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The Effect Of Melatonin On The Sex Hormones In Mice

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Abstract :

Melatonin is a hormone secreted by the pineal gland in response to darkness, because of that it named hormone of darkness. Melatonin has generated an important deal of interest as a therapeutic modality for many diseases especially sleep disorders. The melatonin Play an important part in the regulation of seasonal changes and circadian in many aspects of neuroendocrine and physiology functions. In mammals, melatonin can activating its receptors and binding sites in the hypothalamic-pituitary-gonadal (HPG) axis, melatonin can have an impact on sexual maturation and reproductive activities. This research assume to measure the effect that happened on female sex hormones under the melatonin treatment by using female albino, laboratory-bred mice, 36 female mice were divided to 3 groups, group A which were dosed with 3mg of melatonin, group B with 12mg and group C with no dosing as a control group. The killing process was done in 2 stages (6 and 10 weeks). Blood samples were taken and analyzed. In addition, the results proved significantly higher levels of sex hormones (LH, FSH, estrogen and progesterone). This study summarizes current knowledge of melatonin on the female's sexual hormones.

تأثير الميلاتونين على الهرمونات الجنسيه الانثوية في الفئران

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مستخلص

الميلاتونين هو هرمون تفرزه الغدة الصنوبرية استجابةً للظلام، ولهذا سمي بهرمون الظلام. لقد ولّد الميلاتونين قدرًا كبيرًا من الاهتمام كطريقة علاجية للعديد من الأمراض وخاصة اضطرابات النوم. يلعب الميلاتونين دورًا مهمًا في تنظيم التغيرات الموسمية والساعة البيولوجية في العديد من جوانب وظائف الغدد الصم العصبية و وظائف الأعضاء. في الثدييات، يمكن للميلاتونين تنشيط مستقبلاته ومواقع الارتباط في محور الغدة النخامية–الغدة التناسلية. يمكن أن يكون للميلاتونين تأثير على النضج الجنسي والأنشطة الإنجابية. يفترض هذا البحث قياس التأثير الذي حدث على الهرمونات الجنسية الأنثوية تحت العلاج بالميلاتونين باستخدام أنثى ألبينو، فئران مختبرية، تم تقسيم 36 فأرة إلى ثلاث مجموعات، المجموعة (أ) التي أعطيت 3 ملجم من الميلاتونين، والمجموعة (ب) التي اعطيت 12 ملغ من الميلاتونين و المجموعه (ج) التي لم تعطى ميلاتونين لتكون مجموعه مراقبه . تمت عملية القتل على مرحلتين (6 و 10 أسابيع). تم أخذ عينات الدم وتحليلها. بالإضافة إلى ذلك، أثبتت النتائج ارتفاع مستويات الهرمونات الجنسية بشكل ملحوظ. هذه الدراسه تلخص تأثير عقار الميلاتونين على الهرمونات الجنسيه في اناث الفئران.

1. Introduction

1.1. Melatonin

Melatonin is the hormone that secreted from pineal gland. The discovery of melatonin was in 1958 with chemical formula (N-acetyl-5-methoxytryptamine) Melatonin has many physiological functions in animals , such as influencing circadian rhythms, body temperature, retina physiology, mood, sleep, food intake, locomotor activity, seasonal reproduction, sexual behavior and the body immunity. The pineal gland secretes the melatonin which it is the sleeping hormone in the dark and it helps to regulate the body temperature and the "circadian rhythm" depends on the cycle of 24 h day\night [1].

The receptors of the melatonin have been found in different cells such as granulosa cells from preovulatory follicles [2] and in sperm [3]. It has been determined that semen samples with low and inadequate fertilization rates had decreased melatonin levels [2]. And in females with idiopathic infertility [4]. The circadian disruption in females, who have experienced stress, where melatonin annihilation is present, effect the fertility and the fetal development and raises the risk of miscarriage, early birth, and low birth weight. [5].

1.2. Gonadotropins

Gonadotropins are peptide hormones required for appropriate growth, sexual development, and reproduction that control ovarian and testicular function. The hypothalamic-pituitary-gonadal axis (HPG axis) and two populations of hypothalamic neurons, the gonadotropin-releasing hormone (GnRH) neurons and the kisspeptin neurons, play a major role in the regulation of fertility. [6][7].

