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EFFECT OF MELATONIN ON CARBOHYDRATE METABOLISM AND SOME RELATED HORMONES IN RATS

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ABSTRACT

The effects of melatonin (3 & 30 mg/kg, p.o. daily for 3 months) on serum glucose, insulin, cortisol, testesterone, T3 and T4 levels in adult male rats were investigated. Rats were divided into 3 groups, first and second groups received 3 & 30 mg/ kg melatonin orally as a morining daily dose for 3 months respectively. The third group received solvent only and served as control. Melatonin at 3 mg/ kg dose level enhanced carbohydrate metabolism as it increased serum glucose and insulin levels. It also decreased testosterone level. Both dose levels had no significant effect on serum T3 and T4 levels. However, both dose levels increased serum cortisol level. Melatonin at a dose of 30 mg/ kg level had no significant effect on serum glucose, insulin, and testosterone levels. It is concluded that melatonin at 3 mg/ kg dose level enhances carbohydrate metabolism and has antigonadotrophic action. The data suggest that both dose levels are equal in their action on thyroid function and cortisol level. However the lower dose is more effective on carbohydrate metabolism and testosterone than the higher dose.

INTRODUCTION

Some data suggest that heightened activity of pineal gland may be diabetogenic. The onset of insulin-dependent diabetes mellitus is greater during winter months [1,2,3] when melatonin levels are also higher. Pinealectomy in rats decreases blood glucose level [4] and increases plasma insulin-like activity [5]. However, contradictory data have also been found [6,7,8]. Blindness significantly increases blood glucose level in male rats [9]. In addition pinealectomy increased insulin release from isolated rat islets [8]. Other investigators reported that melatonin had no effect on insulin release [10].

Melatonin decreased T4 levels when administered as daily afternoon injection in male and female hamster [11,12,13]. Melatonin suppressed T3 and T4 secretion in pinealectomized rats [14]. However, exogenous melatonin administration does not influence thyroid functions during light phase when used in the morning [15].

Melatonin decreases the weight of adrenal gland. It also decreases cortisol level when used as afternoon injections in rats [16]. However Gromova and his co-workers found that melatonin increases corticosterone production in rats [17]. Melatonin did not affect cortisol output in male Syrian hamster and had slight stimulatory effect was observed in female adrenal glands [18]. In human, melatonin did not modify cortisol level [19,20,21] in young men. However melatonin enhanced cortisol level in aged but not in young women [22].

Moreover, melatonin causes direct inhibition of testosterone production from rat leydig cells [23]. In normal men, melatonin had no significant effect on secretion of LH, FSH, prolactin or testosterone [24].

The aim of the present work is to investigate the effect of melatonin on carbohydrate and hormones related to carbohydrate metabolism in male rats.

Materials and Methods

Three months-old male rats (National Research Centre, Cairo, Egypt) were housed 5 / cage. They are divided into three groups. The first group received melatonin (Amoun Pharmaceuticals Co, Cairo, Egypt) 3 mg / kg for 3 months. The second group received melatonin 30 mg /kg for 3 months. The third group received solvent (Tween 80 1%) and considered as negative control .At the end of three months, blood was taken from the orbital sinus of the eye. Blood was collected in dry centrifuge tubes and serum was separated. Serum glucose was determined immediately using glucose kit. Testosterone, T3 and T4 were determined in serum by flouroimmunoassy method using Delfia kits (Wallac oy. Turku, Finland). Cortisol and insulin were determined by radioimmunoassy using Diagnostic System Laboratories (DSL) RIA kits ,Texas , USA.

Data are presented as mean ± standard error of mean (SEM). Differences between treated and control groups were analysed for statistical significance either by one-way analysis of variance (ANOVA) or by Student's t-test procedures when appropriate. Differences were considered to be significant at $p < 0.05$. All statistical procedures were analysed by a computer-assisted program (PC state, version, University of Georgia, Athens, Georgia, USA).

