonin, which also contributed to the increased expression of the mRNA of vitamin C transporters in these organs [124].

6. Protective role of melatonin in neonatal diseases

6.1. Perinatal brain injury

Encephalopathies caused by perinatal ischemic hypoxia, such as learning and attention deficits, speech disorders, hyperactivity, and cerebral palsy [123,124] are the leading causes of neurological damage in full-term newborns. Since brain stem cells are highly sensitive to oxygen changes, it is admitted that it may trigger serious injuries in neuronal cells in different cerebral regions [125].

In this type of injury, experimental studies showed a reduction of 28% in encephalic weight [125], accompanied by a reduction of 44.9% in the hemispheres, and of 59.8% in the cerebral cortex [126]; as well as intense synthesis of biomarkers of hypoxia, areas of ischemic necrosis, changes in the morphology of neurons (e.g.: swelling, cell deformation, cytoplasm elongation and condensation), astrogliosis, lower expression of myelin basic protein,significant reduction in the neuron membrane potential and intense ROS synthesis [125], as well as fewer number of cells in different injured brain areas [127] in the evaluated offspring.

Sciatic nerve transection of newborn mice also results in cell death of the neurons whose axons were sectioned. An experiment showed severe astrogliosis (increase in cell volume, and in the volume and number of processes) in the damaged area, as well as increased synthesis of NOS by neurons [128].

In both cases, the treatment with melatonin inhibited brain weight change, promoted significant increase and maintenance of the myelin basic protein expression [125], and reduced the changes in astrocytes and ROS synthesis [125,128]. Moreover, the administration of small doses of this antioxidant reduced motor neuron damage [125,128]. Other studies confirm that melatonin plays an important beneficial role in injuries caused by ischemia/reperfusion by reducing the synthesis of MDA and the concentration of thiobarbituric acid and also by increasing the activity of antioxidant enzymes (e.g.: SOD and catalase), and ATP production [103,127].

In severe inflammatory processes, such as sepsis, melatonin promotes survival by up to 60%, attenuates cerebral edema by increasing blood-brain barrier integrity; reduces apoptosis through the increased expression of Bcl-2 and silent information regulator 1 (a protein which has a neuroprotective effect via deacetylation and suppression of p53e NF-kB), and through the lower expression of FoxO1, p53, NF-κB and Bax; attenuates the inflammatory response resulting from the decreased synthesis of TNF-α and IL-1β, and also reduces OS, favoring the increase of serum levels of SOD and catalase, and the decrease of MDA synthesis [129]. Therefore, it can be noted that melatonin is able to reduce the neurodegeneration caused by hypoxia and inflammation in the perinatal period [126], since it plays a neuroprotective role.

6.2. Chronic lung disease

Bronchopulmonary dysplasia is considered the most common lung disease among newborns. Oxygen toxicity, premature birth, impaired surfactant synthesis and perinatal infection appear to be some of the factors triggering this pulmonary dysfunction. However, hyperoxia is identified as the main mechanism of injury, since the intense concentration of O_2 causes the synthesis of ROS, the reduced antioxidant activity and, finally, OS and parenchymal damage [129,130].

Experimental studies report that the exposure to hyperoxia results in increased synthesis of MDA, NO, lipid peroxidation, and myeloperoxidase activity (an inflammatory cell marker, especially of neutrophil influx). Furthermore, the presence of a small inflammatory infiltrate in the alveolar lumen and septum, as well as morphological changes such as increased alveolar space, thickening of the alveolar septum, reduction in the number of alveoli, increased alveolar diameter, and increased number of cells and interstitial fibroblasts [129,130] must be highlighted. Therefore, melatonin contributes to the increase in the activity of glutathione peroxidase, catalase and SOD, preventing the changes associated with OS [129,130]. The alveoli have preserved dimensions, and a significant reduction of interstitial fibrosis is observed [129,130].

6.3. Necrotizing enterocolitis (NEC)

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in newborns, requiring surgical intervention. Although its etiopathogenesis is unknown, it is believed to be associated with the loss of the intestinal barrier function, lack of digestion and gastrointestinal motility, impaired bowel movement, feeding with formula milk, prematurity, colonization by pathologic bacteria, immature immune system and antioxidant defense, hypoxic/ischemic injury, and increased synthesis of specific factors (e.g.: IL-1β, IL-8, IL-10, IL-12, lipopolysaccharides, NO and ROS) [132,133].

According to a review, the stressor agent triggers the secretion of pro-inflammatory mediators (e.g.: PAF) and cytokines (e.g.: TNF-α, IL-6), responsible for polymorphonuclear recruitment and consequent increased synthesis of ROS, lipid peroxidation and intestinal hypoxic/ischemic injury, which may culminate in the rupture of the intestinal barrier and NEC worsening. Hence, intense OS promotes the activation of extracellular signal-regulated kinase1 and 2, and phosphoinositide 3-kinase [both acting on cellular survival by signalingantiapoptotic pathways], as well as c-Jun N-terminal kinases (JNK) 1 and 2, and p38 MAPK [both associated with cellular death]; in addition it compromises the antioxidant response due to higher ROS concentration or limited action of the antioxidant enzymes particularly among premature infants [130].

