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Original Research

Effects of Pinealectomy and Melatonin Application on Serum Melatonin, Nesfatin-1 and Ghrelin Levels

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ABSTRACT

Objective: In this study, it was aimed to investigate the relationship between the pineal gland and ghrelin and nesfatin-1 hormones in rats.

Methods: A total of 36 male rats were used in the study, and the animals were divided into 4 groups. Group 1, Control; Group 2, Pinealectomy (Px); Group 3, Px+Melatonin; Group 4 Melatonin. After the end of the experimental applications, melatonin, ghrelin and nesfatin-1 levels (ELISA) were determined in the blood samples taken from the animals.

Results: While pinealectomy resulted in suppression of melatonin levels, melatonin supplementation led to a significant increase in blood melatonin levels ($p<0.01$). Melatonin supplementation suppressed ghrelin levels, while pinealectomy increased ghrelin levels ($P<0.01$). On the other hand, Nesfatin-1 levels, which increased with melatonin support, were significantly suppressed by pinealectomy ($p<0.01$).

Conclusion: The findings of the study draw attention to an important relationship between the endocrine activity of the pineal gland and the hormones ghrelin and nesfatin-1, which play a critical role in nutrition. Consequently, administration of melatonin inhibits ghrelin but increases nesfatin-1.

Keywords: Pinealectomy, melatonin, nutrition, nesfatin-1, ghrelin, rat.

INTRODUCTION

The properties of the Nesfatin-1 molecule as a hormone were revealed in 2006. This molecule secreted from the hypothalamus has also attracted the attention of researchers with its role in the regulation of nutrition [1]. The suppressive effect of food intake by Nesfatin-1 is independent of leptin. The effect of Nesfatin-1 occurs only through a melanocortin receptor-dependent mechanism [2,3]. The precursor of this molecule is NUCB2 (pronesfatin), an 82 amino acid peptide that suppresses food intake. Compounds such as precursor protein (NUCB2), nucleobindin-2 (pronesfatin), prohormone converters pronesfatin nesfatin-1 (amino acids 1-82), nesfatin-2 (amino acids 85-163) and nesfatin-3 (amino acids 166-396) occurs [1-4]. Conversion of the NUCB2 molecule to nesfatin-1 is required for the suppressive effect of food intake to occur. [1]. Consequently, Nesfatin-1 is an amino terminal fragment derived from NUCB2. Its amount in the hypothalamic nucleus decreases in starvation. [1]. Therefore, its role in feeding behavior is important.

Ghrelin hormone is produced in the neuroendocrine cells in the fundus and pylorus regions of the stomach where ghrelin is mainly released [5]. Concentration of ghrelin peptide shows about 65% decrease in rats which are subjected to gastrectomy. It is known that in the regulation of ghrelin secretion in the stomach, besides the factors affecting nutrition, hormonal factors are also effective [6]. The ghrelin hormone is not only limited to the digestive system, it is also released in the stomach veins and participates in the general circulation. It has been shown that the hormone ghrelin can cross the blood-brain barrier and affect hypothalamus functions [7]. The hormone ghrelin, which crosses the blood-brain barrier, affects the hypothalamus functions in both humans and some rodents and contributes to the regulation of feeding [8,9]. It has been reported that central and peripheral administration of the hormone ghrelin may increase appetite, leading to increased food intake and consequent obesity in rodents [10]).

Ghrelin, which plays a role in feeding behaviors, is a hormone that increases appetite. Therefore, it is defined as orexigenic hormone [11,12]. The ghrelin hormone secreted from the stomach is carried to the brain through the blood. It is also referred to as a brain-intestinal peptide because it has an appetite-increasing effect in the hypothalamus [13]. This hormone exerts its appetite-increasing effect through the molecule Neuropeptide-Y (NPY), which is a strong stimulant of nutrition in the hypothalamus [14].

There is no consensus on the effect of melatonin (MT) on feeding behaviors. It has been shown that the food intake-enhancing effect of melatonin administration in rats is evident in medium and low dose applications. [15]. This shows that melatonin supplementation in nutritional behaviors may be dose dependent. It has been reported that melatonin does not have a direct effect on food intake, but may have an indirect hyperphagic effect because it suppresses 5-HT2A [16]. In conclusion, melatonin is a hormone associated with feeding behaviors.