RESULTS

Effect on serum glucose level

As indicated by Fig. (1), oral administration of morning daily dose of melatonin (3mg/kg) induced, a significant increase in serum glucose level compared with control values (170.3 ± 7.4 % Vs 100 ± 5.7 %). However 30 mg/kg dose level had no significant effect.

Effect on serum insulin level

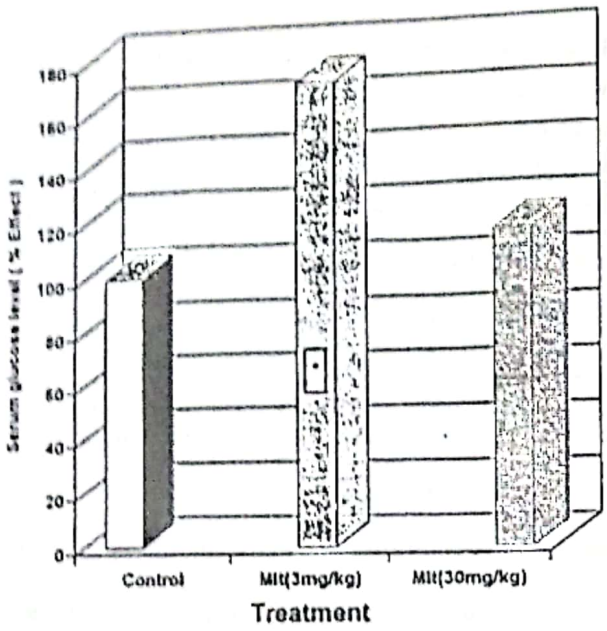
Subacute treatment with melatonin at a dose of 3 mg/kg increased serum insulin level compared with control level (234.9 ± 73.6 % Vs 100 ± 41 %) as shown in Fig. (2). Higher dose of melatonin did not show any effect on serum insulin concentration.

Effect on thyroid hormones

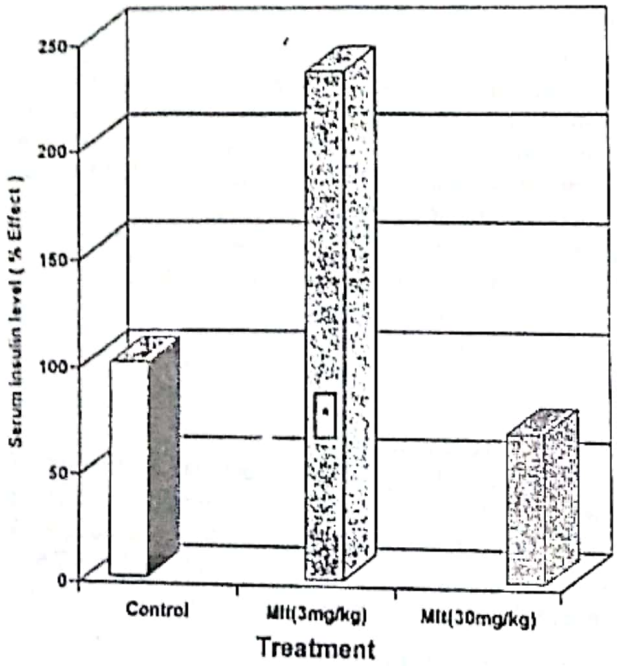
As presented by Figs. (3) and (4), serum levels of T3 and T4 were not significantly affected by Subacute oral melatonin treatment for 3 months in the two dose levels studied.

Effect on serum cortisol level

Serum cortisol level was significantly elevated after oral treatment with 3 & 30 mg/kg melatonin compared with control values (to 366.99 ± 48.5 % and



Fig(1): Effect of oral administration of melatonin (3mg/kg and 30mg/kg) for 3 months on serum glucose level in adult male rats.



Fig(2): Effect of oral administration of melatonin (3mg/kg and 30mg/kg) for 3 months on serum insulin level in adult male rats.

