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RESEARCH ARTICLE

Effect of melatonin administration and induction of hyperprolactinemia in the first third of pregnancy on the adrenal of pinealectomized female rats

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Abstract

This study tested the hypothesis that the administration of melatonin and/or domperidone during the first third of pregnancy affects the morphology of the adrenal of the pinealectomized rats. We used 35 albino rats divided in seven groups. Then, the rats were subjected to pinealectomy and treated with melatonin and/or domperidone for 7 days. The female rats were weighed throughout pregnancy and then the adrenal was removed for histological analysis. Statistical analysis of adrenal weights was performed by non-parametric tests.

The results demonstrated significant increases in the absolute and relative weights of adrenal in the pinealectomized group whose animals were treated with domperidone, increased body weight in the groups of animals that were pinealectomized and treated with melatonin, and in the pinealectomized animals treated with domperidone. Histological analysis revealed that the pinealectomized animals and the group treated with domperidone showed a more enlarged and vacuolated zona fasciculada of the adrenal, whereas in the group of pinealectomized animals treated with melatonin and domperidona the cells of the zona fasciculata were less vacuolated and the medulla was more vascularized, and the appreciable presence hemosiderin. Thus, we conclude that pinealectomy associated with treatment with Domperidone stimulates the adrenal further development, whereas melatonin may inhibit it.

Keywords: Adrenal, Melatonin, Domperidone, Rat, Pinealectomy, Prolactin.

Introduction

The most of seasonal mammalian present's circadian rhythm that may be changed by the levels of prolactin (PRL) and melatonin (Mel) plasma during development [1]. Melatonin is produced and secreted primarily by pinealocytes of the pineal gland. Studies report that in addition to the pineal gland there is evidence that occur synthesis and release of melatonin in the organs of the gastrointestinal tract, kidneys, cells of the immune system, liver, and in some brain regions [2]. This hormone is produced by a rhythmic pattern, with peak secretory at night and almost no synthesis during the day [3].

Prolactin (PRL) displays immunological and reproductive activity in response to photoperiod [4]. This is a peptide hormone and is produced by the anterior pituitary lactotrophs. Its secretion is spontaneous in the absence of hypothalamic stimulation, and its amount is modulated by estrogen, cortisol and thyroxin or bio-feedback mechanism. It's known that prolactin is essential to maintain the corpus luteum in rodents [5]. This hormone is also secreted by the ovary and can be found in the follicular fluid, which participates in the maturation of the oocyte. During pregnancy and lactation, the prolonged period of hyperprolactinemia is necessary for the development of reproductive organs and stimulates the release of secretions through endocrine organs such as the adrenal [6].

PRL has synergistic action with the production of glucocorticoids by the adrenal gland during pregnancy, and it stimulates steroid genesis of the adrenal gland of rats [7]. Studies have reported that treatment with domperidone leads to hyperprolactinemia and that the concentration of steroids produced by the adrenal is closely related to hyperprolactinemia, and may be increased in pregnant rats, because the role of prolactin in the adrenal steroid genesis in pregnant rats have been postulated by the presence receptors for prolactin in this organ [8, 9].

It's also known that the concentrations of PRL are high during the morning and reduced at night, with the contrast levels of the hormone melatonin [10]. Thus, the periodicity is the environmental signal that leads the changes of these hormones being marked by constant illumination, absence of light and /

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or pinealectomy, the latter resulting in an increase in prolactin levels and decreased levels of melatonin [11].

Studies show that pinealectomy produces morphologic alterations in various organs such as brain, retina, follicles in the ovary, prostate gland, immune cells, kidneys, spleen, liver and adrenal [12,13]. Moreover, pinealectomy increases the level of the adrenal cortex hormones and promote morphological changes in the cortex, such as a decrease in mitotic activity [14]. Some studies showed that the morphological analysis of adrenal of rats exposed to absence light showed a delay in the development of the cortical region and nuclear volume suggesting that administration of melatonin or not influence the development of adrenal [15]. In addition, there are studies emphasizing that the mitotic activity of the cells of the adrenal medulla can be altered by treatment with melatonin, which significantly decreases during treatment with this hormone [14].