Literature suggests that the offspring with NEC present lower weight, severe clinical signs (e.g.: severe necrosis, intestinal pneumatosis, loss of tissue integrity and edema), and high synthesis of OS markers (MDA, protein carbonyl, and NO), which demonstrate increased lipid peroxidation, protein oxidation, and production of peroxynitrite. Additionally, the serum levels of TNF-α and IL-1β are increased [131].

The administration of melatonin, in turn, minimizes weight change, and reduces lipopolysaccharide-induced motility disturbances, lipid peroxidation, ROS, MAPK38 activation, inducible nitric oxide synthases transcription and expression, nitrite production in the intestinal tissue, and the expression of proinflammatory mediators [130,131]. On the other hand, it significantly increases the activity of the antioxidant enzymes SOD and glutathione peroxidase, thus reducing the disorders caused by the synthesis of ROS. Finally, milder clinical signs are observed [131]. When associated with prostaglandin E1 (which plays a cytoprotective role in the intestine), the antioxidant activity and the decreased synthesis of MDA appear to be potentiated, however, macroscopic changes, intestinal damage, and apoptosis signaling pathways are significantly attenuated [132].

Finally, Guven et al. (2011) demonstrate that the administration of 10 mg/kg of melatonin daily promoted significant reduction of the proinflammatory cytokines synthesis and increased the activity of antioxidant enzymes in the offspring with NEC, indicating that this hormone has important properties in neonatal NEC treatment [130,131].

6.4. Retinopathy of prematurity (ROP)

Retinopathy of prematurity (ROP) is a disorder that affects approximately 10% of premature infants, and is characterized by neoangiogenesis, hemorrhage, and formation of reticular fibers in the retina. This etiopathogenesis is not yet fully acknowledged. However, immature retinal vascularization, sepsis, hyperoxia, and heart disease induce tissue damage, episodes of hypoxia-ischemia and, consequently, the synthesis of ROS [133–135].

Therefore, OS triggers the death of ganglion cells, edema of Müller cells, vascular injury, changes in the retinal pigment epithelium, and

synthesis of inflammatory mediators. According to experimental studies, there is a higher mRNA expression of TNF- α, IL-1β, and MCP-1, as well as of their respective receptors in the nerve fiber layer, in retinal ganglion cells, blood vessels, and hyaloid vessels after injury due to hypoxia; furthermore, a significant increase in the activity of caspase-3 in the ganglion cells was also observed [135,136]. In addition, the synthesis of MDA is increased and in result, there is increased lipid peroxidation, increased mRNA expression of Filt-1 and Filk-1, and reduction in glutathione peroxidase concentration [135].

Even after conventional therapies, i.e., surgery and laser application, the loss of visual acuity is noted, and depending on the severity of the lesions, vision loss can be observed [133]. However, the treatment with melatonin favors the antioxidant activity in the retina, reduces the synthesis of ROS and consequently, minimizes lipid peroxidation, the synthesis of pro-inflammatory cytokines, the expression of VEGF receptors, the activation of apoptotic pathways, and cell damage in ROP [133,135].

6.5. Surgical neonates

The acute phase response triggered by surgical trauma leads to the synthesis of diverse inflammatory mediators and free radicals. As newborns have an immature antioxidant system, they are more susceptible to the action of ROS, tissue damage, and OS [137,138].

A study demonstrated higher serum levels of IL-6, IL-8, TNF-α and NO after 72 h of postoperative period. In abdominal surgeries accompanied by respiratory distress syndrome, these parameters remained significantly altered for up to seven days. On the other hand, the administration of melatonin solution (2 h/intravenously) in newborns reduced not only the levels of inflammatory mediators, but also of lymphocyte, neutrophil and C-reactive protein count; and, in addition, platelet count increased after 24 h [136].

Other studies also show that melatonin plays an important role in the reduction of MDA synthesis, lipid peroxidation, and cell damage, through increased expression and activity of antioxidant enzymes such as SOD, catalase and glutathione peroxidase in different surgical procedures [125,131,135].

Moreover, melatonin appears to have properties of interest in an anesthetic adjuvant. A review article highlights that, in experimental models, melatonin and its analogs (2-bromomelatonin and phenylmelatonin) have anesthetic property associated with potent antinociceptive effects (*e.g.:* rapid loss of righting reflex). However, its antinociceptive action was considerably less potent than propofol or thiopental, since melatonin was not effective in abolishing the response to tail clamping [137].

In humans, a study with 92 children undergoing elective surgery evaluated the possible effects of melatonin premedication on the infusion of propofol, in comparison with midazolam. Findings highlight that melatonin premedication significantly enhanced the effects of propofol, resulting in significantly lower administered drug doses; since the melatonin group [children that receive 0.5 mg/kg (max 20 mg) oral melatonin premedication] received a mean dose of 2.08 ± 0.59 mg/kg propofol, while the mean dose was 2.85 ± 1.43 mg/kg propofol in the midazolam group [children that receive 0.5 mg/kg (max 20 mg) oral midazolam premedication] before induction anaesthesia [138], reinforcing its use as a promising anesthetic adjuvant.

