Review

Maternal Melatonin Deficiency Leads to Endocrine Pathologies in Children in Early Ontogenesis

Dmitry O. Ivanov [1], Inna I. Evsyukova [2], Ekaterina S. Mironova [3,4,*], Victoria O. Polyakova [1],
Igor M. Kvetnoy [4,5] and Ruslan A. Nasyrov [1]

1   Department of Neonatology, Saint-Petersburg State Pediatric Medical University, Litovskaya Ulitsa, 2,
    St. Petersburg 194100, Russia; doivanov@yandex.ru (D.O.I.); vopol@yandex.ru (V.O.P.);
    rrmd99@mail.ru (R.A.N.)
2   Ott Research Institute of Obstetrics, Gynecology and Reproductology, Mendeleyevskaya Liniya, 3,
    St. Petersburg 199034, Russia; eevs@yandex.ru
3   Saint Petersburg Institute of Bioregulation and Gerontology, Dynamo Ave., 3, St. Petersburg 197110, Russia
4   Saint-Petersburg Research Institute of Phthisiopulmonology, Lygovsky Ave., 2-4, St. Petersburg 191036,
    Russia; igor.kvetnoy@yandex.ru
5   Department of Pathology, Saint-Petersburg State University, University Embankment, 7/9,
    St. Petersburg 199034, Russia
*   Correspondence: katrine1994@mail.ru

Abstract: The review summarizes the results of experimental and clinical studies aimed at elucidating the causes and pathophysiological mechanisms of the development of endocrine pathology in children. The modern data on the role of epigenetic influences in the early ontogenesis of unfavorable factors that violate the patterns of the formation of regulatory mechanisms during periods of critical development of fetal organs and systems and contribute to the delayed development of pathological conditions are considered. The mechanisms of the participation of melatonin in the regulation of metabolic processes and the key role of maternal melatonin in the formation of the circadian system of regulation in the fetus and in the protection of the genetic program of its morphofunctional development during pregnancy complications are presented. Melatonin, by controlling DNA methylation and histone modification, prevents changes in gene expression that are directly related to the programming of endocrine pathology in offspring. Deficiency and absence of the circadian rhythm of maternal melatonin underlies violations of the genetic program for the development of hormonal and metabolic regulatory mechanisms of the functional systems of the child, which determines the programming and implementation of endocrine pathology in early ontogenesis, contributing to its development in later life. The significance of this factor in the pathophysiological mechanisms of endocrine disorders determines a new approach to risk assessment and timely prevention of offspring diseases even at the stage of family planning.

Keywords: melatonin; endocrine pathology; children; early ontogenesis; family planning

1. Introduction

In recent decades, we have seen an increase in endocrine disorders among children and adolescents, which predetermines the annual growth of incidence rates of serious chronic diseases among adults [1]. Thus, the number of obese children and adolescents over the last 40 years has increased from 11 million to 124 million, and there are 216 million overweight children [2]. This epidemic has mostly spread across developed countries in Europe and North America, yet there has been data showing a substantial growth of this pathology in developing countries [3,4]. Over the last decade, in Europe, the overweight (including obesity) rate in boys has peaked to 43% [5]. The metabolic syndrome occurs in 38% and 49.7% of overweight and obese children and adolescents, respectively [6]. By using eight criteria for diagnosing this metabolic syndrome, the authors note its incidence rate

in the U.S. increasing from 6% to 39% among children of 4 to 16 years old [7] and up to 40% among people over 60 years old [8]. It is expected that by 2025 the metabolic syndrome will be diagnosed in 40% of the population in developing countries [9]. There is a concern about an early onset of type 2 diabetes in children, with rapid development of diabetic complications and cardiovascular pathologies [10–12]. Special attention should be given to increasing numbers of macrosomic newborns and the development of visceral obesity in children during the first months of life [13–16]. It is already in early infancy that various functional system disorders (gastrointestinal, cardiovascular, neural, etc.) and type 2 diabetes are diagnosed in such children [17–20]. Therefore, researchers are focused on studying the causes and pathogenic mechanisms of endocrine pathology development in children in early ontogenesis.

2. Causes of Postnatal Endocrine Pathologies in Offspring

Some researchers consider the problem of obesity in view of genetic predisposition to this disease [21]. Thus, they have identified eight monogenous and 50 syndromal forms of obesity, and the 12th version of the Human Obesity Gene Map contains over 600 genetic markers associated with the obesity phenotype. However, while a population's genetic load remains the same, the obesity rates are rising [22].

A high probability of postnatal endocrine pathology development in offspring is currently associated with the epigenetic impact of adverse factors in early ontogenesis, which disrupt the formation of regulatory mechanisms in periods of critical development of the fetus's organs and systems and contribute to the delayed development of pathological states, which take place in the case of maternal obesity and diabetes during pregnancy [23–25].

Researchers consider the effects of chronic bacterial and viral infections during pregnancy and factors such as stress, glucocorticoid therapy, eating habits, lifestyle and social and economic factors [26–30]. Special attention has been drawn to studying adverse consequences of gestational diabetes mellitus which complicates the course of pregnancy in overweight and obese women [31,32], with their share among women of reproductive age having increased to 70% in the USA and to 20–27% in Europe [33].

Based on clinical and experimental studies, various hypotheses have been proposed to explain the aetiopathogenesis of visceral obesity in the first months of life and its consequences both in overweight and underweight or premature newborns [34,35]. Some researchers argue that maternal undernutrition and somatic comorbidity leading to chronic placental insufficiency form the so-called fetal "thrifty phenotype" ("thrifty phenotype hypothesis") which is responsible for subsequent building a strategy of survival, which is then realized through metabolic disorders and obesity development, type 2 diabetes and arterial hypertension [36].

It has been observed that the maternal low-protein diet in pregnancy results in offspring with expressed changes in the pancreas gland, a higher apoptosis rate and lower β-cell proliferation, a disrupted vascularization of Langerhans islets and a lower insulin content, which then leads to the development of type 2 diabetes [37,38]. Other hypotheses address the role of diabetes, metabolic syndrome, obesity, excessive nutrition and a high-fatty diet during pregnancy in the development of hyperglycemia, hyperinsulinemia, hyperleptinemia and increased cortisol levels in the fetus followed by a metabolic response modulation of hypothalamic neurons. Newborn infants had macrosomia, which was later followed by the development of obesity [39–42].

It is believed that excessive protein consumption in the early postnatal period ("Early Protein Hypothesis") leads to a higher concentration of insulinogenic amino acids in the blood plasma which stimulate the production of insulin-like growth factor and insulin, which results in an excessive accumulation of adipose tissue and raises the risk of obesity. The absence of breastfeeding and higher protein levels in artificial feeding are viewed as risk factors for obesity development [43]. In recent decades, researchers' attention has been drawn to studying the role of intestinal microbiota in the development of obesity.

It has been found that in obese pregnant women the content of intestinal microbiota shifts to more bacteria with anti-inflammatory properties (obesity is known to be followed by chronic inflammation). Intestinal microbiota imbalance leads to a higher concentration of short-chain fatty acids which act as signaling molecules and stimulate a cascade of reactions resulting in increased lipogenesis and stored fat [44,45]. Another mechanism is a lower expression of protein (a lipoprotein lipase inhibitor) in the case of dysbiosis.

This results in higher lipase activity, fatty acid uptake and storage in adipose tissue and muscles, which leads to increased stored fat in the organism [46,47]. Some studies have investigated the mechanism that consists of increased permeability of the intestinal barrier for gut microbiota endotoxin which binds with Toll-like receptors and triggers a cascade of reactions, followed by higher production of anti-inflammatory cytokines (TNF-α and IL-6) involved in the development of obesity and insulin resistance [48,49].

3. Melatonin and Regulation of Metabolic Processes

The diversity of etiological factors leading to obesity has drawn researchers' attention to finding a key element that triggers this process. Numerous experimental and clinical studies have established the primary role of disruption of circadian rhythms of metabolic processes in the development of obesity in adults [50–52].

The integration between a cyclic environment and the circadian distribution of physiological and behavioral processes is provided by melatonin whose production circadian rhythms control all endogenous rhythms at tissue, cell and subcell levels [53–55]. This provides synchronization of metabolic processes, a capability to react to endogenous and exogenous impacts and the maintenance of stability and health of the organism [56].

Melatonin is synthesized in the pineal gland whose endocrine function is physiologically controlled by light. The photic information from retinal ganglion cells passes through the retinohypothalamic tract to the suprachiasmatic nuclei (SCN) of the hypothalamus, which are the circadian-rhythm generators or the biological clock. From there, the signals go to the superior cervical ganglia and then reach the pineal gland via sympathetic noradrenergic nerves. The activation of the beta-adrenergic receptors of pinealocytes triggers the synthesis of melatonin from serotonin with N-acetyltransferase (NAT) and hydroxyindole O-methyltransferase (HIOMT) enzymes.

Light suppresses melatonin production and secretion, and therefore its maximum level in human blood is observed at night and its minimum during the daytime [57–59]. Melatonin is not only synthesized in the pineal gland. Extrapineal melatonin is present in almost all organs: the gastrointestinal tract, liver, kidney, adrenal gland, heart, thymus, genital gland, placenta and uterus, as well as in platelets, eosinophiles, leukocytes and other immune system cells [60,61]. Melatonin synthesis in the mitochondria of eukaryotes suggests that melatonin protects cellular organelles against oxidative injury and maintains their physiological function [62].

Melatonin, through passive diffusion from pineal cells, passes to the cerebrospinal fluid and blood flow, thereby triggering chronobiological effects through binding with its receptors in cell membranes of various tissues. The circulating melatonin level reaches its peak at night-time (2–4 a.m.) and its minimum in the morning, with its values in the blood serum during night hours being 5–10 times higher.

Being hydrophilic, the melatonin molecule at the same time is highly lipophilic and therefore can easily pass through the blood-brain and placental barriers, reaching capillaries where 70% of melatonin binds to albumin. Melatonin's half-life is about 30 to 45 min. Melatonin is metabolized in the liver and kidney, as well as in tissues (brain and intestine) where the enzymes involved in the process have been found [63]. The metabolism end-products are 6-sulfatoxymelatonin and acetylsalicylic acid.

Melatonin has a regulating effect through binding to receptors. Two types of membrane receptors (MT1 and MT2) and their localization in chromosomes (4q35 and 11q21-22), as well as nuclear receptors (RORα), have been identified [64]. It is thought through these receptors that melatonin triggers clock gene expression [65].

Circadian genes (*Clock*/*Bmal*) participate in the regulation of glucose and triglycerides levels at daytime [66], and *Bmal* regulates the synthesis of lipids and adipogenesis [67]. Melatonin receptors have been found in hypothalamic suprachiasmatic nuclei, cerebellum, retina, spleen, liver, pancreas, genital and mammary glands, uterus, thymus, gastrointestinal tract, thrombocytes, lymphocytes and adipose tissue [68].

