Review

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Effect of melatonin as a therapeutic strategy against intrauterine growth restriction: a mini-review of current state

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Abstract

Intrauterine growth restriction (IUGR) or intrauterine growth retardation is a condition that the fetus does not grow as expected. And the biometric profile does not match with the age of fetus. This condition is associated with increased mortality and morbidity of the neonates along with increased risk of cardiovascular, lung, and central nervous system damage. Despite close monitoring of high-risk mothers and the development of new therapeutic approaches, the optimal outcome has not been achieved yet that it indicates the importance of investigations on new therapeutic approaches. Melatonin (MLT) is a neurohormone mainly produced by the pineal gland and has a wide range of effects on different organs due to the broad dispersion of its receptors. Moreover, melatonin is produced by the placenta and also its receptors have been found on the surface of this organ. Not only studies showed the importance of this neurohormone on growth and development of fetus but also they proved its highly anti-oxidant properties. As in IUGR the oxidative stress and inflammation increased melatonin could counteract these changes and improved organ's function. In this study, we found that use of MLT could be a good clinical approach for the treatment of IUGR as its high anti-oxidant activity and vasodilation could dampen the mechanisms lead to the IUGR development.

Keywords: anti-oxidant properties, intrauterine growth restriction, melatonin

Introduction

Intrauterine growth restriction (IUGR) is a condition that the fetus is under the 10th percentile for the gestational age from length or body weight aspect[1]. IUGR is a risk factor of increased perinatal morbidity and mortality that it shows the importance of careful monitoring and neonatal assistance[1]. Epigenetic modifications during IUGR development are associated with an increased risk of different diseases such as cardiovascular diseases[2–4]. The incidence of IUGR is between 10 and 15% of newborns per year, which shows the importance of this condition as a challenge with a significant burden for health systems worldwide[5]. IUGR can also be caused by maternal diseases such as diabetes that may affect the amount of amniotic fluid and the placenta[6,7]. Several causes have been proposed for IUGR including toxins and deprivation from certain nutrients or oxygen[4]. Flow restriction and further reduction of utero-placental perfusion with a decrease of oxygen and an increase of oxidative stress are contributing to the development of several pathogenesis conditions that are associated with IUGR such as cardiovascular and neurological diseases[8–10]. In this context, agents that improve blood flow and perfusion along with the reduction of oxidative stress such as melatonin (MLT) could be considered as promising therapeutic targets.

Aaron Lerner and colleagues extracted MLT or 5 methoxy-N-acetyltryptamine from the pineal glands of cows, which could lead to skin lightening in the frogs. This agent further reintroduced as a neurohormone produced by the pineal gland and required for a regular sleep-awake cycle[11,12]. Other organs such

HIGHLIGHTS

- Melatonin has a wide range of effects on different organs due to the broad dispersion of its receptors.
- Melatonin is produced by the placenta and also its receptors have been found on the surface of this organ.
- As in intrauterine growth restriction (IUGR) the oxidative stress and inflammation increased MLT could counteract these changes and improve organ's function.

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as the gastrointestinal tract, cerebellum, and skin are also involved in the production of MLT[11,13–15]. Its production is facilitated during the night via its precursor, tryptophan, in its major source, pinealocytes[16–18]. The trace of this neurohormone production have been found in all evolutionary levels even bacteria[19]. MLT is an anti-oxidative agent which improved inflammation via modification of pro- and anti-inflammatory cytokines such as IL-1-β, IL-4, IL-6, and IL-10[14]. Thus, due to its anti-oxidative effects along with its ability in vasodilation this agent in the field of IUGR treatment has raised attention. In this review, we discussed about the effects of MLT on this condition and as far we know we could not find a review in this field. This review could provide a concept about the efficacy of MLT and its clinical value for using in pregnant mother for both prevention and treatment of IUGR[13,15].