Main Points;

- The results of the current study show that the pineal gland may have important effects on the hormones ghrelin and nesfatin-1, which play critical roles in nutrition.
- In conclusion melatonin supplementation inhibites ghrelin, and but increases nesfatin-1.

Studies about on relation between melatonin and nesfatin-1 are very few in the literature. Studies conducted with some animal species such as frog and fish have shown a possible relationship between nesfatin-1 which plays an important role in the regulation of nutrition and pineal gland [17]. It has been emphasized that melatonin administration causes an increase in gastric ghrelin release in rats [18], and there may be a significant association between pineal gland and ghrelin [19, 20]. Orexigenic effect of ghrelin which is an important hormone in the stimulation of nutrition occurs via NPY. The relationship between Ghrelin hormone which has an important critical effect on NPY and pineal gland is yet to be understood.

The objective of this study was to determine how nesfatin-1 and Ghrelin hormone influenced in rats subjected pinealectomy and melatonin supplementation.

MATERIALS AND METHODS

Experimental procedures of the present study were carried out at Selcuk University Experimental Medicine Research and Application Center. The study protocol was approved by the experimental animal ethics committee of the same center (no: 2015-87).

In the study performed on 36 adult male rats, the animals were divided into 4 groups. While the control group consisted of 6 rats, the administration groups consisted of 10 rats.

Group 1: Control: Animals in this group were not treated.

Group 2: Pinealectomy (Px): The rats in this group underwent pinealectomy under general anesthesia.

Group 3: Px + Melatonin: Rats underwent pinealectomy under general anesthesia and subcutaneous melatonin (5 mg/kg/day) was administered for 1 month after pinealectomy.

Group 4: Melatonin: The rats in this group were given subcutaneous melatonin (5 mg/kg/day melatonin for 4 weeks).

Experimental Procesures

Melatonin Administration

Melatonin was commercially supplied (Sigma M-5250). Melatonin was subcutaneously injected to the rats with a dose of 5 mg/Kg/day at A.M. 10:00. Melatonin injections were carried out at the same hours for 28 days.

Pinealectomy Application

Pinealectomy procedure was performed in rats under general anesthesia. Anesthesia was induced with 60 mg/kg ketamine hydrochloride (Ketalar, Parke – Davis) and 5 mg/ kg xylazine (Rompun, Bayer). Pinealectomy procedure was applied following the method described by Kuszack and Rodin [21].

Blood Collection

After the completion of the experimental stages of the study, all animals were sacrificed under general anesthesia and serum samples were taken. General anesthesia was administered to all animals (with intramuscular administration of a combination of Ketalar (60 mg/kg), Parke-Davis and xylazine (5 mg/kg) "Rompun, Bayer") to avoid animal suffering.

Biochemical Procedures

Melatonin Analysis

Melatonin analysis was carried out using Cusabio Melatonin ELISA test kit (Catalog no: CSB-E13433r). The samples were read at 450 nm with BMG-LABTECH brand SPECTRO start Nano ELICA device (Germany). The results were given as pg/ mL.

Ghrelin Analysis

Ghrelin analysis was performed using Cusabio Rat ELISA test kit (Catalog no: CSB-E9816r). The samples were read at 450 nm with BMG-LABTECH brand SPECTRO start Nano ELICA device (Germany). The results were determined as ng/mL.

Nesfatin-1 Analysis

Nesfatin1 analysis was performed using Cusabio Rat ELISA test kit (Catalog no: CSB-E14378r). The samples were read at 450 nm with BMG-LABTECH brand SPECTRO start Nano ELICA device (Germany). The results were given as ng/mL.

Statistical Analysis

Statistical evaluation of the results was made with SPSS 22.0 statistical software, and arithmetic means and standard deviations were determined. Homogeneity of the data was examined with Shapiro-Wilk test, and the data were found to non-normally distribution. Kruskal-Wallis H test was used in determination of the differences between the groups, and Mann-Whitney U test was utilized to found the group causing difference. P<0.01 values were considered statistically significant.

RESULTS

Comparison of Serum Melatonin Levels Among the Groups

Group 2 has the lower melatonin than other all groups (p<0.01). Serum melatonin levels were higher in the pinealectomy + melatonin supplementation (Group 3) compared to the control (Group 1) and pinealectomy (Group 2) groups (p<0.01). In our study, the highest serum melatonin levels were found in the melatonin group (Group 4) (p<0.01) (Figures 1).