Melatonin is also known as a key regulator of the carbohydrate and adipose metabolism. Its insulin-like hypoglycaemic, anabolic and anticholesterol effects have been demonstrated [69,70]. Numerous experimental molecular studies have demonstrated the mechanisms of functional relationships between melatonin, insulin and glucagon [71,72]. Furthermore, in the pancreas, as well as in other tissues, there are autonomous circadian genes (*Bmal*, *Clock*, *Per1*, *Cry1*), through which epiphyseal melatonin's circadian rhythm provides a synchronizing effect on β- and α-cells [73,74]. Higher melatonin production and lower insulin secretion are observed at night, which is reversed at daytime [75,76].

The circadian amplitude of melatonin levels goes down in the case of night work and an active lifestyle, as well as in sleep disruptions, which leads to hyperinsulinemia, the development of insulin resistance and hyperleptinemia, a set of symptoms which are characteristic for type 2 diabetes [77–80]. The development of these pathological conditions related to low melatonin production and absence of its circadian rhythm is associated with distorted regulation of insulin synthesis and secretion by pancreas β-cells and its binding to target cell membrane receptors, as well as with suppression of GLUT4 and protein content reduction.

An experiment has shown that elimination of the pineal gland in insulin-sensitive tissues (white and brown adipose tissue and skeletal and cardiac muscles) leads to a dramatic drop in GLUT4 mRNA and microsomal and membrane proteins. In addition, in the absence of melatonin, the function of insulin receptors in adipocytes is disrupted, which sharply reduces the uptake of glucose by these cells. The identified effects of pinealectomy disappear after melatonin therapy [81].

In adipose tissue, melatonin regulates the differentiation of adipocytes and the expression of clock genes (*Clock*, *Per1*) there, increasing the expression of their mRNA at night [82]. Furthermore, melatonin entrains the circadian rhythms of lipogenesis, lipolysis and fatty acid and glucose uptake, thereby regulating lipidemia and glycemia, while at the same time supporting the circadian metabolism in muscles, liver and pancreas [73,83]. It is at night that the organism spends significant amounts of energy on supporting its functional systems' vital activities [71].

It has been proved that long-time staying under continuous artificial illumination (which is characteristic for human activity today) suppresses the physiological rhythm of the pineal gland, which results in distorted interactions between melatonin and its receptors, leading to the development of insulin resistance and then to abdominal obesity, arterial hypertension and lipid and carbohydrate metabolism disorder [84–86].

4. The Role of Maternal Melatonin in the Formation of Circadian System in the Fetus

It has been shown that during pregnancy the circadian oscillations of melatonin levels substantially increase, reaching their peak before birth [87]. At the same time, the extrapineal melatonin production increases, especially in the placenta, which ensures the morphological development and stability of placental function and determines optimal adaptation to pregnancy and preparation for childbirth [88]. Additionally, in the placenta, since the earliest stages of pregnancy, there appears to be receptors of melatonin (MT1 and MT2) that enable the cyclic influence of maternal epiphyseal melatonin which activates and synchronizes the rhythmic expression of clock genes in trophoblast cells and endothelial tissue [87]. The circadian rhythm of clock gene activity in the placenta, coinciding with similar clock gene expression in the fetus's liver, determines the development of fetal adaptive metabolic processes and normal growth [89,90].

Maternal epiphyseal melatonin plays an important role in the formation of circadian rhythms of clock genes involved in the regulation of metabolic processes and vital activities

of fetal functional systems. The cyclic variations of melatonin levels coincide in maternal blood and fetal circulation [91]. The rhythmic expression of *Per1*, *Per2*, *Cry1* and *Bmal1* genes is clearly identifiable in fetal hypothalamic suprachiasmatic nuclei already in the middle of gestation. Even before birth, mRNA rhythms are identified there for vasopressin.

Furthermore, nerve fibers of the retinohypothalamic tract are also well identifiable during the second half of gestation [92–94]. It is assumed that the circadian regulation system starts functioning in the fetus with the appearance of receptors to melatonin being transferred from the mother since the earliest stages of pregnancy, providing information on the time of day [84,95,96]. A study of clock genes in a primate fetus demonstrated their circadian expression of varying degrees in the suprachiasmatic nuclei, adrenal gland, thyroid gland, brown adipose tissue and pineal gland, pointing to the role of maternal melatonin circadian signaling in the regulation of cortisol production by the fetal adrenal gland [97].

The circadian rhythm of melatonin secretion in pregnant rats was suppressed by exposure to constant light, which disrupted the clock gene rhythmic expression in all organs of the fetus, and it was reversed only after circadian injections of maternal melatonin [98]. The absence of melatonin secretion circadian rhythms in pregnant rats led to disruption of rhythmic clock gene expression in all sections of the gastrointestinal tract, liver and pancreas [99]. It has been shown that maternal melatonin synchronizes peripheral circadian oscillators in these organs and coordinates their function with clock gene rhythms of suprachiasmatic nuclei and other tissues, including the adenohypophysis and adrenal gland [100,101].

Circadian rhythms of clock gene expression in the fetal large intestine can be determined already by week 33 of intrauterine growth [102]. Furthermore, throughout the antenatal period, maternal melatonin is a key molecule that directs and coordinates the genetic process of developing relationships between clock genes of the infant's organism and forming microbiota [103].

The melatonin synthesis in the fetal pineal gland is controlled by maternal melatonin during the fetus antenatal life [104], thus ensuring the genetic process of morphological and functional development of SCN and epiphysis [105,106]. It has been found that the melatonin rhythm in the maternal blood plasma triggers the fetal circadian system which, in turn, informs other tissues through corticosterone rhythmic signaling. Already in the last 10 weeks of pregnancy, fetal circadian rhythms of the cardiac rate and temperature are synchronized with the melatonin and cortisol content in maternal blood [107]. In absence of the melatonin circadian rhythm in the maternal blood plasma in the second half of pregnancy, there is intrauterine growth retardation, accompanied by delayed development of the circadian activity of the central rhythm driver, hypothalamic suprachiasmatic nuclei [59], changing the clock gene expression levels and disrupting the corticosterone production rhythm [108].

Based on results of experimental and clinical studies, a hypothesis has been proposed, according to which during antenatal life the fetal suprachiasmatic nuclei and organs are peripheral circadian oscillators whose rhythmic activity is triggered by and depends on the state of circadian organization of vital activities in the mother and its primary messenger of biorhythms generated by suprachiasmatic nuclei, i.e., melatonin. This ensures the postnatal integration of endogenous biorhythms of the baby's functional systems into the adult-like circadian system which is regulated by its own suprachiasmatic nuclei in dependence to circadian changes in environment illumination [109].

In normal conditions, the formation of the circadian rhythm of epiphyseal melatonin production goes on rapidly in the first days and weeks of life, while the maternal impact on this process is exercised through breastfeeding as maternal milk contains high levels of melatonin with circadian oscillations [110]. The content of fat and the energy potential of breast milk are dependent on the circadian rhythms of melatonin production [111,112]. At night, breast milk has the highest content of components that, along with other effects, contribute to circadian-rhythm formation. For example, tryptophan and omega-3

polyunsaturated fatty acids inhibit monoamine oxidase and thereby increase the quantity of serotonin (a melatonin precursor) [113,114].

Therefore, in the case of breastfeeding, by the end of the perinatal period, the amount and daily rhythm of melatonin production in children correspond to that in adults [115]. The absence of circadian melatonin production during pregnancy impairs the genetic development of the rhythmic activity of suprachiasmatic nuclei and melatonin production in the fetal pineal gland, which leads to dysregulation of biochemical processes in the organism before and after birth [116,117].

Experimental studies have shown that, in those situations, there is also low epiphyseal melatonin production in offspring, and its circadian rhythm is absent not only at birth but in the postnatal period as well, which predetermines a mechanism of metabolic programming [55,118,119].

Our retrospective study regarding the occurrence of obesity by the end of the first year in 120 infants born from healthy mothers without pregnancy and delivery complications demonstrated that their body weight and length corresponded to normal levels, and there were no gastrointestinal dysfunctions. All the infants were breastfed for a period of 10–12 months and received complimentary feeding starting from 4–5 months. On the other hand, the body weight of 40 infants, born from mothers with obesity and pregnancy complicated by diabetes, exceeded 90–95% in 12 months after birth. They received maternal milk and feed formula for the first 3–4 months only, and complimentary feeding and milk formula from months 5–6 until the end of the first year, and they all had gastrointestinal dysfunctions.

The study of melatonin levels in maternal blood before delivery and in their newborn babies on the third day at day (11–12 a.m.) and night (4–5 a.m.) showed that the infants had melatonin production circadian rhythms if they were present in healthy mothers, although the total level was still lower: 1.9/11.5 and 12.2/81.6 pg/mL (day/night). On the other hand, they were absent in babies born from mothers with obesity and gestational diabetes: 3.6/5.2 and 31.9/35.7 pg/mL, respectively [120]. The excessive body weight and obesity in 6-month infants from diseased mothers suggests that the absence of melatonin production circadian rhythms is associated with an imbalance of energy exchange in early ontogenesis, which leads to the development of obesity.

Thus, in prenatal ontogenesis, maternal melatonin is a key molecule that directs and coordinates the genetic process of the child's morphofunctional development, which is crucial for successful postnatal adaptation to a new environment and for healthy life in subsequent months and years.

5. The State of the Placenta and Fetal Development in the Case of Disruption of Maternal Melatonin Production

It is known that a genetic program is executed in interaction with environment factors, of which the most unfavorable are qualitative and quantitative malnutrition, smoking, narcotics and medications, chronic diseases, obesity, diabetes mellitus and gestational complications (preeclampsia, gestational diabetes, etc.). A complex of pathological processes arising during adaptation to pregnancy has a negative effect on the morphofunctional development of the placenta [121]. The activation of free-radical oxidation, depletion of antioxidant reserves and accumulation of peroxynitrite lead to oxidative stress [122–126]. Protein oxidative modification and lipid peroxidation result in dysfunction of cell membranes, receptors, enzymes, intracellular structures, particularly the endoplasmic reticulum (ER), and endothelial dysfunction [127–129]. The endoplasmic reticulum damage in endothelial cells is exacerbated by oxidation of triglycerides and low-density lipoproteins [130,131]. Endoplasmic reticulum oxidative stress leads to activation of inflammatory responses, inducing the secretion of interleukins (IL-1α, IL-1β), TNF-a and systemic inflammation [132,133].

This may result in disruption of uteroplacental circulation, hormone-producing functions of the placenta and its circadian rhythm, ischemia, chronic placental insufficiency and intrauterine growth retardation [134]. Numerous experimental studies have shown that the development of pathological processes is primarily due to insufficient production of

epiphyseal melatonin and a lack of maternal circadian rhythm, which results in disruption of its synthesis in the placental tissue during pregnancy [87,135–137].