Intrauterine growth restriction: mechanisms and its importance as a public health challenge

The definition of the normal neonate is the neonate with a birth weight in the range of 10th and 90th percentile of his/her age, race, and sex. IUGR is a clinical definition characterized by malnutrition and retardation of growth in the uterus prevalent in underdeveloped and developing countries compared to developed ones[20]. More than 75% of IUGR infants are from Asia followed by Africa and America[18]. About 30 million babies (23.8% of newborns) are suffered from this condition worldwide and about 75% of these babies are from developing regions[21]. Increase of perinatal morbidity and mortality, birth hypoxia, neuron-development disturbance, metabolic syndrome in adult life along with the second leading cause of perinatal mortality are all the complications of IUGR, which further emphasizes on it as a major public health challenge[22,23].

There are three types of IUGR based on clinical and anthropometric features of infants which are: asymmetrical IUGR (malnourished infants), symmetrical (hypoplastic small for date), and mixed[17]. Several factors including maternal factors, genetic, placental, and fetal could affect IUGR. Inter-pregnancy interval (less than 6 or 120 months or more), mother's age, behavioral habits, and maternal infection are maternal factors[16]. Unbalance between the supply of placenta and fetus demand could also lead to this condition. Moreover, genetic studies showed the implication of gene polymorphisms in the development of this condition. Also, in few IUGR cases metabolic disorders and chromosomal abnormalities were the causes of this condition[24].

Various hormones are contributing in fetal growth such as insulin, pituitary, and thyroid hormones. IUGR could be resulted from any disturbance in the secretion and level of these hormones. Insulin is a critical hormone for growth and insulin deficiency resulted in IUGR as it is required for proper utilization and uptake of nutrients[25]. The importance of insulin also have been shown in pre-clinical studies in which agenesis of the pancreas resulted in a reduction of glucose gradient between mother and fetus with further decrease of glucose entrance and development of IUGR[26]. Insulin-like growth factor-I (IGF-I) is another hormone required for fetus growth and development by induction of cell growth, proliferation, and enhancement of glucose and amino acids transportation across mother and fetus[27]. Other hormones including Insulin-like growth factor-II (IGF-II), Insulin-like growth factor binding protein-2 (IGFBP-2), Insulin-like growth factor binding protein-3 (IGFBP-3), and vasoactive intestinal polypeptide (VIP) effects on fetus development and IUGR also have been shown in different studies[28,29]. Glucocorticoids are other critical hormones needed for maturation of several organs such as gastrointestinal tract, liver, kidney, alveoli of lungs, production and release of surfactant, gluconeogenesis, and fatty acid oxidation[30]. MLT is also an important hormone for fetal growth and development. As studies showed, fetal exposure to MLT, which passes through the placenta with different concentrations during day and night induces circadian rhythmicity in the fetus[31]. In vivo results also showed the involvement of this neurohormone in fetal development by an increase of blastocyst maturation or as Ishizuka and colleagues showed that culture of embryo mouse in medium with MLT would increase blastocyst development rate[32,33]. Antenatal close monitoring is developed for early detection of IUGR and despite these antenatal managements the outcome of this situation has not been improved over time[20].

Melatonin as a potent agent against diseases

Pharmacological properties of melatonin and its receptors

N-acetyl-5-methoxytryptamine, which is called MLT is a neurohormone produced from L-tryptophan and its secretion is regulated by circadian rhythm[34,35]. As mentioned before, the main producer of this hormone is pineal gland but other organs such as thymus and retina are contributing in its production[36]. It is a lipophilic molecule and its main actions are mediated via its receptors[37]. Also, MLT-receptor-independent pathways are other mechanisms for MLT to influence on cellular homeostasis[38]. Several MLT receptors have been identified these years including Melatonin receptor (MT) 1, 2, 3 and the MLT nuclear receptor, Retinoic acid receptor-related orphan receptor / retinoid Z receptor (ROR/RZR)[39–41]. MT1 is concentrated mainly on suprachiasmatic nucleus but other brain regions such as cerebellum, substantia nigra, and nucleus accumbans have shares from this dispersion. Expression of MT1 in peripheral tissues such as peripheral blood vessels, aorta, heart, immune system, and even endometrium have been confirmed by various studies[42–45]. MT2 is also expressed in cortex, retina, immune cells, and similar to MT1, in endometrium[42,46–49].