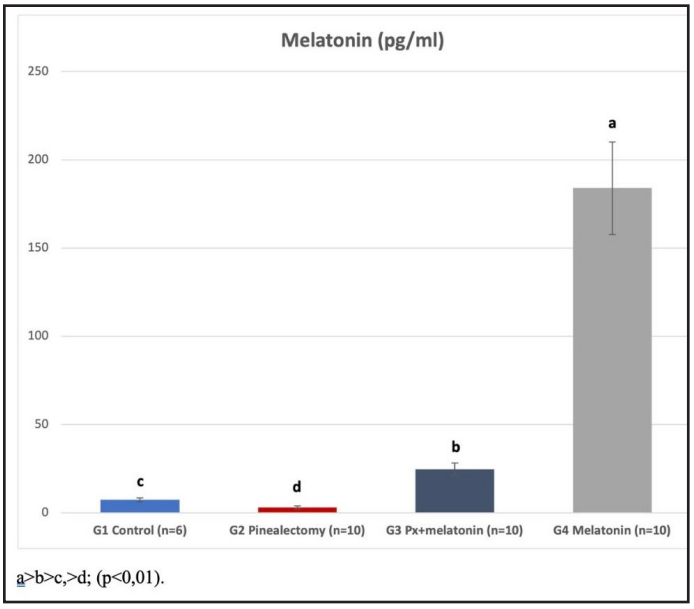

Figure 1. Serum Melatonin Levels of Study Groups

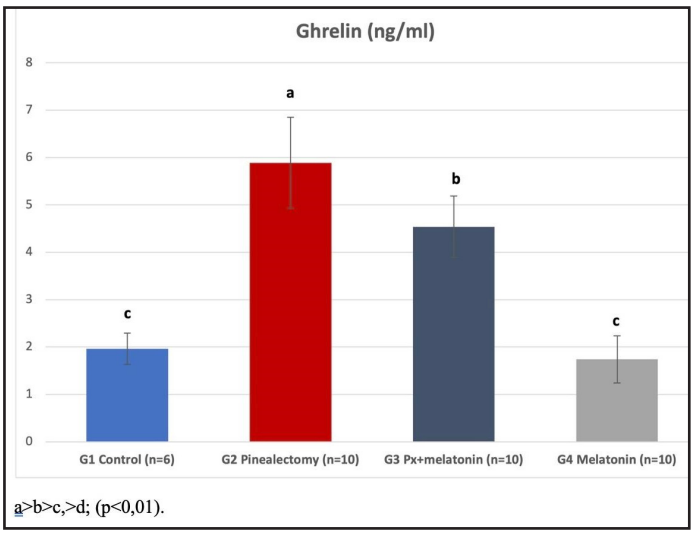

Figure 2. Serum Ghrelin Levels of Study Groups

Comparison of Serum Ghrelin Levels Among the Groups

Lowest serum ghrelin levels were obtained in Group 1 (control) and Group 4 (melatonin group) (P<0.01). Serum ghrelin levels of

Px+melatonin group (Group 3) were higher compared to Groups 1 and 4 (P<0.01), and lower compared to Group 2 (Px group) (P<0.01). The highest serum ghrelin levels were found in the Px group (Group 2) (P<0.01, Figures 2).

Comparison of Serum Nesfatin-1 Levels Among the Groups

Pinealectomy group has the lowest Nesfatin-1 (Group 2) (P<0.01). Nesfatin-1 levels of the Px+melatonin group (Group 3) were higher than that of the control and Px+melatonin groups (P<0.01). The highest serum Nesfatin-1 levels were observed in the melatonin supplementation (Group 4) (P<0.01, Figures 3).