Such pathology is observed in women with chronic pathologies of three or more functional systems (cardiovascular, gastrointestinal, neural, etc.), obesity, diabetes mellitus, metabolic syndrome, endometriosis and polycystic ovary syndrome, as well as in women working at night [138–143]. It has been found that in such women pregnancies are complicated by chronic placental insufficiency, preeclampsia and gestational diabetes [144–147]. Numerous experimental and clinical studies provide evidence that in the case of preeclampsia there is no significant increase in epiphyseal melatonin (which is characteristic for noncomplicated pregnancies) and no melatonin circadian rhythm [88,139,148]. Reduced expression of melatonin receptors and melatonin production [140], as well as expressed oxidative stress [149] and increased levels of anti-inflammatory cytokines (Il-1b, TNF-a, Il-6), have also been observed [137].

Similar changes have been observed in pregnant women with pre- and gestational diabetes, hypertensive syndrome, obesity and in cases of smoking [150–152]. In the case of obesity and gestational diabetes, an alteration occurs in the expression of mRNA insulin receptors and glucose transporters (GLUT-1, GLUT-4) in adipose tissue and skeletal muscle, which significantly affects metabolic processes in the mother–placenta–fetus system [153]. Along with activation of free-radical oxidation, immune, trophic, endocrine and metabolic placental dysfunctions and chronic hypoxia have a damaging impact on the fetus [17,96,154].

This may result in delayed growth or fetal macrosomia, impairing the development of functional systems of the fetus, formation of interconnections between systems and circadian rhythm of their activities [116,135]. It is the fetus's brain that suffers dramatically as it is most sensitive to oxidative stress and free-radical damage in comparison with other tissues [155]. Newborns with intrauterine growth retardation (IUGR) have an increased level of proinflammatory cytokines, as do their mothers who have had preeclampsia [156]. Disruption of maternal melatonin circadian production not only leads to delayed formation of the fetus's specific genes' rhythmic activity but also predetermines the endocrine pathology programming of the offspring [96,108,117,157,158].

6. Maternal Melatonin Deficiency and Endocrine Pathology Programming of the Offspring

In recent decades, numerous experimental and epidemiological studies have proved the role of epigenetic effects on various adverse factors in distorting the formation of regulatory mechanisms during critical development of the fetus's organs and systems, which changes the nature of postnatal adaptive reactions in the new environment and contributes to a delayed development of pathological conditions.

Research into the mechanisms of the regulation of genome functions which are not associated with the DNA structure, i.e., epigenetic regulation, has established the effect of environmental factors on the activity of placental and fetal genes by changing DNA cytosine nucleotide methylation [159]. Covalent histone modifications (acetylation, methylation and phosphorylation) and activities of small regulatory and interfering RNAs also affect gene expression.

The frequency of epimutations due to these processes can exceed the frequency of gene mutations and cause mutability of phenotypic traits of the fetus. Without affecting DNA sequences, primary epimutations change the configuration of chromatin which can be either transcriptionally active or inactive. In that case, developmental pathology may be a consequence of the turning off (imprinting) of genes which normally should be functionally active, and reversely, a result of activation may occur due to hypomethylation of genes which in normal development should remain imprinted [154,160]. Gene-expression disorders are followed by changes in enzyme activity and dysregulation of cell differentiation and development, which eventually leads to a decrease in their number and irreversible morphofunctional disorders.

The environment and the genetic apparatus interact at all stages of placental and fetal development. In the case of hypoxia, in the placenta there is increased methylation in the promoter regions of the TUSC3 gene, and reversely hypomethylation of the p53 gene involved in apoptosis [126,161]. In newborns from mothers with obesity, diabetes and preeclampsia, there were changes in the expression of genes involved in the regulation of brain development, inflammation and immune signaling, carbohydrate and lipid homeostasis and oxidative stress [96,162–164].

Epigenetic changes due to the impact of adverse environmental factors predetermine consequences of perinatal damages. It is known that inflammatory changes in fetal adipose tissue and skeletal muscles of fetuses from mothers with obesity can cause excessive insulin production by the pancreas and insulin resistance [165]. Insulin receptors are highly expressed in the cortex and hippocampus, and synaptic insulin signaling plays a key role in learning and eating-behavior formation [166].

In an experimental study, in the case of maternal obesity and hyperinsulinemia, in the fetus's hippocampus there was expression inhibition of insulin receptor genes and glucose transporters, as well as distorted development of the brain's serotoninergic and dopaminergic systems involved in eating-behavior regulation [167,168]. In the case of chronic hypoxia, a change in expression of the epiphyseal AANAT (arylalkylamine N-acetyltransferase) gene can suppress the synthesis of melatonin [169]. Along with epigenetic mechanisms, hormonal mechanisms play an important role in being able to trigger epigenetic programming in the absence of melatonin [160].

7. Maternal Melatonin Prevents Pathology Programming

Various data obtained in recent decades regarding the mechanisms that determine adverse consequences have proved that only maternal melatonin protects the genetic development program of the mother–placenta–fetus systems from epigenetic damage. By controlling DNA methylation and histone modifications, melatonin prevents changes in the expression of genes that are directly related to the programming of various pathologies' development [170–174]. As evident from experimental studies, such programming can be prevented or lessened by early administration of melatonin [155,175–177].

Thus, experimental studies on various animal models (rats and sheep) have established that, in the presence of adverse environmental factors, melatonin prevents the development of oxidative and nitrative stress in the placenta and fetus [119,136,178–180], suppresses production of proinflammatory cytokines and stimulates the production of anti-inflammatory cytokines in the maternal serum, amniotic fluid and fetal brain [181,182], stabilizes the blood-brain barrier and prevents inflammation development and neural apoptosis [183–186].

Melatonin maintains endoplasmic reticulum homeostasis, providing the protection of metabolic processes in stress conditions [187]. Melatonin administration to rats subjected to nicotine suppressed oxidative stress and reduced lung and liver damage in fetuses [188] and prevented neural-tube defects under hyperglycemia conditions in diabetes [189].

Antenatal melatonin administration in the case of placental insufficiency improved the function of the placenta, normalized the fetal–placental circulation, coronary blood flow, cardiac function and fetal growth [190–192]. Melatonin had multiple positive effects on mitochondria: it reduced the intensity of oxidative stress, maintained the mitochondrial membrane potential, increased the efficiency of ATP production, regulated an optimal balance between pro- and anti-apoptotic proteins, prevented the release of cytochrome C into the cytosol and inhibited caspase 3 activity [178,179,193].

The results of numerous experimental studies that proved the role of melatonin in optimal pregnancy outcomes in pathological conditions [194,195] have served as a basis for developing new approaches to its application in clinical obstetrics, particularly in cases of pregnancies complicated by preeclampsia and intrauterine growth retardation syndrome (Figure 1).
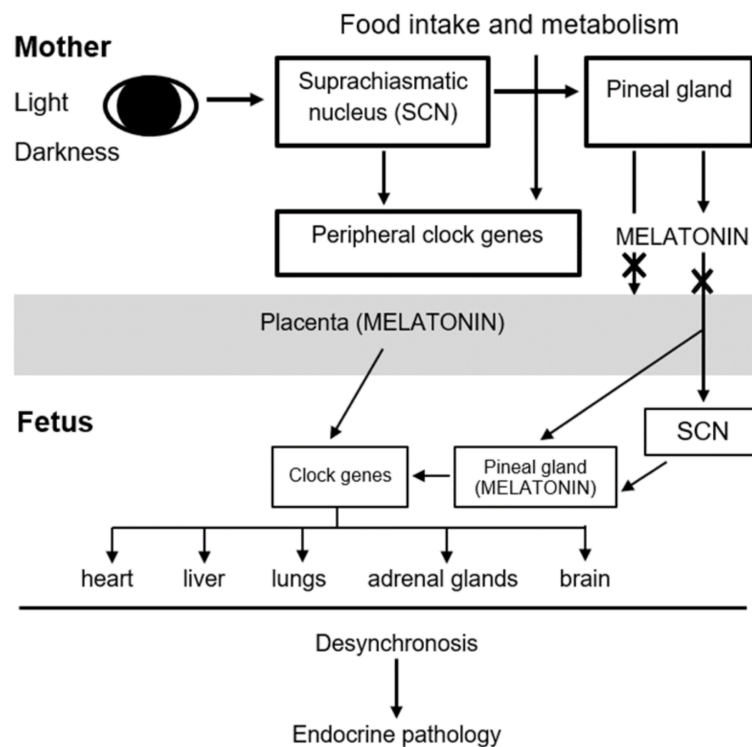
Figure 1. Maternal melatonin deficiency leads to endocrine pathologies in children.

8. Conclusions

Thus, maternal melatonin deficiency and absence of circadian rhythm are behind distortions of genetically programmed development of hormonal and metabolic regulatory mechanisms in the child's functional systems, which predetermines the programming and occurrence of endocrine pathology in early ontogenesis. The primary mechanisms forming this pathology are oxidative stress, mitochondrial damage, epigenetic regulation, glucocorticoid effect and actions of neuroactive steroids, somatolactogens and related peptides, in realization of which the absence or lack of melatonin promotes pathological progression in the following years. The importance of this factor in pathophysiological mechanisms of endocrine disorders determines the need for a new approach to risk assessment and timely prevention of offspring diseases already at the stage of family planning.

References

1. World Health Organization. *Obesity and Overweight*; World Health Organization: Geneva, Switzerland, 2018.
2. WHO. Facts and Figures on Childhood Obesity. Available online: http://www.who.int/end-childhood-obesity/facts/en/ (accessed on 10 January 2020).
3. Nittari, G.; Scuri, S.; Petrelli, F.; Pirillo, I.; di Luca, N.M.; Grappasonni, I. Fighting obesity in children from European World Health Organization member states. Epidemiological data, medical-social aspects, and prevention programs. *Clin. Ter.* **2019**, *170*, e223–e230. [CrossRef]

4. Xu, S.; Xue, Y. Pediatric obesity: Causes, symptoms, prevention and treatment (Review). *Exp. Ther. Med.* **2016**, *11*, 15–20. [CrossRef] [PubMed]

5. Rito, A.I.; Buoncristiano, M.; Spinelli, A.; Salanave, B.; Kunešová, M.; Hejgaard, T.; Solano, M.G.; Fijałkowska, A.; Sturua, L.; Hyska, J.; et al. Association between Characteristics at Birth, Breastfeeding and Obesity in 22 Countries: The WHO European Childhood Obesity Surveillance Initiative—COSI 2015/2017. *Obes. Facts* **2019**, *12*, 226–243. [CrossRef] [PubMed]

6. Weiss, R.; Dziura, J.; Burgert, T.S.; Tamborlane, W.V.; Taksali, S.E.; Yeckel, C.W.; Allen, K.; Lopes, M.; Savoye, M.; Morrison, J.; et al. Obesity and the metabolic syndrome in children and adolescents. *N. Engl. J. Med.* **2004**, *350*, 2362–2374. [CrossRef] [PubMed]

7. Reinehr, T.; de Sousa, G.; Toschke, A.M.; Andler, W. Comparison of metabolic syndrome prevalence using eight different definitions: A critical approach. *Arch. Dis. Child.* **2007**, *92*, 1067–1072. [CrossRef] [PubMed]

8. Ford, E.S. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the US. *Diabetes Care* **2005**, *28*, 2745–2749. [CrossRef]