Excretion of MLT from the body is a cytochrome P450 (CYP450) dependent mechanism through the liver. Sulfation, glucuronidation, and hydroxylation of MLT are preceding before its excretion to increase its solubility and enhancement of its expulsion from the body[50,51]. During process of MLT, several metabolites have been produced such as N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), generated via the kynuric pathway and also from ultraviolet B radiation and free radicals reactions[52]. 6-hydroxymelatonin (6-OHM), cyclic 3-hydroxymelatoni and 5-methoxytryptamine (5-MT) are other metabolites of MLT. These metabolites have proven effects against oxidative stress and UVB-induced damages[53–56].

Melatonin in homeostasis: from the obstetrics aspect

Circadian rhythm, body temperature cycles, and neuroendocrine rhythms all are regulated by MLT and its ingestion would be

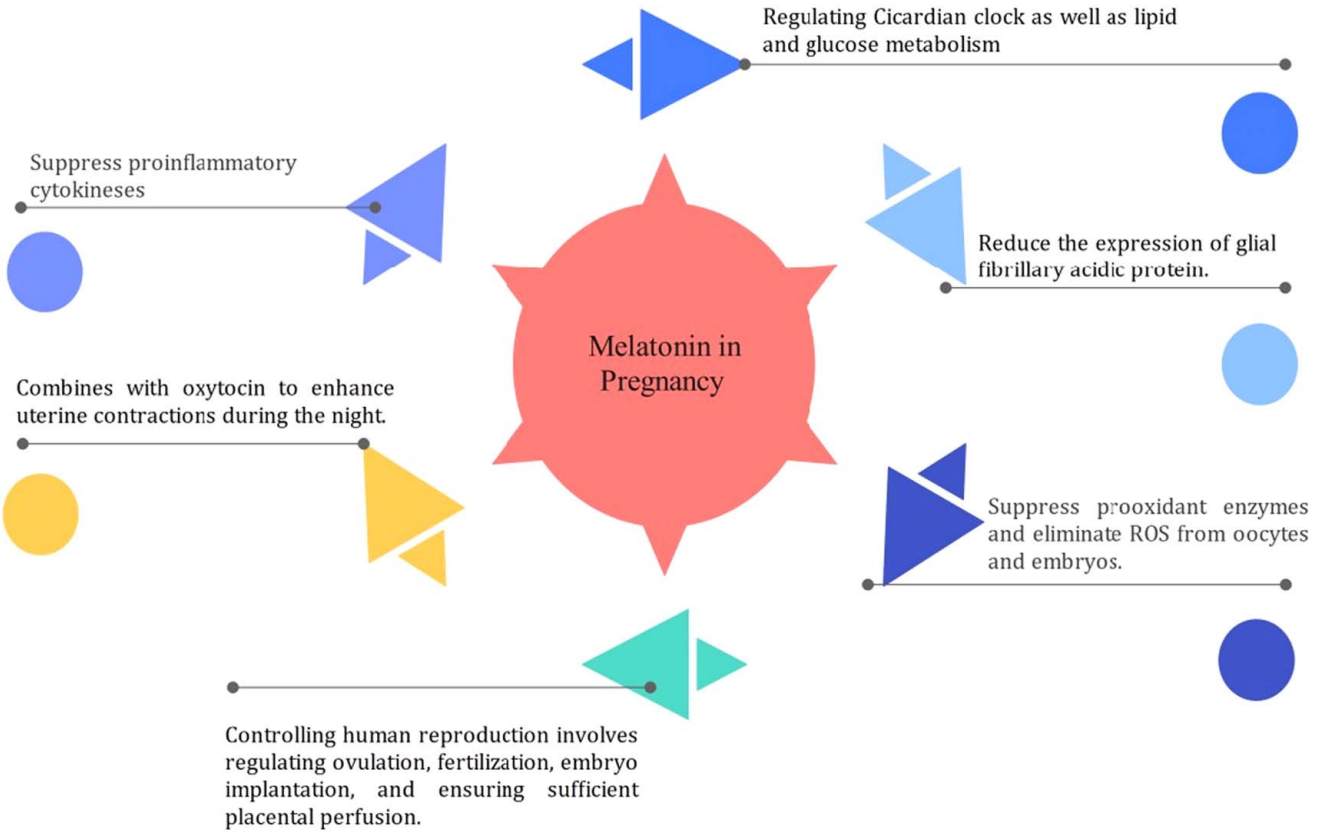

Figure 1. Melatonin effects on both mother and fetus during pregnancy.

