Oxidative Stress on Chicken Ovary

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Poultry ovary is a classic model for studying ovarian biology, follicular development and ovarian cancer. Long-term egg production (also aging in human) or other stress factors induced oxidative stress to cause follicle atresia, which may be the fundamental reason for reducing the fertility; however, our understanding of the molecular mechanisms and changes in microbiota, ovary function and its biomarkers remains limited. Oxidative stress refers to elevated intracellular levels of ROS derived from cellular metabolism or environmental stimuli that cause peroxidation of unsaturated lipids in cell membranes and oxidation of proteins, DNA, and steroid components, leading to further damage of the cell integrity and normal functions (Martínez-Álvarez et al., 2005; Michael et al., 2014; Ma et al., 2018). Oxidative stress has been proven to be linked to internal metabolism for aging (Yeh et al., 2005; Yang et al., 2019), many environmental stressors and chemical toxicants (gamma radiation, mycotoxins, heavy metals, pesticides, etc.) and health disorders (José et al., 2013; Celi and Gabai, 2015; Luoguori et al., 2018; Wang et al., 2019; Paithankar et al., 2021). Moreover, a large number of studies have shown that an excessive increase in ROS production will induce rapid primordial follicle loss and follicular atresia to lead to reproductive dysfunction (Gupta et al., 2006; Tanabe et al., 2011; Devine et al., 2012; Shen et al., 2012; Cao et al., 2018). However, the underlying pathological and molecular mechanism in oxidative stress-induced fertility deterioration remain unexplored. In this study, we established an oxidative stress model to access the effect of excessive ROS on the microbiota and ovary function, and also the effect of melatonin. These findings indicated that oxidative stress could decrease the fertility and influence gut microbiota and body metabolites in layer model, while the melatonin exert an amelioration the ovary oxidative stress through SIRT1-P53/FoxO1 pathway. The microbiota was involved in the OS and melatonin can be used as a target for ovary stress.

follicle atresia | cecal microbiota | metabolomics | melatonin | SIRT1-P53/FoxO1 pathway

1. Introduction

In recent years, there has been a growing interest in the role of reactive oxygen species (ROS) and oxidative stress in female reproduction [1][2]. Oxidative stress refers to elevated intracellular levels of ROS derived from cellular metabolism or environmental stimuli that cause peroxidation of unsaturated lipids in cell membranes and oxidation of proteins and DNA, leading to further damage of the cell integrity and normal functions [3][4]. Oxidative stress has been proven to be linked to the internal mechanism for aging [5][6], many environmental stressors and chemical toxicants (gamma radiation, mycotoxins, heavy metals, pesticides, etc.), and health disorders [7][8][9][10]. Moreover, a large number of studies have shown that an excessive increase in ROS production will induce rapid primordial follicle loss and follicular atresia to lead to reproductive dysfunction [11][12][13][14]. However, the underlying pathological and molecular mechanisms in oxidative stress-induced fertility deterioration remain unexplored.

Recent studies in mammals have found that oxidative stress affected nutrient metabolism, altering the body's homeostasis and exerting detrimental effects on the gut microbiota and intestinal function [15][16]. In addition, it has been proved that gut microbial dysbiosis is closely related to inflammation, diseases, and other stress disorders [17][18]. However, until now, the underlying changes in microbiota and their relationship with reproductive function under oxidative stress conditions had not yet been elucidated.

Melatonin (Mel, N-acetyl-5-methoxytryptamine), is an indoleamine, can be mainly bio-synthesized in the pineal gland and the initial precursor of melatonin biosynthesis is tryptophan [19][20]. Mel is also synthesized in numerous peripheral organs, including the intestine, retina, skin and harderian gland [20][21]. It has been shown that Mel reduces oxidative stress by scavenging pro-oxidative molecules such as superoxide anions and detoxifying oxygen and nitrogen-based toxic reactant [21][22]. Melatonin has been shown to have direct effects on ovarian function and microbiota [6][18][19]. Melatonin is identified in human preovulatory follicular fluid, where its concentration is higher than that in peripheral serum [20]. Previous studies have been suggested that Mel may enhance follicle growth by increasing levels of antioxidant enzymes and reproductive hormones in laying hens [22][23]. These findings suggest that Mel is related to the reproductive process, but the underlying mechanism is unclear.