9. Chan, J.C.; Malik, V.; Jia, W.; Kadowaki, T.; Yajnik, C.S.; Yoon, K.-H.; Xu, F.B. Diabetes in Asia: Epidemiology, risk factors, and pathophysiology. *JAMA* **2009**, *301*, 2129–2140. [CrossRef] [PubMed]

10. McMahon, S.K.; Haynes, A.; Ratnam, N.; Grant, M.T.; Carne, C.L.; Jones, T.W.; Davis, E.A. Increase in type 2 diabetes in children and adolescents in Western Australia. *Med. J. Aust.* **2004**, *180*, 459–461. [CrossRef] [PubMed]

11. Kao, K.T.; Sabin, M.A. Type 2 diabetes mellitus in children and adolescents. *Aust. Fam. Physician* **2016**, *45*, 401–406. [PubMed]

12. Koskinen, J.; Magnussen, C.G.; Sinaiko, A.; Woo, J.; Urbina, E.; Jacobs, D.R., Jr.; Steinberger, J.; Prineas, R.; Sabin, M.A.; Burns, T.; et al. Childhood Age and Associations Between Childhood Metabolic Syndrome and Adult Risk for Metabolic Syndrome, Type 2 Diabetes Mellitus and Carotid Intima Media Thickness: The International Childhood Cardiovascular Cohort Consortium. *J. Am. Heart Assoc.* **2017**, *6*, e005632. [CrossRef] [PubMed]

13. Macrosomia: ACOG Practice Bulletin, Number 216. Committee on Practice Bulletins-Obstetrics. Committee on Practice Bulletins—Obstetrics. *Obstet. Gynecol.* **2020**, *135*, e18–e35. [CrossRef] [PubMed]

14. Sparano, S.; Ahrens, W.; De Henaw, S.; Marild, S.; Molnar, D.; Moreno, L.A.; Suling, M.; Tornaritis, M.; Toomas Veidebaum, T.; Siani, A.; et al. Being macrosomic at birth is an independent predictor of overweight in children: Results from the IDEFICS study. *Matern. Child. Health J.* **2013**, *17*, 1373–1381. [CrossRef] [PubMed]

15. Mierzynski, R.; Dluski, D.; Darmochwal-Kolarz, D.; Poniedziałek-Czajkowska, E.; Leszczynska-Gorzelak, B.; Kimber-Trojnar, Z.; Oleszczuk, J. Intra-uterine Growth Retardation as a Risk Factor of Postnatal Metabolic Disorders. *Curr. Pharm. Biotechnol.* **2016**, *17*, 587–596. [CrossRef] [PubMed]

16. Mericq, V.; Martinez-Aguayo, A.; Uauy, R.; Iñiguez, G.; Van der Steen, M.; Hokken-Koelega, A. Long-term metabolic risk among children born premature or small forgestational age. *Nat. Rev. Endocrinol.* **2017**, *13*, 50–62. [CrossRef] [PubMed]

17. Voerman, E.; Santos, S.; Inskip, H.; Amiano, P.; Barros, H.; Charles, M.A.; Chatzi, L.; Chrousos, G.P.; Corpeleijn, E.; Crozier, S. Association of Gestational Weight Gain with Adverse Maternal and Infant Outcomes. *JAMA* **2019**, *321*, 1702–1715. [CrossRef] [PubMed]

18. Hong, Y.H.; Chung, S.C. Small for gestational age and obesity related comorbidities. *Ann. Pediatr. Endocrinol. Metab.* **2018**, *23*, 4–8. [CrossRef] [PubMed]

19. Ordóñez-Díaz, M.D.; Gil-Campos, M.; Flores-Rojas, K.; Muñoz-Villanueva, M.C.; Aguilera-García, C.M.; de la Torre-Aguilar, M.J.; Pérez-Navero, J.L. Plasma Adipokines Profile in Prepubertal Children with a History of Prematurity or Extrauterine Growth Restriction. *Nutrients* **2020**, *12*, 1201. [CrossRef]

20. Angi, A.; Chiarelli, F. Obesity and Diabetes: A Sword of Damocles for Future Generations. *Biomedicines* **2020**, *8*, 478. [CrossRef]

21. Manco, M.; Dallapiccola, B. Genetics of pediatric obesity. *Pediatrics* **2012**, *130*, 123–133. [CrossRef] [PubMed]

22. Marginean, C.; Melit, L.E. New insights regarding genetic aspects of childhood obesity: A mini review. *Front. Pediatr.* **2018**, *6*, 271. [CrossRef]

23. Cassidy, F.C.; Charalambous, M. Genomic imprinting, growth and maternal-fetal interactions. *J. Exp. Biol.* **2018**, *221* (Suppl. 1), jeb164517. [CrossRef] [PubMed]

24. Kerr, B.; Leiva, A.; Farias, M.; Contreras-Duarte, S.; Toledo, F.; Stolzenbach, F.; Silva, L.; Sobrevia, L. Fetoplacental epigenetic changes associated with maternal metabolic dysfunction. *Placenta* **2018**, *69*, 146–152. [CrossRef] [PubMed]

25. Eerdekens, A.; Verhaeghe, J.; Darras, V.; Naulaers, G.; Van den Berghe, G.; Langouche, L.; Vanhole, C. The placenta in fetal thyroid hormone delivery: From normal physiology to adaptive mechanisms in complicated pregnancies. *J. Matern. Fetal. Neonatal. Med.* **2020**, *33*, 3857–3866. [CrossRef]

26. Santangeli, L.; Sattar, N.; Huda, S.S. Impact of maternal obesity on perinatal and childhood outcomes. *Best Pract. Res. Clin. Obstet. Gynecol.* **2015**, *29*, 438–448. [CrossRef] [PubMed]

27. Grino, M. Prenatal nutritional programming of central obesity and metabolic syndrome: Role of adipose tissue glucocorticoid metabolism. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2005**, *289*, 1233–1235. [CrossRef] [PubMed]

28. Sabin, M.; Kao, K.-T.; Juonala, M.; Baur, L.A.; Wake, M. Prenatal determinants of childhood obesity: A review of risk factors. *J. Paed. Child. Health* **2015**, *51*, 82–86. [CrossRef] [PubMed]

29. Simeoni, U.; Armengaud, J.B.; Siddeek, B.; Tolsa, J.F. Perinatal Origins of Adult Disease. *Neonatology* **2018**, *113*, 393–399. [CrossRef]

30. Santos Ferreira, D.L.; Williams, D.M.; Kangas, A.J.; Soininen, P.; Ala-Korpela, M.; Smith, G.D.; Jarvelin, M.-R.; Lawlor1, D.A. Association of pre-pregnancy body mass index with offspring metabolic profile: Analyses of 3 European prospective birth cohorts. *PLoS Med.* **2017**, *14*, e1002376. [CrossRef]

31. Ferrara, A. Increasing prevalence of gestational diabetes mellitus: A public health perspective. *Diabetes Care* **2007**, *30*, 141–146. [CrossRef] [PubMed]

32. Gabbay-Benziv, R.; Baschat, A.A. Gestational diabetes as one of the "great obstetrical syndromes"—The maternal, placental, and fetal dialog. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2015**, *29*, 150–155. [CrossRef]

33. Devlieger, R.; Benhalima, K.; Damm, P.; Assche, A.V.; Chantal Mathieu, C.; Tahir Mahmood, T.; Dunne, F.; Bogaerts, A. Maternal obesity in Europe: Where do we stand and how to move forward? A scientific paper commissioned by the European board and college of obstetrics and gynecology (EBCOG). *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2016**, *201*, 203–208. [CrossRef]

34. Cho, W.K.; Suh, B.-K. Catch-up growth and catch-up fat in children born small for gestational age. *Korean J. Pediatr.* **2016**, *59*, 1–7. [CrossRef] [PubMed]

35. Koontz, M.B.; Gunzler, D.D.; Presley, L.; Catalano, P.M. Longitudinal changes in infant body composition: Association with childhood obesity. *Pediatr. Obes.* **2014**, *9*, e141–e144. [CrossRef] [PubMed]

36. Hales, C.N.; Barker, D.J.P. The thrifty phenotype hypothesis. *Br. Med. Bull.* **2001**, *60*, 5–20. [CrossRef]

37. Godfrey, K.M.; Lillycrop, K.A.; Burdge, G.C.; Gluckman, P.D.; Hanson, M.A. Non-imprinted epigenetics in fetal and postnatal development and growth. *Nestle Nutr. Inst. Workshop Ser.* **2013**, *71*, 7–63. [CrossRef]

38. Avagliano, L.; Mascherpa, M.; Massa, V.; Doi, P.; Bulfamante, G.P. Fetal pancreatic Langerhans islets size in pregnancies with metabolic disorders. *J. Matern. Fetal Neonatal Med.* **2018**, *6*, 1–6. [CrossRef]

39. Trandafir, L.M.; Temneanu, O.R. Pre and post-natal risk and determination of factors for child obesity. *J. Med. Life* **2016**, *9*, 386–391. [CrossRef] [PubMed]

40. Dabelea, D. The Predisposition to Obesity and Diabetes in Offspring of Diabetic Mothers. *Diabetes Care* **2007**, *30* (Suppl. 2), 169–174. [CrossRef] [PubMed]

41. Monteiro, L.J.; Norman, J.E.; Rice, G.E.; Illanes, S.E. Fetal programming and gestational diabetes mellitus. *Placenta* **2016**, *30*, 54–60. [CrossRef]

42. McCloskey, K.; Ponsonb, A.L.; Collier, F.; Allen, K.; Tang, M.L.K.; Carlin, J.B.; Saffery, M.; Skilton, M.R.; Cheung, M.; Ranganathan, S. The association between higher maternal pre-pregnancy body mass index and increased birth weight, adiposity and inflammation in the newborn. *Pediatr Obes.* **2018**, *13*, 46–53. [CrossRef]

43. Koletzko, B.; Shamir, R.; Truc, D.; Phillip, M. (Eds.) *Nutrition and Growth: Yearbook 2019*; World Review of Nutrition and Dietetics; Karger: Basel, Switzerland, 2019; Volume 119, pp. 119–137. [CrossRef]

44. Zhao, L. The gut microbiota and obesity: From correlation to causality. *Nat. Rev. Microbiol.* **2013**, *11*, 639–647. [CrossRef] [PubMed]

45. Racz, B.; Duskova, M.; Starka, L.; Hainer, V.; Kunesova, M. Links Between the Circadian Rhythm, Obesity and the Microbiom. *Physiol. Res.* **2018**, *67*, S409–S420. [CrossRef]

46. Allin, K.H.; Nielsen, T.; Pedersen, O. Mechanisms in endocrinology: Gut microbiota in patients with type 2 diabetes mellitus. *Eur. J. Endocrinol.* **2015**, *172*, 167–177. [CrossRef] [PubMed]

47. Chu, D.M.; Valentine, G.C.; Seferovic, M.D.; Aagaard, K.M. The Development of the Human Microbiome. Why Moms Matter. *Gastroenterol. Clin. N. Am.* **2019**, *48*, 357–375. [CrossRef] [PubMed]