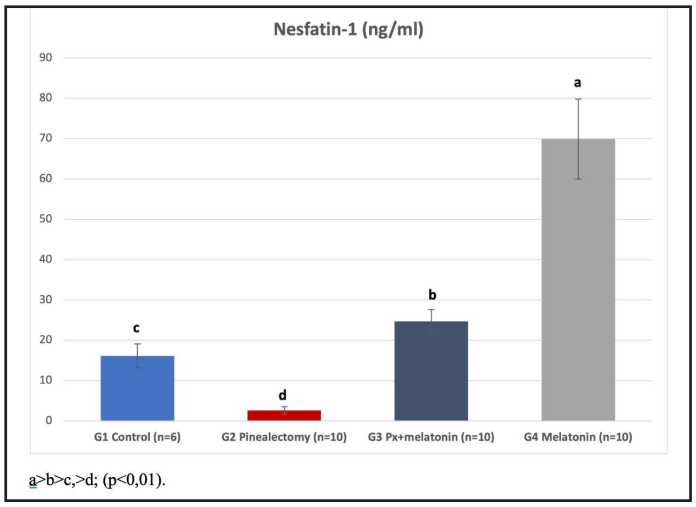

Figure 3. Serum Nesfatin-1 Levels of Study Groups

DISCUSSION

Discussion of Melatonin Results

Pineal gland is the main source of the synthesis and release of melatonin hormone. However, besides pineal gland melatonin synthesis occurs also in "digestive system, respiratory system, kidneys, adrenal glands, structures related to cellular immunity, thyroid gland and placenta" [22, 23]. For this reason, despite decreased melatonin levels in the animals which pineal gland is removed, there are measurable levels of melatonin hormone in the circulation. [23]. In our study, the lowest melatonin levels were obtained in Group 2, which underwent pinealectomy, and the highest melatonin levels were obtained in the groups that received melatonin (G3, G4). Our results regarding melatonin levels show that pinealectomy in animals was successful in this study [23, 24]. This will also enable a more credible discussion of our other results.

Discussion of Ghrelin Results

Results of the studies investigating relationship of the pineal gland and its product melatonin with nutritional behaviour are controversial. Some reports have shown that melatonin affects food intake, fat deposition and body weight in mammals [25]. Melatonin has been reported to cause decreases in fat mass and body weight in Siberian hamster [26] and rats [27]. In contrary, melatonin has been reported to increase fat mass in Syrian hamsters [28] and body weight in racoons [29]. On the other hand, Mustonen et al., [30] determined no any change in body weight after melatonin therapy. However, it is obvious that melatonin plays a role in nutritional behaviour [31]. In the present study, the highest serum Ghrelin levels were determined in Px group (Group 2), and the lowest levels in the control (Group 1) and melatonin (Group 4) groups. Serum ghrelin levels of the Px+melatonin group (Group 3) were higher compared to Groups 1 and 4, and lower compared to the Px group (Group 2). In their study on fish, De Pedro et al. [25] found that chronic melatonin administration creates a tendency to suppression of circulating ghrelin levels. It has been reported that supplementation of the amino acid tryptophan, a precursor in melatonin synthesis, at a dose of 1 g for 5 days increased food intake in dogs but did not change ghrelin levels [32]. Raised ghrelin levels in starvation have been shown to decrease after administration of oral melatonin or tryptophan amino acid both in patients with liver cirrhosis and healthy control persons [33]. Results of the limited number of above mentioned studies indicate to a relationship between melatonin and ghrelin. In our study, increased ghrelin levels were obtained in the pinealectomized rats, while melatonin application in the pinealectomized rats rats significantly decreased ghrelin levels compared to the pinealectomy group. However, ghrelin levels of the px+melatonin group were higher than the controls. A study by Mustonen et al. [20] reporting decreased plasma ghrelin levels with exogenous melatonin application in rats supports our finding that increased ghrelin levels in the pinealectomy group were reduced with melatonin administration. At least it can be said related to our results that, there is an important correlation between pineal gland and ghrelin levels. Removal of the pineal gland results in change also in ghrelin release. Comparing with the studies examining the relationship between melatonin administration and ghrelin, studies investigating the relationship between pinealectomy and ghrelin are quite limited. In their study, Canpolat et al. [16] reported that removal of the pineal gland had no effect on gastric ghrelin, but pinealectomy may significantly influence ghrelin responses in the hypothalamus. Based on this finding, the same authors proposed that pineal gland may be crucial in ghrelin responses in the hypothalamus [16]. A similar result

was reported by Aydin et al. [34]. Results of the ghrelin levels we obtained in this study are partially consistent with above mentioned studies. The number of publications which we could discuss our results one-to-one in all dimensions is quite limited. However, it was found related to our ghrelin results that pinealectomy leads to significant increase in ghrelin levels in rats, and although exogenous melatonin application cause to a decrease in ghrelin levels, this decrease did not reach to the levels of the control subjects. Exogenous melatonin induced anorectic properties, and reduces the expression of ghrelin [35]. Interestingly, no any change was observed in the ghrelin levels of the rats given exogenous melatonin without subjected to pinealectomy compared to the animals in the control group. Based on this result, it can be said that presence of the pineal gland is functionally needed in the regulation of serum ghrelin levels