As an NAD+-dependent protein deacetylase, silent information regulator 1 (SIRT1) is involved in the deacetylation of histones and transcriptional factors regulating the cell cycle, and has been a principal modulator of metabolism and resistance to oxidative stress [24][25][26]. SIRT1 was found to be ubiquitously expressed in the ovaries of animals, and has also been involved in the regulation of ovarian aging, follicular development, and oocyte maturation [24][27]. Previous research has shown that SIRT1 is involved in the protective effects of melatonin [28]; however, the exact mechanism is not elucidated. Foxo1 (forkhead box O1), a member of the FOXO transcription factor family, is an important player in regulating cell fate and combating oxidative stress and a downstream target of SIRT1 [29][30]. Is the SIRT1-FoxO1 pathway involved in the antioxidative stress function of melatonin in the ovary?

The poultry ovary is a classic model for studying ovarian biology, follicular development and ovarian cancer. In this study, we hypothesized that oxidative stress would decrease ovarian function by changing body metabolism and gut microbiota, while Mel administration would prevent oxidative damage and maintain the ovarian function of laying hens. Thus, this study aimed to investigate the negative effect of oxidative stress on ovary function, gut microbiota and serum metabolome in a layer model. We also determined the modulating effect of melatonin on ovarian follicle atresia in order to identify the relationship between melatonin and oxidative stress-induced ovarian dysfunction in vitro.

2. Discussion

Proper functioning of the ovary is critical to maintaining fertility and overall health, and ovarian function depends on the maintenance and normal development of ovarian follicles [31][32]. Accelerated metabolism occurs in rapidly proliferating granulosa cells (GCs) within developing follicles, leading to increased ROS production. Moreover, accumulating evidence demonstrates that excessive ROS are the key signals in the initiation of apoptosis in

granulosa cells of both primordial and growing follicles by diverse stimuli, such as alcohol, radiation, and smoking, as well as malnutrition and obesity [14][33][34]. Melatonin, an endogenous component of follicular fluid, has been suggested to improve GCs resistance to oxidative stress in vitro cell model [35][36][37]. In this study, we investigated the role of Mel in protecting ovarian follicles from atresia via the SIRT1-FoxO1/P53 pathway; we also examined the role of the gut microbiota in this process.

Oxidative stress induces apoptosis and affects cellular homeostasis, which results from dysregulation between antioxidant and pro-oxidant availability [34]. PC and MDA are produced during protein and lipid peroxidation, and they can be indicative of OS [38]. The markedly lower levels of T-SOD, Mn-SOD, T-AOC activities, along with significantly elevated MDA and PC levels within the ovary of tBHP challenged layers (OS group) suggest the presence of oxidative damage and also indicates that our model was successfully established in the current study.

We observed that OS decreased the layers' reproductive performance as indicated by the lower egg-laying rate, decreased hormone levels (lower estradiol, FSH, IGF-1), and also by the smaller primordial follicle reserve and increased atresia in the ovaries of the tBHP challenged layers. In our previous study, we also found that oxidative stress (induced by high levels of molybdenum and vanadium) decreased egg production in layers and the addition of antioxidants (tea polyphenols) was able to reverse this effect by improving the antioxidant capacity and gut microbiota balance [9][39]. Studies in mammals have found that oxidative stress can reduce the number of follicles in each stage of the ovarian cycle and impair ovarian function [40][41][42][43][44]. Additionally, previous studies have also reported that oxidative stress decreases hormone secretion (including lower estradiol, FSH, LH and IGF-1) and impairs the glutathione redox cycle [42][45]. Recent animal studies indicate that IGF-1 exerts antioxidant effects and anti-inflammatory effects in animals [46][47]. Leptin was demonstrated to exert an important role in the regulation of ovarian folliculogenesis indirectly via control of luteinizing hormone and FSH secretion [44]; however, the OS did not affect leptin levels, but decreased LH and FSH levels in the current study.

Interestingly, both melatonin and serotonin serum levels were decreased after the OS challenge, but the levels of melatonin and serotonin levels were enhanced in the ovary, while the addition of melatonin in the in vitro experiment was able to reverse these adverse effects induced by the tBHP challenge. To date, there is a paucity of data elucidating the mechanism contributing to the gut–ovary axis in the literature. In the present study, we aimed to establish a link between the gastrointestinal microbiome and ovarian function. In the current study, we found that the microbial diversity was reduced by the tBHP challenge. In agreement with our observations, another study also reported that mice fed a high-fat diet resulted in oxidative stress and the increased ROS levels disrupted the intestinal microenvironment, ultimately resulting in dysbiosis [48][49].