48. Vandenplas, Y.; Carnielli, V.P.; Ksiazyk, J.; Luna, M.S.; Migacheva, N.; Mosselmans, J.M.; Picaud, J.C.; Possner, M.; Singhal, A.; Wabitsch, M. Factors affecting early-life intestinal microbiota development. *Nutrition* **2020**, *78*, 110812. [CrossRef]

49. Canfora, E.E.; Jocken, J.W.; Blaak, E.E. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat. Rev. Endocrinol.* **2015**, *11*, 577–591. [CrossRef]

50. Gamble, K.L.; Berry, R.; Frank, S.J.; Young, M.E. Circadian clock control of endocrine factors. *Nat. Rev. Endocrinol.* **2014**, *10*, 466–475. [CrossRef]

51. Johnston, J.D.; Ordovas, J.M.; Scheer, F.A.; Turek, F.W. Circadian rhythms, metabolism, and chrononutrition in rodents and humans. *Adv. Nutr.* **2016**, *7*, 399–406. [CrossRef]

52. Laermans, J.; Depoortere, I. Chronobesity: Role of the circadian system in the obesity epidemic. *Obes. Rev.* **2016**, *17*, 108–125. [CrossRef]

53. Hardeland, R.; Madrid, J.A.; Tan, D.X.; Reiter, R.J. Melatonin, the circadian multioscillator system and health: The need for detailed analyses of peripheral melatonin signaling. *J. Pineal Res.* **2012**, *52*, 139–166. [CrossRef]

54. Menaker, M.; Murphy, Z.C.; Sellix, M.T. Central control of peripheral oscillators. *Curr. Opin. Neurobiol.* **2013**, *23*, 741–746. [CrossRef]

55. Amaral, F.G.D.; Andrade-Silva, J.; Kuwabara, W.M.T.; Cipolla-Neto, J. New insights into the function of melatonin and its role in metabolic disturbances. *Expert. Rev. Endocrinol. Metab.* **2019**, *14*, 293–300. [CrossRef]

56. Ding, G.; Gong, Y.; Eckel-Mahan, K.L.; Sun, Z. Central Circadian Clock Regulates Energy Metabolism. *Adv. Exp. Med. Biol.* **2018**, *1090*, 79–103. [CrossRef]

57. Dibner, C.; Schibler, U.; Albrecht, U. The mammalian circadian timing system. *Ann. Rev. Physiol.* **2010**, *72*, 517–549. [CrossRef] [PubMed]

58. Reiter, R.J.; Rosales-Corral, S.; Coto-Montes, A.; Boga, J.A.; Tan, D.-X.; Davis, J.M.; Konturek, S.J.; Brzozowski, T. The photoperiod, circadian regulation and chronodisruption: The requisite inter play between the suprachiasmatic nuclei and the pineal and gut melatonin. *J. Physiol. Pharmacol.* **2011**, *62*, 269–274.

59. Welsh, D.K.; Takahashi, J.S.; Kay, S.A. Suprachiasmatic nucleus: Cell autonomy and network properties. *Ann. Rev. Physiol.* **2010**, *72*, 551–557. [CrossRef]

60. Kvetnoy, I.M. Extrapineal melatonin: Location and role within diffuse neuroendocrine system. *Histochem. J.* **1999**, *31*, 1–12. [CrossRef]

61. Venegas, C.; García, J.A.; Escames, G.; Ortiz, F.; López, A.; Doerrier, C.; García-Corzo, L.; López, L.C.; Reiter, R.J.; Acuña-Castroviejo, D. Extrapineal melatonin: Analysis of its subcellular distribution and daily fluctuations. *J. Pineal Res.* **2012**, *52*, 217–227. [CrossRef] [PubMed]

62. Tan, D.X.; Manchester, L.C.; Liu, X.; Rosales-Corral, S.A.; Acuna-Castroviejo, D.; Reiter, R.J. Mitochondria and chloroplasts as the original sites of melatonin synthesis: A hypothesis related to melatonin's primary function and evolution in eukaryotes. *J. Pineal Res.* **2013**, *54*, 127–138. [CrossRef]

63. Ma, X.; Idle, J.R.; Krausz, K.W.; Gonzalez, F.J.J. Metabolism of melatonin by human cytochromes p450. *Drug Metab. Dispos.* **2005**, *33*, 489–494. [CrossRef] [PubMed]

64. Dubocovich, M.L. Melatonin receptors: Role on sleep and circadian rhythm regulation. *Sleep Med.* **2007**, *8* (Suppl. 3), 34–42. [CrossRef] [PubMed]

65. Peliciari-Garcia, R.A.; Zanquetta, M.M.; Andrade-Silva, J.; Gomes, D.A.; Barreto-Chaves, M.L.; Cipolla-Neto, J. Expression of circadian clock and melatonin receptors within cultured rat cardiomyocytes. *Chronobiol. Int.* **2011**, *28*, 21–30. [CrossRef]

66. Rudic, R.D.; McNamara, P.; Curtis, A.M.; Boston, R.C.; Panda, S.; Hogenesch, J.B.; Fitzgerald, G.A. BMAL1 and CLOCK, two essential components of the circadian clock, ate involved in glucose homeostasis. *PLoS Biol.* **2004**, *2*, e377. [CrossRef]

67. Shimba, S.; Ishii, N.; Ohta, Y.; Ohno, T.; Watabe, Y.; Hayashi, M.; Wada, T.; Aoyagi, T.; Tezuka, M. Brain et muscle Arnt-like protein-1 (BMAL1), a component of the molecular clock, regulates adipogenesis. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 12071–12076. [CrossRef]

68. Slonimski, R.M.; Reiter, R.J.; Schlabritz-Loutsevith, N.; Ostrom, R.S.; Slominski, A.T. Melatonin membrane receptors in peripheral tissues: Distribution and functions. *Mol. Cell. Endocrinol.* **2012**, *351*, 152–166. [CrossRef]

69. Pandi-Perumal, S.R.; Srinivasan, V.; Maestroni, G.J.M.; Cardinali, D.P.; Poegeller, B.; Hardeland, R. Melatonin. Nature's most versatile biological signal ? *FEBS J.* **2006**, *273*, 2813–2838. [CrossRef] [PubMed]

70. Lo, C.-C.; Lin, S.-H.; Chang, J.-S.; Chien, Y.-W. Effects of Melatonin on Glucose Homeostasis, Antioxidant Ability, and Adipokine Secretion in ICR Mice with NA/STZ-Induced Hyperglycemia. *Nutrients* **2017**, *9*, 1187. [CrossRef] [PubMed]

71. Stacchiotti, A.; Favero, G.; Giugno, L.; Lavazza, A.; Reiter, R.J.; Rodella, L.F.; Rezzani, R. Mitochondrial and metabolic dysfunction in renal convoluted tubules of obese mice: Protective role of melatonin. *PLoS ONE* **2014**, *9*, e111141. [CrossRef] [PubMed]

72. Peschke, E.; Bähr, I.; Mühlbauer, E. Melatonin and pancreatic islets: Interrelationships between melatonin, insulin and glucagon. *Int. J. Mol. Sci.* **2013**, *14*, 6981–7015. [CrossRef]

73. Peschke, E.; Bahr, I.; Muhlbauer, E. Experimental and clinical aspects of melatonin and clock genes in diabetes. *J. Pineal Res.* **2015**, *59*, 1–23. [CrossRef] [PubMed]

74. Picinato, M.C.; Hirata, A.E.; Cipolla-Neto, J.; Curi, R.; Carvalho, C.R.O.; Anhê, G.F.; Carpinelli, A.R. Activation of insulin and IGF-1 signaling pathways by melatonin through MT1 receptor in isolated rat pancreatic islets. *J. Pineal Res.* **2008**, *44*, 88–94. [CrossRef]

75. Nogueira, T.C.; Lellis-Santos, C.; Jesus, D.S.; Taneda, M.; Rodrigues, S.C.; Amaral, F.G.; Lopes, A.M.S.; Cipolla-Neto, J.; Bordin, S.; Anhê, G.F. Absence of melatonin induces night-time hepatic insulin resistance and increased gluconeogenesis due to stimulation of nocturnal unfolded protein response. *Endocrinology* **2011**, *152*, 1253–1263. [CrossRef]

76. Owino, S.; Sanchez-Bretano, A.; Tchio, C.; Cecon, E.; Karamitri, A.; Dam, J.; Jockers, R.; Piccione, G.; Noh, H.L.; Kim, T.; et al. Nocturnal activation of melatonin receptor type 1 signaling modulates diurnal insulin sensitivity via regulation of PI3K activity. *J. Pineal Res.* **2018**, *64*. [CrossRef]

77. Karamitri, A.; Jockers, R. Melatonin in type 2 diabetes mellitus and obesity. *Nat. Rev. Endocrinol.* **2019**, *15*, 105–125. [CrossRef]

78. Buxton, O.M.; Cain, S.W.; O'Connor, S.P.; Porter, J.H.; Duffy, J.F.; Wang, W.; Czeisler, C.A.; Shea, S.A. Adverse metabolic consequencein humans of prolonged sleep restriction combined with circadian disruption. *Sci. Transl. Med.* **2012**, *4*, 129ra43. [CrossRef] [PubMed]

79. Marcheva, B.; Ramsey, K.M.; Buhr, E.D.; Kobayashi, Y.; Su, H.; Ko, C.H.; Ivanova, G.; Omura, C.; Mo, S.; Vitaterna, M.H.; et al. Disruption of the clock components CLOCK and BMAL1 leads to hipoinsulinaemia and diabetes. *Nature* **2010**, *466*, 627–631. [CrossRef] [PubMed]

80. She, M.; Hou, H.; Wang, Z.; Zhang, C.; Laudon, M.; Yin, W. Melatonin rescues 3T3-L1 adipocytes from FFA-induced insulin resistance by inhibiting phosphorylation of IRS-1 on Ser307. *Biochimie* **2014**, *103*, 126–130. [CrossRef]

81. Alonso-Vale, M.I.; Andreotti, S.; Mukai, P.Y.; Borges-Silva, C.D.; Peres, S.B.; Cipolla-Neto, J.; Lima, F.B. Melatonin and the circadian entrainment of metabolic and hormonal activities in primary isolated adipocytes. *J. Pineal Res.* **2008**, *45*, 422–429. [CrossRef]

82. Asher, G.; Sassone-Corsi, P. Time for food: The intimate interplay between nutrition, metabolism, and the circadian clock. *Cell* **2015**, *161*, 84–92. [CrossRef]

83. Plano, S.A.; Casiraghi, L.P.; Garcia Moro, P.; Paladino, N.; Golombek, D.A.; Chiesa, J.J. Circadian and metabolic effects of light: Implications in weight homeostasis and health. *Front. Neurol.* **2017**, *8*, 558. [CrossRef] [PubMed]

84. Lucassen, E.A.; Rother, K.I.; Cizza, G. Interacting epidemics? Sleep curtailment, insulin resistance, and obesity. *Ann. N. Y. Acad. Sci.* **2012**, *1264*, 110–134. [CrossRef] [PubMed]