Pinealectomized rats and treated with prolactin showed an increased renal cAMP, which stimulates the activity of adenylyl cyclase and the development of adrenal cortical region, and one opposite effect when animals are treated with melatonin [16]. A change in the normal circadian rhythm of pregnant rats, either by pinealectomy or by treatment with prolactin yields a sensitivity of stimulating the adrenal gland to produce estrogen and corticosteroids as well as promoting further development both of the adrenal glands as well as embryonic development [17].

Furthermore, the zona fasciculata, zona medullar and zona reticularis of adrenals from pregnant rats is modulated by the presence of steroids stimulated by hyperprolactinemy [18]. In contrast, when pregnant rats show an increase in the concentration of plasma melatonin has an inhibition in the production of corticosteroids, resulting in inhibition of hyperprolactinemia and estrogen production. However, little is known about the relationship of melatonin associated with prolactin. So, we decided to test the hypothesis that the administration of melatonin and/or domperidone during first third of pregnancy, affects the morphology of the adrenal gland of female pinealectomized rats.

Methodology

We used 35 Wistar albino rats (Rattus norvegicus albinus), 90 days old, coming from the Department of Animal Morphology and Physiology, from Federal Rural University of Pernambuco. These animals were kept in cages with food and water ad libitum. Females were randomly divided in seven groups each consisting of 5 animals, namely:

Group I - sham-pinealectomized rats kept in light / dark cycle of 12/12 hours during the pregnancy; Group II - pinealectomizaded rats kept in light / dark cycle 12/12 hours during the pregnancy; Group III-pinealectomized rats kept in light / dark cycle of 12/12 hours and treated with melatonin during pregnancy; Group IV-pinealectomized rats kept in light / dark cycle of 12/12 hours and induced to hyperprolactinemia during pregnancy; Group V - pinealectomized rats kept in light / dark cycle of 12/12 hours, and treated with melatonin and induced to hyperprolactinemia; Group VI-rats kept in light / dark cycle of 12/12 hours, treated with saline + ethanol; Group VII-rats kept in light / dark cycle of 12/12 hours, treated with saline.

After separation of the respective groups, the animals were treated for 7 days. The experimental protocol was approved by the Institutional Ethics Committee, number 23082.009629/2010.

Pinealectomy

The pinealectomy was performed in animals previously anesthetized with 40mg/kg pentobarbital intraperitoneally [19, 20]. Then, it was performed the trichotomy and asepsis of the dorsal area of the head. It was made one incision in the dorsal midline of the head with a low-speed hand piece and a dental drill No. 05, and one fragment was removed from the circular cap. This fragment was placed in 0.9% saline. After removal of the bone fragment we performed the ligation of venous sinus for withdrawal of the pineal [21]. Next, the bone fragment was reattached and the skin sutured. For the prevention of post-surgical pain it was administered buprenorphine (Tengesic®) at a dose of 0.05 mg / kg subcutaneously every 12 hours and ampicillin 30mg intramuscularly (IM), both for a period of five days to prevent encephalitis and pain resulting from surgical procedures [22-25].

Treatment with melatonin

The treatment with melatonin was performed according to the methodology proposed by [26]. The melatonin was obtained from Sigma, St. Louis, MO, USA and given at a dose of 200 µg melatonin per 100g body weight of the animal via subcutaneous injections in the early evening (18:00). The melatonin was dissolved in one volume of ethanol (0.02 mL) and diluted in 0.9% saline (0.9% NaCl). The animals of the placebo group received respectively 0.9% NaCl solution and 0.02 mL of ethanol.

Treatment with Domperidone (DOMP)

The hyperprolactinemia was performed with subcutaneous injection of domperidone (4 mg per kilogram of body weight) daily.

Histological Analysis

Five females from each group were euthanized after 7 days of treatment. For this, they were anesthetized with ketamine hydrochloride (80 mg / kg) and xylazine (6 mg / kg) intramuscularly. Then, we proceed to the removal of the adrenal, which was immediately weighed and then immersed in Bouin liquid, remaining the same for 48 hours. After that, the adrenal was cleaved and subjected to routine histological technique. Then the blocks were cut and stained with hematoxylin and eosin (HE) and examined under a light microscope.