Discussion of Nesfatin-1 Results

Present study indicated that Nesfatin-1 levels were lowest in pinealectomy group. Nesfatin-1 levels of the Px+melatonin (Group 3) were higher compared to the control and Px+melatonin groups. The highest serum Nesfatin-1 levels were observed in the melatonin supplementation. Nesfatin-1 can be considered as a newly defined peptide. The most important interesting effect of Nesfatin-1 is its leptin independent food intake suppressing effect [36]. Nesfatin-1 which has been reported as the satiety molecule in the hypothalamus and cerebrospinal fluid [1], has also been reported to be found in diffrent hypothalamic nucleus such as the ARC, PVN, SON and lateral hypothalamic area [1] in various organisms. Various experiments have supported inhibitory role of Nesfatin-1 on food intake [1, 36] and indicated that it may have glucose regulatory effect in diabetic mice [36]. The mentioned studies have demonstrated that Nesfatin-1 may also play a role in the regulation of metabolism. Interestingly; nesfatin-1 like reactivity has been found in the pineal gland of frogs [17], that suggest a potential relationship between the pineal gland and its product melatonin, and nesfatin-1. Nesfatin -1 is known to decrease nocturnal feed intake in rats, and at the same time it has been suggested that serotonin may also have a role in appetite suppressing effects of Nesfatin-1 [37]. Melatonin synthesized by serotonin and the presence of a high-level rhythmic secretion at night [23], is similar to the findings of the study by Stengel ve Taché. Many study have proposed that melatonin is effective on nutritional behaviour, and this effect especially occurs via leptin which suppresses appetite [23,31,38]. We could not found a study in Med-line screening to compare our results one-to-one. There is no any study drawing attention to the relationship between melatonin and nesfatin-1 except for the study by Senejani et al. [17] which was conducted on frogs and emphasized the potential association between the pineal gland and nesfatin-1. Previous study showed that some central regulators are important in different metabolism such as controlling proliferation and function. These regulators are neuropeptide Y (NPY), cocaine- and amphetamine-regulated transcript (CART), melatonin and leptin. In our study, CART has not been investigated but it has a relationship pineal gland. In future studies, this relationship may be investigated in much more detail [39].

In the present study; we found significant suppression in nesfatin-1 levels in the pinealectomized rats, and obtained increased nesfatin-1 levels with melatonin supplement in the pinealectomized rats compared to the control animals. However, more interestingly we obtained the highest nesfatin-1 levels in the group which we administered melatonin. We think that this result in our study is the first in the literature.

Based on the results we obtained from this study, it can be said that pineal gland is needed in the regulation of ghrelin and nesfatin-1 levels, thus their functions, and even pineal gland may play an important role in nutritional behaviour of the mentioned hormones.

Limitations

The limiting factor in the current study is that the relationship between the pineal gland and ghrelin and nesfatin-1 was not demonstrated with various melatonin doses and administration times. Elimination of this gap in future studies may enable us to access new and critical information.

CONCLUSION

Our findings show that;

1.Pinealectomy leads to a significant increased ghrelin which is a stimulator of food intake.

2.Melatonin administration reverses this increase in the pinealectomized rats.

3.Again in this study, we obtained significant suppression in nesfatin-1 in rats, and increased nesfatin-1 with melatonin supplement in the pinealectomized rats compared to the control animals.

4.However, more importantly we obtained the highest nesfatin-1 levels in melatonin alone group.

5.According to the results obtained in the present study, endocrine activity of the pineal gland plays a critical role in the regulation of ghrelin and nesfatin-1 levels and thus their functions.

Research Data Policy and Data Availability Statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Compliance with Ethical Standards: This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Experimental Animals Ethics Board of Selcuk University Experimental Medicine Research and Application Center (2015-87). This research was performed on the animals (rat).

Conflict of Interest: The authors declare that they have no potential conficts of interest to disclose.

Author Contributions: SS, EM, SBB and OU made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; SBB, RM and AKB drafted the work or revised it critically for important intellectual content, approved the version to be published. The authors declare that all data were generated in-house and that no paper mill was used.

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