85. Nacamura, N.Y.; Tamura, H.; Kashida, S.; Takayama, H.; Yagamata, Y.; Karube, A.; Sugino, N.; Kato, H. Changes of serum melatonin level and its relationship to feto-placental unit during pregnancy. *J. Pineal Res.* **2001**, *30*, 29–33. [CrossRef]

86. Reiter, R.J.; Tan, D.X.; Korkmaz, A.; Rosales-Corral, S.A. Melatonin and stabile circadian rhythms optimize maternal, placental and fetal physiology. *Hum. Reprod.* **2014**, *20*, 293–307. [CrossRef]

87. Mark, P.J.; Crew, R.C.; Wharfe, M.D.; Waddell, B.J. Rhythmic Three-Part Harmony: The Complex Interaction of Maternal, Placental and Fetal Circadian Systems. *J. Biol. Rhythm.* **2017**, *32*, 534–549. [CrossRef] [PubMed]

88. Waddell, B.J.; Wharfe, M.D.; Crew, R.C.; Mark, P.J. A rhythmic placenta? Circadian variation Clock genes and placental function. *Placenta* **2012**, *33*, 533–539. [CrossRef] [PubMed]

89. Kennawey, D.J. Melatonin and development physiology and pharmacology. *Sem. Perinatol.* **2000**, *24*, 258–266. [CrossRef]

90. Kovacikova, Z.; Sladek, M.; Bendova, Z.; MIllnerova, H.; Simova, A. Expression of clock and clock-driven genes in the rat suprachiasmatic nucleus during late fetal and early postnatal development. *Biol. Rhythm.* **2006**, *21*, 140–148. [CrossRef]

91. Gozeri, E.; Celik, H.; Ozercan, I.; Gurates, B.; Poltat, S.A.; Hanay, F. The effect of circadian rhythm changes on fetal and placental development. *Neuroendocrinol. Lett.* **2008**, *29*, 87–90.

92. Seron-Ferre, M.; Torres-Farfan, C.; Forcelledo, M.L.; Valenzuela, G.J. The development of circadian rhythms in the fetus and neonate. *Semin. Perinatol.* **2001**, *25*, 363–370. [CrossRef]

93. Seron-Ferre, M.; Valenzuela, G.J.; Torres-Farfan, C. Circadian clocks during embryonic and fetal development. *Birth Defects Res.* **2007**, *81*, 204–214. [CrossRef]

94. Varcoe, T.J.; Boden, M.J.; Voultsios, A.; Salkel, M.D.; Rattanatray, L.; Kennaway, D.J. Characterisation of the Maternal Response to Chronic Phase Shifts during Gestation in the Rat: Implications for Fetal Metabolic Programming. *PLoS ONE* **2013**, *8*, e53800. [CrossRef]

95. Torres-Farfan, C.; Seron-Ferre, M.; Dinet, V.; Korf, H.W. Immunocytochemical demonstration of day/night changes of clock gene protein levels in the murine adrenal gland: Differences between melatonin-proficient (C3H) and melatonin-deficient (C57BL) mice. *J. Pineal Res.* **2006**, *40*, 64–70. [CrossRef]

96. Torres-Farfan, C.; Rocco, V.; Monso, C.; Valenzuela, F.J.; Campino, C.; Germain, A.; Torrealba, F.; Valenzuela, G.J.; Seron-Ferre, M. Maternal melatonin effects on clock gene expression in a nonhuman primate fetus. *Endocrinology* **2006**, *147*, 4618–4626. [CrossRef] [PubMed]

97. Ramracheva, R.D.; Muller, D.S.; Squires, P.E.; Brereton, H.; Sugden, D.; Huang, G.C.; Amiel, S.A.; Jones, P.M.; Persaud, S.J. Function and expression of melatonin receptors on human pancreatic islets. *J. Pineal Res.* **2008**, *44*, 273–279. [CrossRef]

98. Edwards, S.M.; Solveig, A.; Dunlop, A.L.; Corwin, E.J. The Maternal Gut Microbiome during Pregnancy. *MCN Am. J. Matern. Child. Nurs.* **2017**, *42*, 310–317. [CrossRef] [PubMed]

99. Mazzoccoli, G.; Pazienza, V.; Vinciguerra, M. Clock Genes and Clock-Controlled Genes in the Regulation of Metabolic Rhythms. *Chronobiol. Int.* **2012**, *29*, 227–251. [CrossRef] [PubMed]

100. Polidarova, L.; Olejnikova, L.; Pauslyova, L.; Sladek, M.; Sotak, M.; Pacha, J.; Sumova, A. Development and entrainment of the colonic circadian clock during ontogenesis. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2014**, *306*, G346–G356. [CrossRef]

101. Arendt, J. Melatonin and human rhythms. *Chronobiol. Int.* **2006**, *23*, 21–37. [CrossRef] [PubMed]

102. Weinert, D. Ontogenetic development of the mammalian circadian system. *Chronobiol. Int.* **2005**, *22*, 179–205. [CrossRef]

103. Colella, M.; Biran, V.; Baud, O. Melatonin and the newborn brain. *Early Hum. Dev.* **2016**, *102*, 1–3. [CrossRef]

104. Thomas, L.; Drew, J.E.; Abramovich, D.R.; Williams, L.M. The role of melatonin in the human fetus (review). *Int. J. Mol. Med.* **1998**, *1*, 539–543. [CrossRef] [PubMed]

105. Mirmiran, M.; Maas, Y.G.; Ariagno, R.L. Development of fetal and neonatal sleep and circadian rhythms. *Sleep. Med. Rev.* **2003**, *7*, 321–334. [CrossRef]

106. Mendez, N.; Abarzua-Catalan, L.N.; Galdames, H.A.; Spichiger, C.; Richter, H.G.; Valenzuela, G.J.; Seron-Ferre, M.; Torres-Farfan, C. Timed Maternal Melatonin Treatment Reverses Circadian Disruption of the Fetal Adrenal Clock Imposed by Exposure to Constant Light. *PLoS ONE* **2012**, *7*, e42713. [CrossRef]

107. Seron-Ferre, M.; Mendez, M.; Abarzua-Catalan, L.; Vilches, N.; Valenzuela, F.J.; Reynolds, H.E.; Llanos, A.J.; Rojas, A.; Valenzuela, G.J.; Torres-Farfan, C. Circadian rhythms in the fetus. *Mol. Cell. Endocrinol.* **2012**, *349*, 68–75. [CrossRef] [PubMed]

108. Molad, M.; Ashkenazi, L.; Gover, A.; Lavie-Nevo, K.; Zaltsberg-Barak, T.; Shaked-Mishan, P.; Soloveichik, M.; Kessel, I.; Rotschild, A.; Etzioni, T. Melatonin Stability in Human Milk. *Breastfeed. Med.* **2019**, *14*, 680–682. [CrossRef] [PubMed]

109. Moran-Lev, H.; Mimouni, F.B.; Ovental, A.; Mangel, L.; Mandel, D.; Lubetzky, R. Circadian Macronutrients Variations over the First 7 Weeks of Human Milk Feeding of Preterm Infants. *Breastfeed. Med.* **2015**, *10*, 366–370. [CrossRef] [PubMed]

110. Wang, Y.; Guo, W.; Xu, H.; Tang, K.; Zan, L.; Yang, W. Melatonin suppresses milk fat synthesis by inhibiting the Mtor signaling pathway via the MT1 receptor in bovine mammary epithelial cells. *J. Pineal Res.* **2019**, *67*, e12593. [CrossRef]

111. Katzer, D.; Pauli, L.; Mueller, A.; Reutter, H.; Reinsberg, I.; Fimmers, R.; Bartmann, P.; Bagci, S. Melatonin concentrations and antioxidative capacity of human breast milk according to gestational age and the time of day. *J. Hum. Lact.* **2016**, *32*, NP105–NP110. [CrossRef] [PubMed]

112. Maas, C.; Franz, A.R.; Shunova, A.; Mathes, M.; Bleeker, C.; Poets, C.F.; Schleicher, E.; Bernhard, W. Choline and polyunsaturated fatty acids in preterm infant's maternal milk. *Eur. J. Nutr.* **2017**, *56*, 1733–1742. [CrossRef] [PubMed]

113. Ardura, J.; Gutierrez, R.; Andres, J.; Agapito, T. Emergence and evolution of the circadian rhythm of melatonin in children. *Horm. Res.* **2003**, *59*, 66–72. [CrossRef]

114. Motta-Teixeira, L.C.; Machado-Nils, A.V.; Battagello, D.S.; Diniz, G.B.; Andrade-Silva, J.; Silva, S., Jr.; Matos, R.A.; do Amaral, F.G.; Xavier, G.F.; Bittencourt, J.C.; et al. The absence of maternal pineal melatonin rhythm during pregnancy and lactation impairs offspring physical growth, neurodevelopment, and behavior. *Horm. Behav.* **2018**, *105*, 146–156. [CrossRef] [PubMed]

115. Ferreira, D.S.; Amaral, F.G.; Mesquita, C.C.; Barbosa, A.P.L.; Lellis-Santos, C.; Turati, A.O.; Santos, R.; Sollon, C.S.; Gomes, P.R.; Juliana, A.; et al. Maternal melatonin programs the daily pattern of energy metabolism in adult offspring. *PLoS ONE* **2012**, *7*, e38795. [CrossRef] [PubMed]

116. Kennaway, D.J. Programming of the fetal suprachiasmatic nucleus and subsequent adult rhythmicity. *Trends Endocrinol. Metab.* **2002**, *13*, 398–402. [CrossRef]

117. Chen, Y.-C.; Sheen, J.-M.; Tiao, M.-M.; Tain, Y.L.; Huang, L.T. Role of Melatonin in Fetal Programming in Compromised Pregnancies. *Int. J. Mol. Sci.* **2013**, *14*, 5380. [CrossRef] [PubMed]

118. Ivanov, D.O.; Evsyukova, I.I.; Mazzoccoli, G.; Anderson, G.; Polyakova, V.O.; Kvetnoy, I.M.; Carbone, A.; Nasyrov, R.A. The Role of Prenatal Melatonin in the Regulation of Childhood Obesity. *Biology* **2020**, *9*, 72. [CrossRef]

119. Thornburg, K.L.; Kolahi, K.; Pierce, M.; Valent, A.; Drake, V.; Louey, S. Biological Features of Placental Programming. *Placenta* **2016**, *48* (Suppl. 1), 47–53. [CrossRef]

120. Al-Gubory, K.H.; Fowler, P.A.; Garrel, C. The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. *Intern. J. Biochem. Cell. Biol.* **2010**, *42*, 1634–1650. [CrossRef] [PubMed]

121. Tamura, H.; Nakamura, Y.; Terron, M.P.; Flores, L.J.; Manchester, L.S.; Tan, D.-X.; Sugino, N.; Reiter, R.J. Melatonin and pregnancy in the human. *Reprod. Toxicol.* **2008**, *25*, 291–303. [CrossRef]