*** Significantly different from control value at P<0.05**

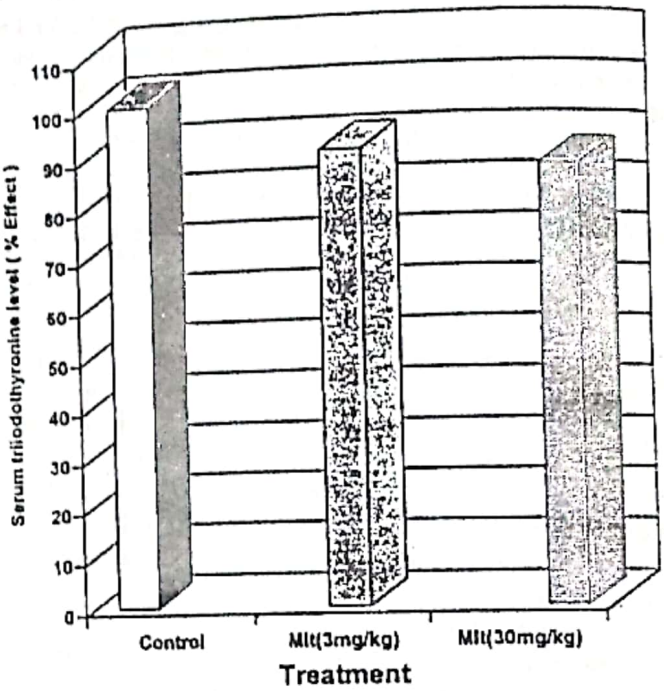
271.8 ± 48.5 % respectively compared with 100 ± 19.4 % in control group) as presented in Fig. (5).

Effect on serum testosterone level

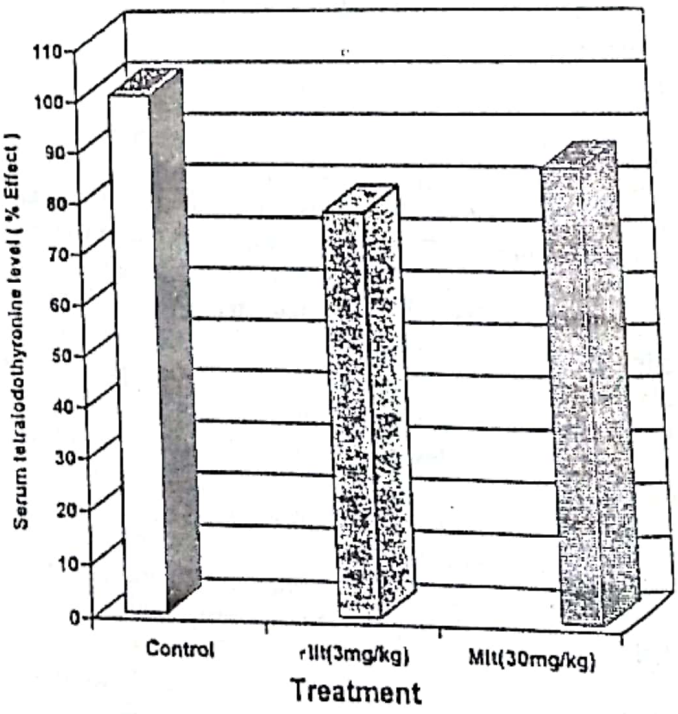
Melatonin at a dose 3 mg/kg daily for 3 month significantly reduced serum testosterone concentration (from 100 ± 21 % to 30.37 ±11.4 %) as illustrated by Fig.(6). Higher dose of melatonin did not significantly affect serum level of testosterone.