Statistical Analysis

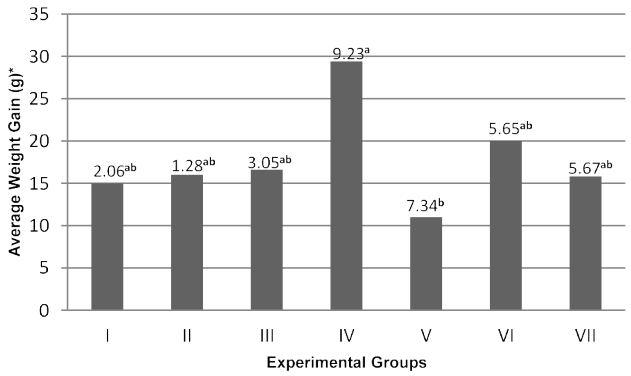
Statistical analysis of the adrenal weight was held in a

computer program InStat ®, where data were evaluated using nonparametric Kruskal-Wallis with post-hoc Dunn (P <0.05).

Results

The statistical analysis concerning the body weights showed that there were significant differences between sham-pinealectomized (Group I) and pinealectomized (Group II) when compared with the group of pinealectomized and treated with melatonin (Group III) and the pinealectomized and treated with melatonin and domperidone (group V), showing an increase in body weight in the groups III and V (Table 1).

Regarding to the absolute weights of the adrenals it was shown that there were significant differences between sham-pinealectomized (Group I), pinealectomized (Group II) and pinealectomized and treated with melatonin and domperidone (Group V) when compared with the group of pinealectomized and treated with domperidone (Group IV), demonstrating a greater absolute weight of the adrenal glands in this group (Table 1). In regarding to the relative weight there was significant differences between the pinealectomized group (Group II) and pinealectomized and treated with domperidone (Group IV) compared with the group pinealectomized and treated with melatonin and domperidone (Group V) where there was a lower weight in the animals of the Group V (Table 1).



*Means followed by the same letter don't differ significantly by the non-parametric Kruskal-Wallis with post-hoc Dunn.

Figure 1: Mean (± standard deviation) of body weight gain of rats of different experimental groups (P <0, 05).

Data concerning to the body weight gain are shown in (Figure 1), in which we can observe a significant increase in weight gain in pinealectomized female rats and treated with domperidone (group IV) when compared to the pinealectomized rats treated with melatonin and domperidone (group V).

The results of the histological analysis showed that all experimental groups showed the cortical layer (and associated areas: glomerulosa, fasciculata and reticularis) and medulla well defined. The placebo group (Group VI and VII), pinealectomized (Group II) and sham-pinealectomized (Group I) showed the zona fasciculata cells with lipid vacuoles and polyhedral, and medulla region of the adrenal appeared vascularized (Figure 2A). In the pinealectomized group and treated with domperidone zona fasciculata cells were found more voluminous and more vacuolated (Figure 2B). The group of pinealectomized and treated with melatonin and the group of pinealectomized and treated with domperidone and melatonin showed polyhedral cells, but apparently with less vacuolization when compared with the group of pinealectomized and treated with domperidone (Figure 2C). However, the medulla region of the group of pinealectomized and treated with melatonin and domperidone (Group V) appeared to be more vascularized and with a large amount of hemosiderin deposits (Figure 2D).

Discussion

The results of this study demonstrated a significant increase in absolute and relative weights of adrenals of the group of pinealectomized animals that were treated with domperidone (Group IV), an increase in the body weight in the group of pinealectomized animals treated with melatonin (Group III), and weight gain in the pinealectomized females treated with domperidone. Furthermore, histological analysis revealed that the pinealectomized animals treated with domperidone (Group IV) had adrenal zona fasciculata with voluminous and most vacuolated, whereas in group of pinealectomized animals treated with melatonin and domperidone (Group V) the zona fasciculata cells seemed less vacuolated, and the medulla was more vascularized, as well as presence of appreciable hemosiderin. According [14] and [27], administration of