122. Qiu, C.; Phung, T.T.T.; Vadachkoria, S.; Muy-Rivera, M.; Sanchez, S.E.; Williams, M.A. Oxidized Lou-Density Lipoprotein (Oxidized LDL) and the Risk of Preeclampsia. *Physiol. Res.* **2006**, *55*, 491–500. [PubMed]

123. Muatt, L. Placental adaptive responses and fetal programming. *J. Physiol.* **2006**, *572*, 25–30. [CrossRef] [PubMed]

124. Thompson, L.P.; Al-Hasan, Y. Impact of Oxidative Stress in Fetal Programming. *J. Pregnancy* **2012**, *2012*, 582748. [CrossRef] [PubMed]

125. Lenna, S.; Han, R.; Trojanowska, M. Endoplasmic reticulum stress and endothelial dysfunction. *IUBMB Life* **2014**, *66*, 530–537. [CrossRef]

126. Marciniak, S.J.; Ron, D. Endoplasmic reticulum stress signaling in disease. *Physiol. Rev.* **2006**, *86*, 1133–1149. [CrossRef]

127. Bouchlariotou, S.; Liakopoulos, V.; Dovas, S.; Giannopoulou, M.; Kiropoulos, T.; Zarogiannis, S.; Gatselos, G.; Zachopoulos, T.; Kyriakou, D.S.; Kallitsaris, A.; et al. Noctural hypertension is associated with an exacerbation of the endothelial damage in preeclamhsia. *Am. J. Nephrol.* **2008**, *28*, 424–430. [CrossRef] [PubMed]

128. Sanson, M.; Auge, N.; Vindis, C.; Muller, C.; Bando, Y.; Thiers, J.C.; Marachet, M.-A.; Zarkovic, K.; Sawa, Y.; Salvayre, R.; et al. Oxidized low-density lipoproteins trigger endoplasmic reticulum stress in vascular cells: Prevention by oxygen-regulated protein 150 expression. *Circ. Res.* **2009**, *104*, 328–336. [CrossRef]

129. Sanchez-Vera, I.; Bonet, B.; Viana, M.; Quintanar, A.; Martin, M.D.; Blanco, P.; Sergio Donnay, S.; Albi, M. Changes in plasma lipids and increased low density lipoprotein susceptibility to oxidation in pregnancies complicated by gestational diabetes: Consequences of obesity. *Metabolism* **2007**, *56*, 1527–1533. [CrossRef] [PubMed]

130. Liong, S.; Lappas, M. Endoplasmic reticulum stress is increased in adipose tissue of women with gestational diabetes. *PLoS ONE* **2015**, *10*, e0122633. [CrossRef] [PubMed]

131. Reynolds, L.P.; Caton, J.S.; Redmer, D.A.; Grazul-Bilska, A.T.; Vonnahme, K.A.; Borowicz, P.P.; Luther, J.S.; Wallace, J.M.; Wu, G.; Spencer, T.E. Evidence for atered placental blood flow and vascularity in compromised pregnancies. *J. Physiol.* **2006**, *572*, 51–58. [CrossRef] [PubMed]

132. Voiculescu, S.E.; Zygouropoulos, N.; Zahiu, C.D.; Zagrean, A.M. Role of melatonin in embryofetal development. *J. Med. Life* **2014**, *7*, 488–492. [PubMed]

133. Nagai, R.; Watanabe, K.; Wakatsuki, A.; Hamada, F.; Shinohara, K.; Hayashi, Y.; Imamura, R.; Fukaya, T. Melatonin preserves fetal growth in rats by protecting against ischemia-reperfusion-induced oxidative-nitrosative mitochondrial damage in placenta. *J. Pineal Res.* **2008**, *45*, 271–276. [CrossRef]

134. Berbets, A.; Koval, H.; Barbe, A.; Albota, O.; Yuzko, O. Melatonin decreases and cytokines increase in women with placental insufficiency. *J. Matern. Fetal Neonatal. Med.* **2021**, *34*, 373–378. [CrossRef]

135. Forrestel, A.C.; Miedlich, S.U.; Yurcheshen, M.; Wittlin, S.D.; Sellix, M.T. Chronomedicine and type 2 diabetes: Shining some light on melatonin. *Diabetologia* **2017**, *60*, 808–822. [CrossRef]

136. Zeng, K.; Gao, Y.; Wan, J.; Ton, M.; Lee, A.C.; Zhao, M.; Chen, Q. The reduction in circulating levels of melatonin may be associated with the development of preeclampsia. *J. Hum. Hypertens* **2016**, *30*, 666–671. [CrossRef]

137. Lanoix, D.; Guerin, P.; Vaillancourt, C. Placental melatonin production and melatonin receptor expression are altered in preeclampsia: New insights into the role of this hormone in pregnancy. *J. Pineal Res.* **2012**, *53*, 417–425. [CrossRef]

138. Stenvers, D.G.; Scheer, F.A.J.L.; Schrauwen, P.; la Fleur, S.E.; Kalsbeek, A. Circadian clocks and insulin resistance. *Nat. Rev. Endocrinol.* **2019**, *15*, 7589. [CrossRef]

139. Nduhirabandi, F.; du Toit, E.F.; Lochner, A. Melatonin and the metabolic syndrome: A tool for effective therapy in obesity-associated abnormalities? *Acta Physiol.* **2012**, *205*, 209–223. [CrossRef] [PubMed]

140. Cai, C.; Vandermeer, B.; Khurana, R.; Nerenberg, K.; Featherstone, R.; Sebastianski, M.; Davenport, M.H. The Impact of Occupational Shift Work and Working Hours during Pregnancy on Health Outcomes: A Systematic Review and Meta-Analysis. *Am. J. Obstet. Gynecol.* **2019**, *221*, 563–576. [CrossRef] [PubMed]

141. Bouchlariotou, S.; Liakopoulos, V.; Giannopoulou, M.; Arampatzis, S.; Eleftheriadis, T.; Mertens, P.R.; Zintzaras, E.; Messinis, I.E.; Stefanidis, I. Melatonin secretion is impaired in women with preeclampsia and abnormal circadian blood pressure rhythm. *Ren. Fail.* **2014**, *36*, 1001–1007. [CrossRef] [PubMed]

142. Aylamazyan, E.K.; Evsyukova, I.I.; Yarmolinskayai, M.I. The role of melatonin in the development of gestational diabetes. *MOJ Curr. Res. Rev.* **2018**, *1*, 159–162. [CrossRef]

143. Tranquilli, A.L.; Turi, A.; Giannubilo, S.R.; Garbati, E. Circadian melatonin concentration rhythm is lost in pregnant women with altered blood pressure rhythm. *Gynecol. Endocrinol.* **2004**, *18*, 124–129. [CrossRef] [PubMed]

144. Wu, J.L.; Jia, J.; He, M.Z.; Zeng, Y.; Zhang, J.Y.; Shi, E.J.; Lai, S.Y.; Zhou, X.; Sharifu, L.M.; Feng, L. Placental Origins of Preeclampsia: Potential Therapeutic Targets. *Curr. Med. Sci.* **2019**, *39*, 190–195. [CrossRef] [PubMed]

145. Shalal, M.M.; Kadhim, I.M.; Abbas, N.S.; Abdulsattar, G. Measuring of Plasma Melatonin Level in Patients with Preeclampsia. *J. Fac. Med. Baghdad.* **2017**, *59*, 234–238. [CrossRef]

146. Gupta, S.; Aziz, N.; Sekhon, L.; Agarwal, R.; Mansour, G.; Li, J.; Agarwal, A. Lipid peroxidation and antioxidant status in preeclampsia. A systematic review. *Obstet. Gynecol. Survey.* **2009**, *64*, 750–759. [CrossRef]

147. Shimada, M.; Seki, H.; Samejima, M.; Hayase, M.; Shirai, F. Salivary melatonin levels and sleep-wake rhythms in pregnant women with hypertensive and glucose metabolic disorders: A prospective analysis. *Biosci Trends.* **2016**, *10*, 34–41. [CrossRef] [PubMed]

148. Yamamoto, R.; Yamamoto, R.; Rocha, L.P.; Mchado, J.P.; Guimaraes, C.S.; Reis, M.A.; Correa, R.R. Increase of placental sensitivity to melatonin and the alteration to its local synthesis in hypertensive syndromes in pregnancy. *Hypertens Pregnancy* **2013**, *32*, 120–128. [CrossRef]

149. Sarr, O.; Yang, K.; Regnault, T.R.H. In Utero Programming of Later Adiposity: The Role of Fetal Growth Restriction. *J. Pregnancy* **2012**, *2012*, 134758. [CrossRef]

150. Colomiere, M.; Permezel, M.; Lappas, M. Diabetes and obesity during pregnancy alter insulin signaling and glucose transporter expression in maternal skeletal muscle and subcutaneous adipose tissue. *J. Mol. Endocrinol.* **2010**, *44*, 213–223. [CrossRef]

151. Jansson, T.; Powell, T.L. Role of the placenta in fetal programming: Underlying mechanisms and potential interventional approaches. *Clin Sci.* **2007**, *113*, 1–13. [CrossRef]

152. Rodrigues, H.F.; Etchebehere, R.M.; Bernardes, N.; Meirelles, M.F.; Galvao, P.C.; Penna, R.L.; Dos Reis Monteiro, M.L.G.; de Oliveira Guimarães, C.S.; de Paula Antunes Teixeira, V.; Dos Reis, M.A.; et al. Melatonin treatment in fetal and neonatal diseases. *Pathol. Res. Pract.* **2018**, *214*, 1940–1951. [CrossRef] [PubMed]

153. Guillemette, L.; Lacroix, M.; Allard, C.; Patenaude, J.; Battista, M.C.; Doyon, M.; Moreau, J.; Menard, J.; Ardilouze, J.-L.; Perron, P. Preeclampsia is associated with an increased pro-inflammatory profile in newborns. *J. Reprod. Immunol.* **2015**, *112*, 111–114. [CrossRef] [PubMed]

154. Tain, Y.-L.; Huang, L.-T.; Hs, C.-N. Developmental Programming of Adult Disease: Reprogramming by Melatonin? *Int. J. Mol. Sci.* **2017**, *18*, 426. [CrossRef] [PubMed]

155. Feng, P.; Hu, Y.; Vurbic, D.; Guo, Y. Maternal Stress Induces Adult Reduced REM sleep and Melatonin Level. *Dev. Neurobiol.* **2012**, *72*, 677–687. [CrossRef] [PubMed]

156. Maltepe, E.; Bakardjiev, A.I.; Fisher, S.J. The placenta: Transcriptional? Epigenetic? And physiological integration during development. *J. Clin. Investig.* **2010**, *120*, 1016–1025. [CrossRef] [PubMed]

157. Fowden, A.L.; Forhead, A.J. Endocrine mechanisms of intrauterine programming. *Reproduction* **2006**, *204*, 515–526. [CrossRef] [PubMed]

158. Robins, J.C.; Marsit, C.J.; Padbury, J.F.; Sharma, S.S. Endocrine disruptors, environmental oxygen, epigenetics and pregnancy. *Front. Biosci.* **2011**, *3*, 690–700. [CrossRef]