The LH surge is mediated by the Kisspeptin neurons in the anterior ventral periventricular area, whereas the hypothalamic Kisspeptin neuron population, situated in the arcuate nucleus, is involved in the process., transmits data about the metabolic state to the HPG axis and releases GnRH.[8][9]. The hypothalamus releases the gonadotropin-releasing hormone (GnRH) in a pulsatile manner, which operates on the anterior pituitary lobe to control gonadotropin synthesis before eventually causing the blood to release LH and follicle-stimulating hormone (FSH).. LH and FSH both contribute to the ovarian follicles' ability to produce steroid hormones (estrogens) in fe-

males. [10]. Also, the LH peak causes the mouse ovary's master clock gene (BMAL1) to continuously express its genes and proteins. [11].

1.2.1. Estrogen (E2)

Estrogen is a steroid hormone it is mainly produced by the female ovaries. The follicles in the ovaries released estrogen. Also, after the egg released from the follicle or from the placenta the E2 then will secrete by the corpus luteum. It is connected to the female reproductive system and is in charge of forming the feminine sex traits. Estrogen is often divided to estrone, and estriol, estradiol.

Estrogen has inclusive important physiological effects on the cardiovascular maturation and growth, skeletal, endocrine and metabolic systems [12]. The population of some nations, like China, is progressively aging, which means that women will live almost one-third of their lives without the protection of estrogen [13]. E2, a steroid hormone that is fat-soluble, is crucial to the physiology and growth of numerous organ systems, including the breasts, uterus, heart, and bones [14]. The estrogens have a 24-hour circadian rhythm while they are in the follicular phase [15].

1.2.2. Progesterone

Progesterone is a neuroactive and neurosteroid, produced primarily by the placenta and corpus luteum [16]. The first isolation of progesterone was in 1934 during the investigation of endocrine function of the corpus luteum [17]. The preovulatory follicles have two main functions, first create progesterone synthetically, and then transform progesterone into estrogens. [18]. Although other factors may also play a significant role in this switchover of steroid synthesis, LH and FSH both play a significant role in boosting steroid production in the ovaries. Acetylcholine and serotonin increase the release of progesterone from granulosa cells; meanwhile nicotine and noradrenaline greatly reduce progesterone synthesis. [19]. Through the progesterone receptor membrane component-1 (PGRMC1), apoptotic genes suppress and follicular growth is promoted. Progesterone directly affects granulosa cells [18]. The progesterone receptor that does not belong to genomic receptors is found in the cell membrane. Progesterone elevation appears to trigger an LH surge, which in turn triggers ovulation. Progesterone improves gonadotropin pituitary sensitivity to go-

nadotropin-releasing hormone (GnRH) secretion.

Just before ovulation, the granulosa cells of the dominant follicle begin to vacuolate and acquire the yellow pigment lutein, which is the first step in their transformation into large luteal cells. [20]. Progesterone stimulates the luteal cells, which in turn promotes the circulation of cholesterol substrate at a low level. LH and human chorionic gonadotropin (hCG) receptors are absent from large luteal cells. but are more capable of producing steroids. The small luteal cells carry LH and hCG receptors and are connected to the larger cells by gap junctions. These cells are most likely descended from the theca cells. Large luteal cells respond to LH stimulation and produce progesterone thanks to the quick signal transfer between the cells.

1.2.3. Follicle stimulating hormone (FSH)

Follicle stimulating hormone (FSH) is a glycoprotein hormone it is one of the gonadotrophic hormones, is produced by the anterior pituitary gland in the brain. It is one of the important hormones that maintain normal functioning of the reproductive system in both female and male. FSH regulates folliculogenesis in the ovary. Also, It controls implantation, the production of sex steroid hormones, and the process of getting the reproductive system ready for conception and pregnancy. FSH facilitates the growth of the testicles and spermatogenesis in males. [21]. FSH has important role in bone resorption via improving osteoclast generation and activity while boosting survival [22]. More recent studies have observed that FSH is a primary regulator of energy homeostasis and body fat [23].

1.2.4. Luteinizing hormone (LH)

Luteinizing hormone is a glycoprotein hormone synthesized and secreted by the anterior pituitary gland as a result of high-frequency GnRH release. LH is the hormone that promotes ovulation, prepares up fertilization, facilitates uterine implantation, and stimulates theca and luteinized granulosa cells in the ovaries to produce progesterone..

In the ovary, LH interacts with Theca cells that are close to granulosa cells. For the development of follicles, these cells create androgens that diffuse into the granulosa cells and change into estrogen. [24]. The LH surge creates the circumstances for follicular eruption

by increasing the activity of the proteolytic enzymes that weaken the ovarian wall and permit the entry of the egg. After the oocyte is released, the follicular remnants consist of luteinized granulosa cells and theca. Progesterone, the hormone responsible for maintaining the uterine environment favorable for accepting a fertilized embryo, is now produced by them.. [25].

