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EC ENDOCRINOLOGY AND METABOLIC RESEARCH

Research Article

Comparison of the Effects of Melatonin and Resveratrol on Ovarian Insufficiency due to Cisplatin

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Received: July 27, 2020; **Published:** August 14, 2020

Abstract

Objective: This study was planned to investigate the possible effect of melatonin and resveratrol (RSV) on ovarian reserve in animals exposed to chemotherapy-induced premature ovarian insufficiency (POI).

Methods: Twenty-eight female rats were divided in four groups with 7 rats in each The groups consisted of a vehicle-treated control group (group 1), chemotherapy-treated rats followed by intraperitoneal RSV (group 2) or chemotherapy-treated rats followed by melatonin (group 3) or chemotherapy-treated rats followed by melatonin plus RSV (group 4). The cisplatin was administered intraperitoneally once daily at doses of 2.0 mg/kg for ten days. Rats in group 2 and 3 were given RSV (75 mg/kg, i.p) or melatonin (2 mg/kg, i.p) respectively. Rats in group 4 melatonin plus RSV were applied (75 mg/kg RSV plus 2 mg /kg melatonin). Animals in the treatment and control groups were sacrificed two weeks later and their ovaries were excised for histopathological analysis.

Results: Total follicle count was found increased in animal on RSV compared to animal on melatonin. The ovaries of the rats in the vehicle-treated rats exhibited follicles in all stages of development. While the ovaries of the rats in the RSV or melatonin showed significantly increased numbers of primary and secondary follicles they exhibited increased numbers of primordial follicles. Co-administration of melatonin and RSV more effectively prevented cisplatin-induced follicle disruption. The total body weights of the animals either receiving RSV or melatonin or melatonin plus RSV increased.

Conclusion: Melatonin or resveratrol administration improve ovarian reserve in rats with cisplatin-induced POI.

Keywords: *Melatonin; Resveratrol; Premature Ovarian İnsufficiency; Follicle*

Introduction

Last decade, use of follicle preserving agents such as melatonin and resveratrol (RSV) has become prevalent although their effects on developing follicles has not clearly known yet. To investigate whether melatonin or RSV has an impact on ovarian follicles are exposed to anti-cancer drugs, the developmental process of follicles needs to be known. Although the oocyte protective mechanism of action of these two molecules is not known clearly, some mechanisms are explained in experimental models. Resveratrol (RSV) is a polyphenol found in grapes that has exhibited antioxidant, cell survival improving and anti-cancer properties [1,2]. The oocyte preserving effects of melatonin could be derived from their antioxidant, antiapoptotic or cell cycle regulatory actions. Melatonin is a strong scavenger of oxygen radical and it can improve oocyte maturation [3]. Previous study demonstrated that melatonin administartion increases the number of metaphase II oocytes [4]. Meltonin also regulates cell cycle regulatory action of intracellular molecules and inhibit apoptosis [5].

Currently, it is largely unclear whether melatonin or RSV prevent the follicle damage resulting by chemotherapy. This experimental study was, therefore, planned for the purpose of determining the influence of melatonin and resveratrol supplementation on the number of follicles with different developmental stages in animal with cisplatin induced ovarian damage.

Materials and Methods

Twenty-eight female Wistar Albino strains weighing 250-300 grams were kept under standard environmental, heat, housing and feeding conditions. They were equally divided in 4 groups with 7 rats in each. The groups consisted of a vehicle-treated control group (group 1), chemotherapy-treated rats followed by intraperitoneal RSV (group 2) or chemotherapy-treated rats followed by melatonin (group 3) or chemotherapy-treated rats followed by melatonin plus RSV (group 4). POI was established by 10 consecutive days of intraperitoneal injection of cisplatin that was administered once daily. The cisplatin was administered intraperitoneally once daily at doses of 2.5 mg/kg for ten days. Rats in group 2 and 3 were given RSV (150 mg/kg, i.p) and melatonin (2 mg/kg, i.p) respectively. Rats in group 4 melatonin plus RSV were applied (75 mg/kg RSV plus 2 mg/kg melatonin). Animals in the treatment and control groups were sacrificed two weeks later, and their ovaries were excised for histopathological analysis. Treatment with melatonin or RSV was started at the 1st day of cisplatin and continued for 10 days. Control animals received injections of saline solution. Animals in each group were observed daily for clinical signs including weight loss and food intake. Animals in each group underwent ovariectomy two weeks later the first injection of cisplatin and their ovaries were used for follicle count. The SPSS software 21.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Shapiro-Wilk and Kolmogorov Smirnov tests were used to determine the normality of the samples. Mann-Whitney U test was used for comparisons of results. Data were given as mean ± standard deviation. P value < 0.05 was accepted as statistically significant.