associated with induction of sleep-in human[57–60]. MLT is also required for fetal growth and development by establishment and synchronization of diurnal rhythms and biological clock. Regulation of Hcg and maintaining its production in range is another activity of MLT[61,62]. Moreover, MLT is essential from ovulation until pregnancy and child delivery as with its anti-oxidant activity and immunomodulatory effects it scavengers free radicals to prevent damage to oocyte and embryo and further helping proliferation and implantation in endometrium[63,64]. Additionally, placenta is a source of MLT and also has MLT receptors. Two main cells of surface of placenta are mononuclear villous cytotrophoblast and the multinucleated syncytiotrophoblast. MLT is needed for the formation of syncytiotrophoblast. Furthermore, anti-oxidant activity of this molecule inhibits ROS to induce damage to placenta and keep the turnover of the syncitiotrophoblast[65]. Effects of MLT on pregnancy and fetus have been summarized in Fig. 1.

Role of melatonin in intrauterine growth restriction

PIGF or Placental growth factor is required for trophoblast proliferation and also is a pro-angiogenic factor[66]. In a case-control study conducted by Berbet and colleagues fourteen pregnant women whom diagnosed with IUGR were included to assess their MLT and PIGF blood levels. Compared with control group, MLT and PIGF levels were reduced significantly in the umbilical blood in IUGR group which showed the probable protective actions of these molecules against IUGR development[13]. However, study of Candia and colleagues yielded to the different results. The aim of their study was the assessment of the effects of antenatal MLT treatment during the last trimester of pregnant sheep diagnosed with IUGR. Interestingly, their results showed the exacerbation of IUGR symptoms in neonates including reduction of neonatal biometry and birth weight following the treatment with MLT. They found significant increase of the length of the gestation by 7.5% in the

Table 1

Effects of melatonin on different organs affected by intrauterine growth restriction

Dose	Organ	Model	Outcome	References
0.1 mg/kg	CNS	*In vivo*	Improvement of astrocyte attachment to blood vessels and reduction of albumin extravasation and hemorrhage	[76]
0.25 mg, 2 mg	Cardiovascular system	*In vivo*	Reduction of stiffening of coronary arteries, improvement of ischemia-reperfusion injury, and fatal oxygenation	[75]
6 mg	CNS	*In vivo*	Improvement of myelination of white matter brain regions along with reduction of inflammation	[77]
0.1 mg/kg	Lung	*In vivo*	MLT did not prevent structural changes and lung damages following IUGR	[78]
5 mg	Placenta, kidney, heart	*In vivo*	Improvement of utero-placental hemodynamics, kidney and heart	[79]

CNS, central nervous system; IUGR, intrauterine growth restriction; MLT, melatonin.

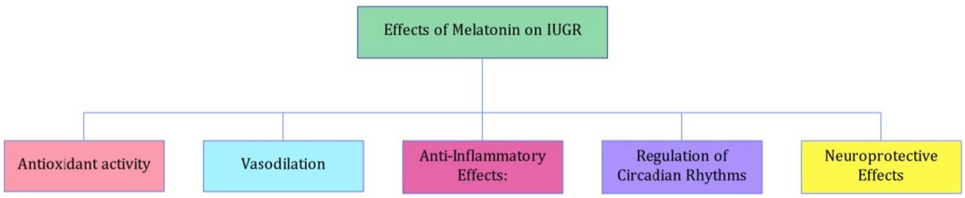

Figure 2. Melatonin effects on IUGR. IUGR, intrauterine growth restriction.

sheep treated by MLT. These results create doubts for prescribing this agent for pregnant women[67].