DISCUSSION

Results of the present study showed significant increase in serum glucose level in case of 3 mg/Kg melatonin. These finding confirm the observations that

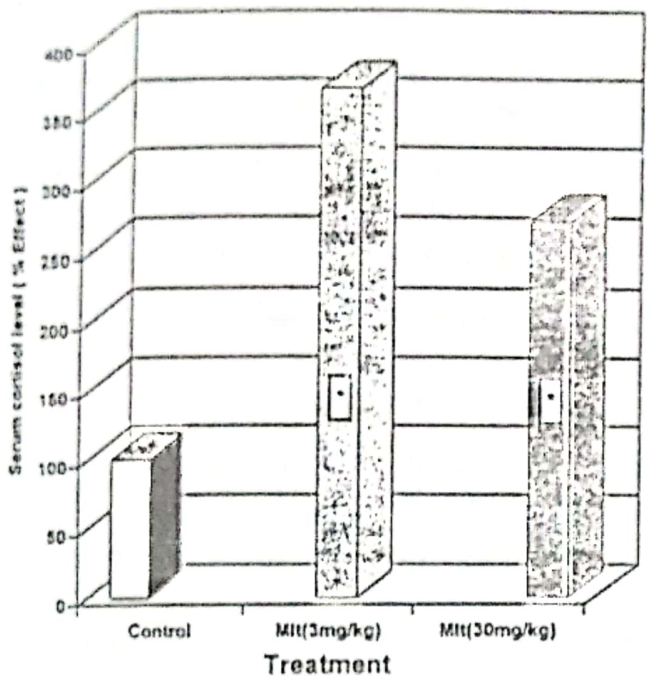


Fig(3): Effect of oral administration of melatonin (3mg/kg and 30mg/kg) for 3 months on serum triiodothyronine (T3) level in adult male rats.

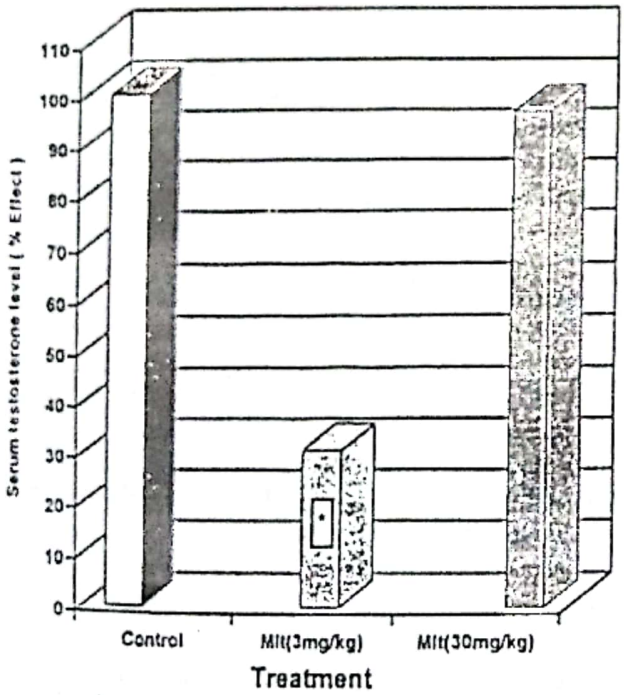


Fig(4): Effect of oral administration of melatonin (3mg/kg and 30mg/kg) for 3 months on serum tetraiodothyronine (T4) level in adult male rats.

*** Significantly different from control value at P<0.05**



Fig(5): Effect of oral administration of melatonin (3mg/kg and 30mg/kg) for 3 months on serum cortisol level in adult male rats.



Fig(6): Effect of oral administration of melatonin (3mg/kg and 30mg/kg) for 3 months on serum testosterone level in adult male rats.
* Significantly different from control value at P<0.05

pinealectomy decreases blood glucose level [25]. Moreover, our results are in agreement with Burns who found that exogenous melatonin increase blood glucose level in monkey [26]. The increase in serum glucose may be as a consequence of the increase in cortisol level (shown in the present study). This increase in serum glucose level is expected to increase insulin release leading to an elivated serum insulin concentration. On the other hand, pinealectomy decreases blood glucose levels [26]

The finding that melatonin, at the two dose levels studied, has no effect on thyroid hormones. These observations confirm similar results reported by Kniazewiski and his co-workers[15] that exogenous melatonin administration in rats does not influence the thyroid functions during light phase. Moreover they reported also that both pinealectomy and exogenous melatonin administration did not influence thyroid activity.