Experimental groups	N 5	Maternal body weight (g)*	Absolute weights of the adrenals (g/par)*	Relative weights of the adrenals*
I		207.8 ± 5.45^{a}	0.160 ± 0,0093^{a}	0.00079 ± 2.80^{ab}
II		205.2 ± 5.67^{a}	0.199 ± 0,0206^{a}	0.00101 ± 1.04^{a}
III		249.6 ± 8.17^{b}	0.182 ± 0,0103^{ab}	0.00075 ± 6.80^{ab}
IV		243 ± 6.70^{ab}	0.265 ± 0,0195^{b}	0.00115 ± 1.04^{a}
V		249.8 ±1.09^{b}	0.138 ± 0,0056^{a}	0.00055 ± 3.36^{b}
VI		215.6 ± 5.50^{ab}	0.189 ± 0,0178^{ab}	0.00082 ± 9.24^{ab}
VII		224.2 ± 4.43^{ab}	0.177 ± 0,0458^{ab}	0.00071 ± 9.33^{ab}
		P 0,0004	P 0,0009	P 0,0001

*Means followed by the same letter don't differ significantly by the non-parametric Kruskal-Wallis with post-hoc Dunn (P < 0, 05).

Table 1: Mean (± standard deviation) of the maternal body weight, absolute and relative weights of the adrenals.

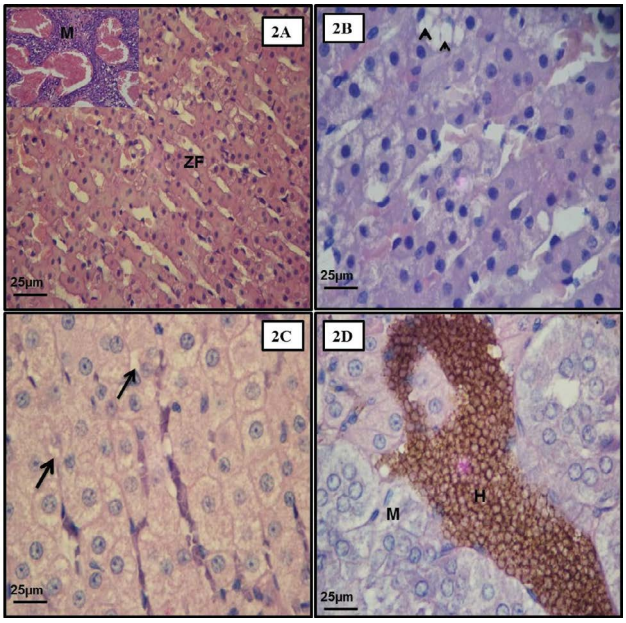


Figure 2: Histological analysis of adrenal of various experimental groups. 2A - zona fasciculata (ZF) sham-pinealectomized group (Group I) and polyhedral cells with lipid vacuoles, and detail medullary region (M) vascularized. H-E. 2B - the zona fasciculate cells were found more bulky and vacuolated (arrowhead) in the pinealectomized and treated with domperidone. H-E. 2C-polyhedral cells, vacuolization and less bulky group pinealectomized and treated with melatonin and domperidone (arrow). H-E. 2D - Loads of hemosiderin deposits (H) in the medullary region (M) and the group pinealectomized and treated with melatonin and domperidone. H-E.

melatonin after pinealectomy can block adrenal hypertrophy. Moreover, according to [28] the absence of the pineal treatment associated with prolactin cause weight gain in adrenals of non-pregnant females.