159. Allard, C.; Desgagne, V.; Patenaude, J.; Lacroix, M.; Guillemette, L.; Battista, M.C.; Doyon, M.; Ménard, J.; Ardilouze, J.L.; Perron, P.; et al. Mendelian randomization supports causality between maternal hyperglycemia and epigenetic regulation of leptin gene in newborns. *Epigenetics* **2015**, *10*, 342–351. [CrossRef]

160. Edlow, A.G.; Hui, L.; Wick, H.C.; Fried, I.; Bianchi, D.W. Assessing the fetal effects of maternal obesity via transcriptomic analysis of cord blood: A prospective case-control study. *BJOG* **2016**, *123*, 180–189. [CrossRef] [PubMed]

161. Perrone, S.; Santacroce, A.; Picardi, A.; Buonocore, G. Fetal programming and early identification of newborns at high risk of free radical-mediated diseases. *World J. Clin. Pediatr.* **2016**, *5*, 172–181. [CrossRef] [PubMed]

162. Murabayashi, N.; Sugiyama, T.; Zhang, L.; Kamimoto, Y.; Umekawa, T.; Ma, N.; Sagawa, N. Maternal high-fat diets cause insulin resistance through inflammatory changes in fetal adipose tissue. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2013**, *169*, 39–44. [CrossRef] [PubMed]

163. Zhao, W.Q.; Alkon, D.L. Role of insulin and insulin receptor in learning and memory. *Mol. Cell. Endocrinol.* **2001**, *177*, 125–134. [CrossRef]

164. Sullivan, E.L.; Riper, K.M.; Lockard, R.; Valleau, J.C. Maternal high-fat diet programming of the neuroendocrine system and behavior. *Horm. Behav.* **2015**, *76*, 153–161. [CrossRef] [PubMed]

165. Vucetic, Z.; Kimmel, J.; Totoki, K.; Hollenbeck, E.; Reyes, T.M. Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. *Endocrinology* **2010**, *151*, 4756–4764. [CrossRef] [PubMed]

166. Yang, Y.; Sun, B.; Huang, G.; Xu, L.; Pan, J.; Fang, C.; Li, M.; Li, G.; Tao, Y.; Yang, X.; et al. Up-regulation of mi-R-325-3p suppresses pineal aralkylamine N-acetyltrasferase (Aanat) after neonatal hypoxia-ischemia brain injury in rats. *Brain Res.* **2017**, *1668*, 28–35. [CrossRef] [PubMed]

167. Korkmaz, A.; Rosales-Corral, S.; Reiter, R.J. Gene regulation by melatonin linked to epigenetic phenomena. *Gene* **2012**, *503*, 1–11. [CrossRef]

168. Korkmaz, A.; Reiter, R.J. Epigenetic Regulation: A New Research Area for Melatonin. *J. Pineal Res.* **2008**, *44*, 41–44. [CrossRef]

169. Sharma, R.; Ottenhof, T.; Rzeczkowska, P.A.; Niles, L.P. Epigenetic Targets for Melatonin: Induction of Histone H3 Hyperacetylation and Gene Expression in C17.2 Neural Stem Cells. *J. Pineal Res.* **2008**, *45*, 277–284. [CrossRef] [PubMed]

170. Calberg, C. Gene regulation by melatonin. *Ann. N. Y. Acad. Sci.* **2000**, *917*, 387–396. [CrossRef] [PubMed]

171. Galano, A.; Tan, D.X.; Reiter, R.J. Melatonin: A Versatile Protector against Oxidative DNA Damage. *Molecules* **2018**, *23*, 530. [CrossRef] [PubMed]

172. Ciswternas, C.D.; Compagnucci, M.V.; Conti, N.R.; Ponce, R.H.; Vermouth, N.T. Protective effect of maternal prenatal melatonin administration on rat pups born to mothers submitted to constant light during gestation. *Braz. J. Med. Biol. Res.* **2010**, *43*, 874–882. [CrossRef]

173. Sagrillo-Fagundes, L.; Bienvenue-Pariseault, J.; Vaillancourt, C. Melatonin:The smart molecule that differentially modulates autophagy in tumor and normal cells. *PLoS ONE* **2019**, *14*, e0202458. [CrossRef]

174. Perez-Gonzalez, A.; Castaneda-Arriaga, R.; Alvarez-Idaboy, J.R.; Reiter, R.J.; Galano, A. Melatonin and its metabolites as chemical agents capable of directly repairing oxidized DNA. *J. Pineal Res.* **2019**, *66*, e12539. [CrossRef] [PubMed]

175. Ireland, K.E.; Maloyan, A.; Myatt, L. Melatonin Improves Mitochondrial Respiration in Syncytiotrophoblasts From Placentas of Obese Women. *Reprod. Sci.* **2018**, *25*, 120–130. [CrossRef] [PubMed]

176. Lopez, A.; Garcia, J.A.; Escames, G.; Venegas, C.; Ortiz, F.; Lopez, L.C.; Acuna-Castroviejo, D. Melatonin Protects the Mitochondria from Oxidative Damage Reducing Oxygen Consumption, Membrane Potential, and Superoxide Anion Production. *J. Pineal Res.* **2009**, *46*, 188–198. [CrossRef]

177. Reiter, R.J.; Rosales-Corral, S.; Tan, D.X.; Jou, M.J.; Galano, A.; Hu, B. Melatonin as a mitochondria-targeted antioxidant: One of evolution's best ideas. *Cell. Mol. Life. Sci.* **2017**, *74*, 3863–3881. [CrossRef]

178. Xu, D.-X.; Wang, H.; Ning, H.; Zhao, L.; Chen, Y.-H. Maternally administered melatonin differentially regulates lipopolysaccharide-induced proinflammatory and anti-infammatory cytokines in maternal serum, amniotic fluid, fetal live, and fetal brain. *J. Pineal Res.* **2007**, *43*, 74–79. [CrossRef] [PubMed]

179. Chitimus, D.M.; Popescu, M.R.; Voiculescu, S.E.; Panaitescu, A.M.; Pavel, B.; Lagrean, L.; Zagrean, A.-M. Melatonin's Impact on Antioxidative and Anti-Inflamatory Reprogramming in Homeostasis and Disease. *Biomolecules* **2020**, *10*, 1211. [CrossRef] [PubMed]

180. Carloni, S.; Proietti, F.; Rocchi, M.; Longini, M.; Marseglia, L.; D'Angelo, G.; Balduini, W.; Gitto, E.; Buonocore, G. Melatonin Pharmacokinetics Following Oral Administration in Preterm Neonates. *Molecules* **2017**, *22*, 2115. [CrossRef] [PubMed]

181. Olivier, P.; Fontaine, R.H.; Loron, G.; Steenwinckel, J.V.; Biran, V.; Massonneau, V. Melatonin Promotes Oligodendroglial Maturation of Injured White Matter in Neonatal Rats. *PLoS ONE* **2009**, *4*, e7128. [CrossRef]

182. Welin, A.K.; Svedin, P.; Lapatto, R.; Sultan, B.; Hagberg, H.; Gressens, P.; Kjellmer, I.; Mallard, C. Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. *Pediatr. Res.* **2007**, *61*, 153–158. [CrossRef] [PubMed]

183. Miller, S.L.; Yawno, T.; Alers, N.O.; Castillo-Melendez, M.; Supramaniam, V.G.; VanZyl, N.; Sabaretnam, T.; Loose, J.M.; Drummond, G.R.; Walker, D.W.; et al. Antenatal antioxidant treatment with melatonin to decrease newborn neurodevelopmental deficits and brain injury caused by fetal growth restriction. *J. Pineal Res.* **2014**, *56*, 283–294. [CrossRef]

184. Yawno, T.; Castillo-Melendez, M.; Jenkin, G.; Wallace, E.M.; Walker, D.W.; Miller, S.L. Mechanisms of Melatonin-Induced Protection in the Brain of Late Gestation Fetal Sheep in Response to Hypoxia. *Dev. Neurosci.* **2012**, *34*, 543–551. [CrossRef]

185. Hu, W.; Ma, Z.; Di, S.; Jiang, S.; Li, Y.; Fan, C.; Yang, Y.; Wang, D. Snapshot: Implications for melatonin in endoplasmic reticulum homeostasis. *Br. J. Pharmacol.* **2016**, *173*, 3431–3442. [CrossRef] [PubMed]

186. El-Sokkary, G.H.; Cuzzocrea, S.; Reiter, R.J. Effect of chronic nicotine administration on the rat lung and liver: Beneficial role of melatonin. *Toxicology* **2007**, *239*, 60–67. [CrossRef]

187. Liu, S.; Guo, Y.; Yuan, Q.; Pan, Y.; Wang, L.; Liu, Q.; Wang, F.; Wang, J.; Hao, A. Melatonin prevents neural tube defects in the offspring of diabetic pregnancy. *J. Pineal Res.* **2015**, *59*, 508–517. [CrossRef]

188. Lemley, C.O.; Vonnahme, R.A. Alterations in uteroplacental hemodynamics during melatonin supplementation in sheep and cattle. *J. Anim. Sci.* **2017**, *95*, 2211–2221. [CrossRef]

189. Richter, H.J.; Hansell, J.A.; Raut, S.; Glussani, D.A. Melatonin improves placental efficiency and birth weight increases the placental expression of antioxidant enzymes in undernourished pregnancy. *J. Pineal Res.* **2009**, *46*, 357–364. [CrossRef] [PubMed]

190. Nawathe, A.; David, A.L. Prophylaxis and treatment of fetal growth restriction. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2018**, *49*, 66–78. [CrossRef] [PubMed]

191. Sales, F.; Peralta, O.A.; Narbona, E.; McCoard, S.; Gonzalez-Bulnes, A.; Parraquez, V.H. Rapid Communication: Maternal melatonin implants improve fetal oxygen supply and body weight at term in sheep. *J. Anim. Sci.* **2019**, *97*, 839–845. [CrossRef] [PubMed]

192. Tare, M.; Parkington, H.C.; Wallace, E.M.; Sutherland, A.E.; Lim, R.; Yawno, T.; Coleman, H.A.; Jenkin, G.; Miller, S.L. Maternal melatonin administration mitigates coronary stiffness and endothelial dysfunction, and improves heart resilience to insult in growth restricted lambs. *J. Physiol.* **2014**, *592*, 2695–2709. [CrossRef] [PubMed]
193. Tan, D.X.; Manchester, L.C.; Qin, L.; Reiter, R.J. Melatonin: A Mitochondrial Targeting Molecule Involving Mitochondrial Protection and Dynamics. *Int. J. Mol. Sci.* **2016**, *17*, 2124. [CrossRef] [PubMed]
194. Marseglia, L.; Manti, S.; D'Angelo, G.; Gitto, E.; Barberi, I. Melatonin for the newborn. *J. Pediatr. Neonat. Individ. Med.* **2014**, *3*, e030232. [CrossRef]
195. Wilkinson, D.; Shepherd, E.; Wallace, E.M. Melatonin for women in pregnancy for neuroprotection of the fetus. *Cochrane Database Syst. Rev.* **2016**, *3*, CDO10527. [CrossRef] [PubMed]