Results

Total follicle count was found increased in animal on RSV compared to animal on melatonin. But the difference did not reach the statistical significance. The ovaries of the rats in the vehicle-treated rats exhibited follicles in all stages of development. While the ovaries of the rats in the RSV or melatonin showed significantly increased numbers of primary and secondary follicles they exhibited increased numbers of primordial follicles. Co-administration of melatonin and RSV more effectively prevented cisplatin-induced follicle disruption. Rats were on melatonin or RSV showed vaginal smears with superficial cells exhibiting estrogenic effect. The total follicle number in the vehicle-treated animals was approximately 1.2 times that of animals in group 2 and group 3. The total number of follicles in the control group was higher than melatonin and RSV. Sinificantly increased total body weight was observed in control animals at the end of second weeks. On the other hand, rats in the melatonin or RSV groups showed insignificant weight loss compared to control animals. Co-administration of melatonin plus RSV prevented significant weight loss. The total body weight differences of animals in the melatonin or RSV group did not reach statistical significance.

Discussion

Premature ovarian insufficiency due to chemotherapy is an important problem for young cancer women during reproductive period. Many different treatments have been developed to prevent chemotherapy-induced ovarian damage. While some off label drugs are used for this purpose, many herbal supplements have been tried for the same purpose. However, none of the drugs or supplements used fully prevented ovarian damage. Both melatonin and RSV have been used in many experimental studies to prevent ovarian damage due to chemotherapy [1-6]. However, most of the studies reported different results. Some studies have reported that mealtonin or RSV reduced chemotherapy-induced follicle damage, while other studies have reported that these molecules do not have any protective effects on the ovaries. In our study, both RSV and melatonin significantly reduced follicle damage due to ciplatin. The decrease in the number of primary and secondary follicles in the group receiving melatonin or RSV or in groups receiving RSV plus melatonin was prevented. A recent study reported that melatonin preserved the ovarian reserve by preventing numerical reduction in the dormant follicle pool [6]. Our study results coincide with the results of this study.

In this study, both RSV and melatonin's protective effect on primary or secondary follicle was insufficient. On the other hand, we found that the co-administration of RSV and melatonin enhances the protective effect of both molecules against cisplatin-induced ovarian failure in rat model. Co-administration of melatonin and RSV more effectively prevented the developing follicle in animals with cisplatin-induced ovarian damage. Simultaneous treatment with RSV and melatonin almost prevented the loss of the number of primordial and secondary follicles in rats exposed to cisplatin when compared with the individual administration of each molecule. These findings suggest that RSV plus melatonin treatment during cisplatin treatment can be used as a follicle preserving adjuvant therapy in young female cancer patients undergoing chemotherapy due to many different types of cancer diagnosis [1-6].

We can list the mechanisms underlying the oocyte protective effect of melatonin and RSV as follows. Both molecules have antioxidant and antiapopitotic effects. Especially melatonin is one of the strongest antioxidants known. RSV also has effects similar to melatonin. Free oxygen radicals due to cisplatin can be blocked by melatonin and RSv, thereby minimizing the damaging effects on the follicles [1-6]. The combined use of melatonin and RSV increases the follicle-protective effects, resulting in a stronger effect.

Conclusion

Co-administration of RSV and melatonin on animals exposed to cisplatin prevent ovarian follicles loss. The protective effect of these two molecules was especially seen in primary and secondary follicle pool. For these reasons, the combination of RSV and melatonin can be used as a follicle protector before and during chemotherapy in young cancer patients who go to chemotherapy.

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Volume 5 Issue 9 September 2020