In mammals, the production of melatonin by the pineal gland is mainly controlled by the suprachiasmatic nucleus of the hypothalamus. The pineal influences the gonads and estrous cyclicity in female rats, besides acting as a modulator of reproduction in mammals, influencing hormonal levels of estrogen and progesterone [2]. In this study we used pregnant female rats. They were treated for 7 days with melatonin and / or domperidone. It is also known that the activity of the adrenal is dependent on both the hormones such as aldosterone, estrogen and adrenocorticotrophic hormones, as well as trophic factors (e.g., vascular endothelial growth factor) [29]. For example, [18] reported that hyperprolactinemia in pinealectomized rats and mice can be induced by administration of domperidone, and that it appears to increase the absolute and relative weight of the adrenal. And, [29] working with pinealectomized female rats treated with melatonin observed cells with brownish cytoplasm and they concluded that they were apoptotic cells. They suggested that the occurrence of these cells into apoptosis is related to the presence of hemosiderin. In our pinealectomized group treated with melatonin and domperidone, the group that showed the lowest weight in the adrenal glands, were also found appreciable amounts of hemosiderin, which, according to [30], the increase of hemosiderin and treated group pinealectomized with domperidone and melatonin may be a major reason for the size of the adrenal be higher in pinealectomized and treated with domperidone than in the other groups. Moreover, the same author reported that melatonin treatment leads to an increase in food intake which would explain the increased maternal weight in the female rats of the Group pinealectomized and treated with melatonin during pregnancy.

The findings [29] which concluded that in pinealectomized animals there was a decrease in the percentage of apoptosis in zona reticular and zona fasciculate is in conflict with [31], which studied observed in the medullar region and in the adrenal cortical of hypophysectomized rats by observing cells in apoptosis exclusively in the area zona reticular, suggesting that the adrenocorticotrophic hormone was the only pituitary hormone able to block apoptosis in cells from other regions of the adrenal cortex. It is worth noting also that there is a great production of cortisol during pregnancy by the maternal adrenal glands and melatonin could be related with this process [32] as according to [28], melatonin can act by inhibiting cortisol production by the adrenal gland, and decreasing the steroidogenic activity of this gland during pregnancy, causing a minor development of this organ, which would explain that the group of pinealectomized animals treated with melatonin showed a low adrenal weight when compared with the other groups.

However, it is known that melatonin has an opposite effect to that of prolactin (leading to a lower developing adrenal gland), and the release of prolactin synergistic with the action of glucocorticoids and that under certain conditions prolactin acts directly on the adrenal gland to stimulate steroidogenesis, production of adrenocorticotrophic hormones and consequent increase in the adrenal development [33]. [34-36], reported that hyperprolactinemia in female rats leads to an increase in absolute and relative weight of the adrenals. In addition, [11] demonstrated that treatment with prolactin or induction to hyperprolactinemia leads to adrenal hypertrophy in response to an increased production of adrenocorticotrophic hormones, which according to [9], domperidone induce adrenal hypertrophy as a result of hyperprolactinemia also decreasing, gonadal hormones.

Furthermore, [27] demonstrated that the adrenal hypertrophy resulting from pinealectomy associated prolactin, can be blocked by administration of melatonin, leaving us to conclude that the increase in weight of the adrenals of the group of pinealectomized female rats treated with domperidone is a consequence of hypertrophy of the adrenocorticotrophic cells stimulated by hyperprolactinemia. Our results are in agreement with studies performed by [5], who observed changes in the morphology of the adrenal after pinealectomy and treatment with prolactin noting significant differences only in cells in the zona fasciculata. According to the same author, the zona fasciculata is the widest of all three areas of the adrenal, which makes about 80% of the total adrenal cortex. Their cells

appeared polyhedral with several vacuolated cells, due probably to the stimulation of adrenocortical cells for the production of ACTH. In addition, morphological and morphometric studies of the adrenal glands in adult female rats that were subjected to treatment with melatonin showed inhibition of the cortical of the adrenal and in the nuclear volume of the cells [18]. [37] Further reported that the administration of melatonin in rats causes an atrophy of the zona fasciculata cells, confirming the results of this study, suggesting that prolactin was able to induce cell proliferation in the zona fasciculata of the adrenal by stimulating the production of corticotrophic and the melatonin has one opposite effect. In regarding to the most vascularization in the pinealectomized group treated with domperidone and melatonin can be explained by the fact domperidone abolished the inhibitory effect of melatonin for the production of angiogenic factors and have been outstanding because of their induction leading hyperprolactinemia, and , increased by the adrenal steroidogenesis with consequent production of factors that stimulate vascular development, since it is known that increased prolactin leads to a consequent increase of estrogenic hormones which stimulate the production of angiogenic factors [29]. Thus, we conclude that pinealectomy associated with treatment with domperidone stimulates the adrenal development, whereas melatonin may inhibit it.

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