In this study, we observed that Firmicutes and Bacteroidetes were the most abundant at the phylum level, and Bacteroides and Lactobacillus were the dominant genera in all dietary treatments. The Firmicutes to Bacteroidetes ratio is an important biomarker of gastrointestinal functionality and can be used as an indicator of eubiosis conditions in the gastrointestinal tract [50]. Previous studies have also demonstrated that the gut microbiota of obese subjects (humans) is characterized by a lower abundance of Firmicutes and a higher abundance of Bacteroidetes compared to their lean counterparts [43]. At the same time, it has been reported that oxidative stress

has significantly increased the estimators of richness and community diversity of the gut microbiota of sows [49]. In addition, other studies have demonstrated that during conditions of intestinal dysbiosis, an excessive bioavailability of ROS molecules can contribute to an increase in oxidative stress [51][52]. It could be argued that these discrepancies may be related to the form of the type of animal or the level of oxidative stress.

In this study, although the cecal microbiota of the OS group was slightly similar to that of the CON one, the abundance of *Marinifilaceae, Odoribacter* and *Bacteroides_plebeius* in the OS group was significantly increased. Bacteroidetes are plant polysaccharide degraders and propionate producers that can improve intestinal barrier function and reduce inflammation and oxidative stress [38][53]. It has been reported that the relative abundance of Bacteroides is enriched in the gut of the host treated with antioxidants [54]. Our observation is in agreement with that of Wang [55], who found that oxidative stress significantly increases the relative abundance of *Bacteroides_f_Bacteroidaceae* in the gut of sows.

In this study, we observed that tryptophan metabolism, pyruvate metabolism, and the TCA cycle were disrupted by the tBHP challenge. While serotonin was upregulated, anthranilic acid, succinic acid, and oxaloacetate were downregulated. Tryptophan is an essential amino acid and is generally considered as the second-limiting amino acid in the most based diets of layers. Tryptophan metabolized in animals comes from two sources: one is an endogenous amino acid that is broken down by tissue protein, and the other is the exogenous amino acid that is digested and absorbed from the diet [56]. It has been reported that oxidative stress significantly decreased tryptophan/large neutral amino acids and serotonin concentrations in pigs, suggesting that oxidative stress might increase tryptophan metabolism [57]. This is consistent with our research results.

The tryptophan metabolism has been associated with various nutrients such as carbohydrates, proteins during the metabolic process [58]. An increase in the metabolism of tryptophan during oxidative stress could affect other physiological processes. On the other hand, tryptophan is also the precursor of Mel, and which can also be synthesized in the ovary [22]. Therefore, the decreasing levels of tryptophan in serum may correspond to the higher Mel and serotonin in the ovary. Pyruvate can realize the mutual conversion of carbohydrates, lipids, and amino acids in the body through the acetyl CoA and tricarboxylic acid cycles [59]. Therefore, pyruvate plays an important pivotal role in the metabolic connection of the three major nutrients. Moreover, the increased metabolism of pyruvate in cases of oxidative stress may be related to the increased need for oxygen and energy during the production of ROS.

It has been shown that supplementing exogenous pyruvate can prevent oxidative tissue stress [60]; however, in this study, we observed that oxidative stress promoted pyruvate metabolism. This apparent discrepancy may be due to different experimental models and different tissues tested, which needs to be clarified in further investigations. Oxidative stress could affect the levels of metabolites from glycolysis and the TCA cycle and production of adenine nucleotides [61]. In addition, it has been shown that an increase in oxidative stress and a decrease in the TCA cycle enzymes activity may cause the distal peripheral nerve to rely on truncated TCA cycle metabolism in rats [62]. Tryptophan catabolism has been recognized as an important player in inflammation and immune response. In this study, we found that oxidative stress caused a decrease in succinic acid and oxaloacetate in the TCA, which is

consistent with previous studies. Oxidative stress will hinder the TCA and pyruvate metabolism, and ultimately affect the metabolism of carbohydrates, lipids, and amino acids.

SIRT1 is an NAD+-dependent protein deacetylase, and it has been proved to be involved in the protective effects of melatonin [63]. In this study, we found that melatonin levels were decreased in oxidative stress and the exogenous addition of Mel could mitigate the negative impact of oxidative stress and improve ovarian functionality in tBHP challenged layers. It has been shown that SIRT1 exerts its beneficial effects via the reduction of oxidative stress and endoplasmic reticulum stress in mitochondria [28][64]. Our results also indicated that the SIRT1 was increased by melatonin addition in vitro and decreased FoxO1 and P53 expression. As reported previously, melatonin was able to protect mouse granulosa cells against oxidative damage by inhibiting FoxO1-mediated autophagy [64][65].

The animal model we used (ovaries from laying hens) may be different from the ovaries of productive mammalian animals. There are distinct histological and physiological differences according to the reproductive stage of the animal. Moreover, “a link between the gastrointestinal microbiome and ovarian function” could be speculated in the current animal model, but cannot be established for other species and humans especially. However, the literature about oxidative stress on the ovary function of poultry is not well elucidated, which needs to be explored in future studies.

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