In another study, Wu and colleagues developed an in vivo model of IUGR via heat stress and assessed MLT effects on this condition via the gut-placenta-fetus axis. They found that following MLT treatment gut microbiota was replenished in pregnant mice and LPS-producing bacteria were reduced while butyrate-producing microflora (Butyricimonas) were increased. Furthermore, the integrity of gut and placenta were improved significantly compared with control group. Moreover, they showed inactivation of Toll-like receptor 4 (TLR4)/Mitogen-activated protein kinases (MAPK) /vascular endothelial growth factor (VEGF) signaling pathway and further inhibition of placenta abnormal angiogenesis resulted in enhancement of nutrients transportation and fetal weight[68].

One of the main complications of IUGR is neurodevelopmental deficits and brain injury as the fatal brain is very susceptible to different damages especially oxidative stress and during IUGR, the oxidative stress related biomarkers increased significantly[69–71]. Miller and colleagues, hypothesized that MLT could dampen these effects due to the MLT anti-oxidant activity. Antenatal intravenous administration of MLT until term in IUGR-developed sheep was performed. Neurological examination and postmortem brain study 24 h after birth were performed to identify the possible pathologies. IUGR lambs needed significantly more time for the development of different behaviors such as suckling and standing. An increase of lipid peroxidation, axonal damage, and white matter hypomyelination was significant in IUGR lambs' brains. Administration of MLT antenatally was associated with reduction of oxidative stress, improvement of axonal damages, and myelination. In line with these brain improvement, better and faster normal behavior development was also seen in these animals following maternal MLT treatment. This study suggested that MLT could be useful for neuroprotection of fetus if consume during pregnancy[72].

Another complication of IUGR is sleep disturbance and cardiovascular problems of fetus, which could cause problems in adulthood and also increase the risk of atherosclerosis, fibrosis, along with impairment of metabolism and development of metabolic syndrome, which itself is a critical risk factor of cardiovascular diseases[73,74]. Investigation of Tare and colleagues was performed on sheep to assess the effects of MLT on negative effects of IUGR on cardiovascular system. Single umbilical artery ligation on day 105–110 of pregnancy was performed to induce IUGR. Their results showed significant improvement of fetal oxygenation along with improvement of contractile function in the right ventricle and coronary flow. Moreover, Ischemia-reperfusion-induced infarct area was greater in IUGR hearts compared to control group which was reduced following MLT treatment. Furthermore, stiffness of coronary arteries was also prevented following antenatal MLT administration. All of these results pointed to the advantages of MLT as a cardioprotective agent during IUGR pregnancy[75].

Collectively, the clinical application of MLT at least in the field of IUGR has still significant controversies as guarantee further investigations both *in vitro* and *in vivo*. MLT, as mentioned before has vasodilation effects, but its effects compared to conventional vasodilators should assessed in further researches. These studies and also other effects of MLT for IUGR have been summarized in Table 1 and Fig. 2.

Conclusions

With wide expression of MTs along the body and the highly anti-oxidant activity of MLT, this agent could influence different tissues and organs, which gives this neurohormone a high potential for using in different diseases and protection against oxidative damages. IUGR by an increase of pro-inflammatory cytokines and free radicals could induce oxidative damages to fetus organs and further resulted in a wide range of cardiovascular, CNS, lung and other organs diseases. Studies could not find a definitive strategy against IUGR but researchers pointed that MLT with its highly anti-oxidant and anti-inflammatory properties could be used as a complementary treatment in this condition. There are divergent results in this field as some studies even pointed to that MLT could exacerbate IUGR symptoms and other ones have reverse results. As a limitation of our study, we could not cover all of the studies used this agent for treatment of IUGR and it is possible that some studies have not been included. Moreover, we could not find the net effect of MLT on IUGR, which indicates the need for higher-level evidences such as systematic reviews and meta-analysis. Thus, use of this agent especially during fetal development and growth need more investigations to confirm its safety and to ensure that there are no significant side effects for mother or fetus.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author contribution

S.Y.R., M.R., R.A., Z.A. and S.M. contributed in data collection and manuscript drafting. All authors approved the final version for submission. R.A. oversaw the study.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

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Guarantor

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