Melatonin, a possible promising panacea for premature ovarian failure

Melatonina, obiecujące panaceum na zespół przedwczesnego wygasania czynności jajników

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Summary

Premature ovarian failure (POF) is characterized by impairment of ovarian function unrelated to elevated follicle-stimulating hormone (FSH) before the age of 40. The consequence of POF is severe and distinctive, presenting from infertility to symptoms caused by hormone deprivation. The mechanism of POF remains unclear and current treatments are therefore ineffective. Melatonin (N-acetyl-5-methoxytryptamine) is a neuroendocrinal hormone chiefly secreted by the pineal body. Melatonin exerts extensive physiological and pharmacological effects on the biological rhythm, oxidative stress, reproduction, autoimmune and tumourigenesis. However, current researches have not yet brought melatonin into the study of POF. In the present review, we have involved state-of-the-art research progress of melatonin in ovary with regard to oxidation, follicle formation and function, and ovarian autoimmune disorders since these aspects mainly dispose to POF development. The features that melatonin scavenges reactive oxygen species (ROS), directly and indirectly induces follicle maturation, ovulation and inhibits apoptosis, and modulates autoimmune derangements in the ovaries are highly indicative that melatonin can effect in combating POF. Also, in this respect we have discussed the possibility of applying melatonin in the treatment of POF and have listed evidence of studies *in vitro* and *in vivo*. Vacant research directions are subsequently suggested and the future application of melatonin in POF treatment is prospected.

Key words: melatonin, premature ovarian failure, oxidative stress.

Premature ovarian failure (POF) indicates a consecutive menstrual disorder, e.g. menopause, abnormal amount of menstruation, and aberrant endometrorrhagia for over 4 months. In the meantime, serum level of follicle-stimulating hormone reaches menopausal threshold, namely ≥ 40 mIU/ml. Such terminology has been questioned recently for being insolent and inconclusive of the prognosis, and is proposed to be named as primary ovarian insufficiency (POI) in lieu. In the present review, we still describe the disease as POF in accordance with most of the literature. The incidence of POF varies from 1 : 10 000 at the age of 20, to 1 : 1000 at 30, and eventually up to 1 : 100 in the forties with a tendency of increasing yearly [1]. Consequences of POF are distinctive yet severe, including sterility, osteoporosis and increased risk of cardiovascular events etc. Whereas the mechanism of POF onset remains majorly unclear resulting in inefficient treatments which are mostly symptom-based, it is of note that several causes are more disposed to cause POF on observation, including chemo- and radio-therapy and deranged autoimmune status. In the survey of possible treatment of POF, we notice melatonin (MLT), an endogenous pluripotent factor exerting various effects in regulating reproduction, oxidative stress and immunologic homeostasis. Interestingly, such regulations cover almost every aspect of the impairment POF brings about, which validates MLT as a possible cure for the disease.

Features of melatonin

Melatonin was first extracted and recognized by Lerner *et al.* in 1958. It belongs to indoleamine hormones with a chemical structure of N-acetyl-5-methoxytryptamine [2]. Though mainly synthesized in the pituitary gland, MLT is also distributed in the gastrointestinal system, skin etc. It is of note that the secretion of MLT in pituitary gland and iris presents a rhythmic pattern, which is elevated at night and is decreased in the daytime. Metabolism of MLT can also be influenced by drugs that interfere with 5-hydroxytryptamine (5-HT), the precursor of MLT. Receptors of MLT are extensively distributed in the skin, liver, kidney, brain and reproductive systems and can be sorted into MT-1, -2 and -3;

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the former two are family members of 7-G protein coupling receptors. Studies on MLT have vastly revealed its beneficial aspects mainly in anti-oxidation, anti-carcinogenesis, autoimmune regulation and reproductive modulation [3].

Melatonin in the ovary

In 1987, Brzezinski *et al.* detected the existence of MLT in pre-ovulatory follicle fluid in humans, which was at higher concentration in contrast to serum level [4]. It was at first thought to be an active intake of MLT by the ovaries from the circulation until Itoh *et al.* identified several requisite enzymes for MLT synthesis in the ovary and inferred that MLT could also be secreted by the ovarian granulocytes [5]. Niles *et al.* further reported identification of MTs on the cytomembrane of granulosa cells and assumed that MLT may exert direct effects on the ovary [6]. It has been reported that MLT level is decreased in post-menopausal and POF population, explicable for the impaired sleeping quality of such people [7]. Nonetheless, investigation on the direct linkage between MLT and POF remains unexplored. Below, we review the current experience that offer us a sound postulation that MLT may become a therapy of POF, and in the meantime, we propose where studies can further be done.

Melatonin and oxidation

One of the important causes of POF is chemo- and radio- therapy. Among teenagers with malignant ovarian diseases, the storage function of ovary is often impaired after such treatments which, in turn, increase the risk of POF development. The primary follicle amount is in negative correlation with radiation intensity [8]. Chemotherapy, as well as the ionizing radiation induced by radiotherapy may cause the release of large amounts of reactive oxygen species (ROS). Aside from exogenous ROS, ovulation itself is recognized as an inflammatory reaction which produces notable amounts of endogenous ROS. Zhang *et al.* have reported that ROS can induce apoptosis of quiescent stage oocyte *in vitro*. Gupta *et al.* have pointed out that oxidation and lack of antioxidase (SOD, GPx, etc.) can lead to atresia of antral follicle. Such evidence indicates that oxidation plays a pivotal role in the process of POF.