Melatonin is also recommended for analgesia among neonates, since they are more susceptible to pain and to the exposure to painful invasive procedures than older infants. Improvement of sleep quality, and the reduction of anxiety and pain [137] are among its main properties. Although its mechanisms of action are not fully understood, it is believed that melatonin increases β-endorphin secretion by the pituitary gland; being the naloxone (an opioid-receptor antagonist), responsible for preventing β-endorphin binding to the opioid receptors and antagonizing melatonin nociceptive effects [137,139]. Other receptors seem to be involved in different signaling pathways: benzodiazepinergic, muscarinic, nicotinic, serotonergic, α1-adrenergic, α2-adrenergic, and MT1/MT2 melatonergic receptors (in central nervous system) [137].

It is known that, at molecular and cellular levels, melatonin can modulate its functions through opioids and GABA- receptors by reducing intracellular concentration of cAMP, since opiate receptor agonists and melatonin membrane receptors reduce the concentration of this intracellular messenger [137,140]. Another mechanism associated with analgesia would be the inhibition of NO synthesis, decreasing both NF-κB, the expression of cyclooxygenase and prostaglandins and the polymorphonuclear recruitment to the inflammation site [137,141].

A study on the analgesic activity of melatonin during endotracheal intubation and its inflammatory responses in 60 premature infants (30 infants treated with melatonin plus common sedation and analgesia and 30 infants treated with only common sedation and analgesia) showed a significant reduction in pain score (at 12, 24, 48 and 72 h), and in pro-inflammatory and anti-inflammatory cytokines levels [IL-6, IL-8, IL-10 and IL-12] (at 24, 48 and 72 h) in the group treated with melatonin during intubation and mechanical ventilation, in comparison with the group treated with common sedation and analgesia. This study suggests the use of melatonin as an adjunct analgesic therapy during procedural pain, especially when an inflammatory component is involved [140].

6.6. Cardiomyopathy

Dysfunctions that cause hypoxic-ischemic damage present cardiovascular effects during the perinatal period. Among them we can cite bradycardia by sensitivity of the carotid chemoreceptors, as well as peripheral vasoconstriction by chemoreceptors, and synthesis of constricting substances (e.g.: catecholamines) in the blood [142].

Studies show that in acute hypoxia, melatonin reduces the increase in blood pressure, femoral vascular resistance, serum levels of glucose and lactate, as well as catecholamine concentrations [142]. This indoleamine also favors the increase of coronary blood flow and the response of vascular endothelium to bradykinin; stabilizes ventricular contractility, reduces the infarction area, concomitantly to the myocardial ischemia-reperfusion injury and the thickening of the vascular wall; and it also leads to a lower expression of type-II and type-III collagen [143,144].

The use of melatonin to prevent ischemic damages also minimizes myocardial changes in myocardiocytes, since there is an increased SOD activity in this organelle and, thus, reduced syntheses of MDA and H_2O_2. Cardiomyocytes present a higher expression of Janus kinase 2, and of the signal transducer and activator of transcription 3 (both involved in cardioprotection against ischemic damage and reduction of OS), and lower expressions of Bcl2, Bax and cytosolic cytochrome c [143]. Therefore, the deleterious effects of OS in cardiac dysfunction are minimized.

7. Conclusion

Oxidative stress is associated with the etiopathogenesis of different gestational changes, such as recurrent miscarriages, PE, IUGR and fetal death. The exacerbated consumption of the antioxidant enzymes SOD, catalase and glutathione peroxidase, and the increased synthesis of ROS, such as $O^{\cdot-}$, $ONOO^-$ and $OH^{\cdot}$, result in the peroxidation of phospholipids and endothelial dysfunction, impaired trophoblast invasion, impaired decidualization, and remodeling of maternal spiral arteries.

Therefore, not only does the state of hypoxia triggered by poor placentation favor the increase of ROS synthesis, but it harms the placental membranes during fetal development. Furthermore, it causes other disorders such as bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, renal failure, neuronal injury, and intraventricular hemorrhage in postnatal life.

Melatonin has notable physiological functions, such as the stimulation of progesterone synthesis and maintenance of pregnancy. Thus, it is postulated that melatonin induces specific biochemical responses that

regulate cell proliferation in the fetus, and that its antioxidant action favors the bioavailability of NO, and consequently of placental perfusion, as well as fetus nutrition and oxygenation, since changes in the synthesis of maternal melatonin are observed in different gestational changes.

Therefore, the therapeutic action of melatonin is the subject of major studies aiming to minimize or prevent different injuries that affect this pediatric age group, such as IUGR, encephalopathy, chronic lung disease, retinopathy of prematurity and necrotizing enterocolitis. The promising results produced by the antioxidant and anti-inflammatory properties of this hormone, indicate that it is an important therapy for the clinical treatment of these entities.

Acknowledgements

We thank Conselho Nacional de Desenvolvimento Cientifico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), and Fundação de Ensino e Pesquisa de Uberaba (FUNEPU) for financial support.

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