The present investigation demonstrated that melatonin administration at the two dose levels studied (3 and 30 mg /Kg) in the morning for three months induced a significant increase in serum cortisol level, the lower dose being more effective than the higher dose. The effect of melatonin on cortisol level could be explained according to the report of Marinova and his co-workers [27] who found that melatonin by reducing the affinity of residual hippocampus adrenocortical steroid receptors, may further imbalance hypothalmo-pitutary-adrenal axis negative feedbacks and favour an increase in cortisol level. Melatonin may magnify cortisol response to ACTH by an action of adrenal levels [28,29,30].

Our results showed that melatonin administration for three months in a dose of 3 mg/kg induced a significant decrease in serum testosterone level. However, the large dose (30 mg/ kg) had no effect on serum testosterone level. These results are in accordance with other investigations which demonstrated an inhibitory effect of melatonin on testosterone secretion [31,32,33,24]. The suggested mechanism for melatonin inhibitory action on testosterone is that melatonin may act at brain and pituitary level [35, 36] as it was found that melatonin inhibits luteinizing hormone releasing hormone (LHRH)-induced luteinizing hormone (LH) release through an action involving inhibition of calcium (Ca 2+) influx [37]. However a direct action at gonadal level may be present [38,39] as melatonin receptors are found on rat leydig cells.

The observation that higher dose level of melatonin (30 mg/kg) had no significant effect on testosterone could be explained by the capability of melatonin for desensitizing or down regulating its receptors [40] where melatonin availability in large dose for long period saturates the proposed melatonin receptors in different parts (Leydig cells, pituitary, brain.....ect). So, these receptors become insensitive and remain in perpetual state of down regulation [41, 42].

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تأثير الميلاتونين علي أيض الكربوهيدرات و بعض الهرمونات ذات العلاقة

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أجري هذا البحث علي ذكور الفئران البالغة ، و قد تم تقسيم الفئران إلي مجموعات. المجموعة الأولي تم إعطائها جرعة من الميلاتونين بمقدار ٣ ملغم/كلغم ، أما المجموعة الثانية فقد تم إعطائها جرعة من الميلاتونين بمقدار ٣٠ ملغم/كلغم. المجموعة الثالثة تم استخدامها كضابط و تم إعطائها كافة السوائل المعطاة للمجموعتين السابقتين و غير حاوية علي الميلاتونين يومياً و لمدة ثلاثة أشهر. وجد أن الميلاتونين بجرعة مقدارها ٣ملغم/كلغم تساعد علي زيادة معنوية في مستوي الجلكوز و الأنسولين في مصل دم الفئران و من جهة أخري وجد انخفاض معنوي في مستوي هرمون التستوستيرون و كذلك وجد أن كلتا الجرعتين لا تأثير معنوي لهما علي مستوي هرموني الغدة الدرقية الثلاثي و الرباعي ((T4, T3 في مصل دم تلك المجموعتين. من ناحية أخري وجد أن كلتا الجرعتين تزيد من مستوي هرمون الكورتيزول زيادة معنوية في مصل الفئران. بالإضافة إلي ذلك وجد أن جرعة الميلاتونين ٣٠ملغم/كلغم ليس لها تأثير معنوي علي مستوي الجلكوز ، الأنسولين و التستوستيرون في مصل الفئران.

يمكن الاستنتاج أن الميلاتونين بجرعة ٣ملغم/كلغم تساعد علي زيادة أيض الكربوهيدرات و لها تأثير سلبي علي الغدد المنتجة للهرمونات الجنسية. لذلك يمكن الاقتراح بأن كلتا الجرعتين من الميلاتونين لها تأثير متساوي علي أعمال الغدة الدرقية و مستوي الكورتيزول في مصل الدم، و في كل الأحوال فإن الجرعة الصغيرة من الميلاتونين لها تأثير أكبر علي أيض الكبروهيدرات و هرمون التستوستيرون من الجرعة الكبيرة.