It has been assumed that POF is not but simple premature menopause, yet a manifestation of decrepitude [9]. MLT, however, can resist the apoptosis and decrepitude caused by oxidative stress. As the scavenger of ROS, MLT has been proven in a number studies to exert anti-oxidation effect extensively [10]. MLT may directly capture free radicals and transform them into molecules with less toxicity, or, indirectly resist ROS by elevating the antioxidase level. Not limited with MLT itself, the metabolic products thereof also possess potent activity of anti-oxidation [11]. Lissoni *et al.* have applied MLT in the process of chemotherapy performed on patients with solid malignant tumours and have reported reduction of adverse events caused by oxidative stress e.g. thrombocytopenia, cardio- and neuro- toxicity [12]. Similar functions of MLT have additionally been reported in breast cancer and prostate cancer where MLT also acts as an anti-tumourigenic factor [13]. Furthermore, in IVF-ET patients, MLT is detected to be negatively correlated with 8-OHdG, a sort of ROS, whose concentration is in close relation to follicular degeneration [14]. The above-mentioned evidence indicates that MLT and POF can possibly be connected with regard to oxidation and this is a field where studies should be done.

Melatonin and follicle

Follicular atresia and dysfunction account critically for POF. Current postulations of the detailed mechanism state that gene mutation causes primary ovarian follicle depletion, that mutation in FSH receptor causes disorder in follicle development and ovulatory signalling pathway, and that synthetic derangement of ovarian aromatase induces follicular dysfunction. Those pathologic changes eventually result in luteinized unruptured follicle syndrome (LUFS), even follicular atresia, namely POF [9, 15]. Nakamura *et al.* found that MLT concentration in pre-ovulatory follicular fluid was 3-fold higher than serum level and that MLT level was higher in larger follicles [16]. Treatment with MLT in sterile females resulted in MLT aggregation in their follicles [14].

Ovulation is a complicated process in which multiple factors e.g. oestrogen, androgen, progesterone and prostaglandin (PG) are co-functioning in a complex pathway [15]. Adriaens *et al.* report that MLT stimulates ovulation with a better antral follicle amount, follicular size and maturation in vitro. They have also observed that the progesterone and androgen level is elevated after MLT application and the changes are in positive correlation [17]. In the study of oesophagus, MLT is reported to elevate the PGE level [18]. Injection of MLT in goats is revealed to increase the oocyte capability in cleavage and development [19]. Tamura *et al.* have treated 115 failed IVF patients with MLT and have reported a higher fecundability [14]. Thus, it is reasonable to assume that MLT plays a crucial role in follicle formation and ovulation, where further studies should be conducted in a POF population. Not limited with direct influence on the ovarian function, MLT may also co-effect with distinctive factors whose functions in ovaries are broadly studied. BMP15 belongs to the TGF-β family and acts pivotally in ovulation. A reproductive defect is observed in BMP15 knock-out mouse model and TGF-β activity is increased by MLT stimulation in rats [20-21].

IGF-I is an anti-apoptotic factor in follicular formation and MLT has been proven to stimulate the production of IGF-I in granulocytes [22-23]. To sum up, MLT can possibly possess the anti-apoptotic effect in follicular formation which leaves a broad area of research.

Melatonin and autoimmune

It is reported that 10% to 30% of POF patients also have immune disorders [24]. In subjects with adrenal autoimmunity, autoimmune oophoritis is usually identified in histological exams: vast infiltration of lymphocytes, plasmacytes and macrophage cells. The factors released by these inflammatory cells have impaired the ovarian function and accelerated atresia. In POF patients, various anti-ovary antibodies can still be detected in dearth of histological inflammatory change. One of the important causes is the imbalance between effector T cells and regulatory T cells observed in POF patients [25].

The value of MLT application in several autoimmune diseases has been verified due to its exquisite immunomodulation [26]. MLT can combine with lymphocytes and monocytes via special sites and regulate such function. In the meantime, MLT is capable of affecting T cell related factors such as IL-2, IL-6 and TNF to maintain immune balance (immunostasis) [27]. Voznesenskaya *et al.* have constructed autoimmune-induced POF mouse model and have discovered that exogenous MLT at 5 mg/kg can relieve autoimmune reaction, improve maturation and elevate follicular survival rate. However, they point out that the injection should be made before the ovarian antigen is introduced [28]. More evidence should be gathered to validate the exact effectiveness of MLT application against POF in which a complete series of autoimmune-related factors should be investigated to outline a detailed signalling pathway.

Prospects

Thus far, there is no research on MLT application in POF while it has been revealed that MLT treatment may bring exciting outcomes. Current opinions concerning MLT have no longer been constrained within circadian rhythms regulation. The pluripotent functions of MLT have gradually converted into therapeutic practice in myocardial and Alzheimer researches [29-30]. It is also noted that the anti-tumourigenic effect of MLT may also contribute to development of novel auxiliary therapies against cancer and bring hope to prevent iatrogenic POF.

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