1.3. Effects of Melatonin on female sexual Hormones

The effect of melatonin on the sexual hormones level and its role in reproductive activities has been proved in numerous published studies. Via receptor activation that located in axis called hypothalamic pituitary gonadal axis [26]

In the preovulatory follicles the melatonin has a role in progesterone synthesis by the human granulosa when the melatonin is in high level. In ovaries, melatonin may interfere with the steroid receptor, especially progesterone receptor [27]. That's mean melatonin can affect the ovaries in many ways such as:

1- Boosting the synthesis of progesterone both in vivo and in vitro
2- Improving the embryo and increasing the chance of fertilization
3- Antagonizing estrogen action and improving thecae cell quality
4- Increasing estrogen production [28].

Sexual Development and the Circadian Clock

The process of Sexual development is not under endocrine control solely but also the level of the circadian regulation has a function in this process [29]. Circadian regulation and Reproductive organs influences many sexual developmental processes, such as the timing of gonadotropin secretion, which has been under the influence of circadian regulation itself, both gonadotropins secretion and regarding GnRH release [30].

2. Materials and Methods

Ethical statement

Informed consent according to the Declaration of Helsinki was obtained from ethics committee of College of Science, Mustansiriyah University (Ref. No.: BCSMU/0123/00033Z).

Experimental Design and Animal Treatment

Thirty-six female's laboratory mice were bought from the Iraqi center for cancer research in Al-Qadisya, Baghdad. The animals were housed in cages made of polypropylene (43 cm × 30

cm × 15 cm) Animals had access to food and water. Within a temperature controlled (23 ± 2 °C) with constant 12 h light–dark cycles. The mice were divided into three groups. Group A that treated with 3mg melatonin, group B treated with 12mg melatonin and group C which is control group. The juvenile mice that been chosen for this study were at postnatal days 10–24.The Mice received melatonin (puritan's pride/ USA) every evening (8:00 PM) at doses of 3mg/kg and 12 mg/kg (melatonin was dissolved in Distilled water to the final Concentration of 1.06% and 4.2% sequentially) .

The killing process was done through two periods duration. The first groups were killed after 6 weeks for each tree groups, collect the blood samples and then conduct the required test.While the second kill will be after 10 weeks for each three groups and conduct the required test.

Determination of Hormone

For the detection of hormone, Blood samples were taken from each group through the venous vein in the eyelid. Then the serum was obtained by centrifugation at 3000 rpm for 10 min and stored at −18 °C. The serum levels of hormones were operated by cobas 6000 analyzer of chemistry.

Statically analysis

Results were expressed in terms of mean ± SE or percentage (%) of case frequency. The data were examined for many comparisons after one-way analysis of variance (ANOVA), using Fisher's test or t-test. Regression analysis utilizing analysis of combined variance was done (ANCOVA). Statview 5.0 was used to conduct all of the statistic analysis of these experiments. When $p< 0.05$ was reached, the differences were considered significant.

3. Results and Discussion

Table 1. Mice Sex hormones levels for six weeks and 10 weeks (mean ± SD)

groups	LH (mIU/ml)		FSH (mIU/ml)		Progesterone (ng/dl)		Estrogen (pg/dl)		Testosterone (ng/dl)	
	Six weeks	Ten weeks	Six weeks	Ten weeks	Six weeks	Ten weeks	Six weeks	Ten weeks	Six weeks	Ten weeks
control	0.115± 0.004	0.110± 0.021	0.375± 0.017	0.329± 0.010	1.448± 0.047	2.185± 0.23	20.615± 1.5	29.295± 1.10	2.518± 0.012	2.372± 0.080
3mg	0.144± 0.009	0.157± 0.005	0.366± 0.021	0.389± 0.007	3.702± 0.743	5.108± 0.42	26.710± 2.68	34.028± 2.83	2.142± 0.022	3.078± 0.137
12mg	0.190± 0.007	0.212± 0.022	0.388± 0.013	0.407± 0.009	4.126± 0.464	7.056± 0.48	25.710± 1.68	35.906± 1.22	2.722± 0.106	3.074± 0.380

3.1 The LH result

The result showed significant increment in the LH levels that treated with melatonin compared to control group, also LH levels increased more with the extend period of time.

In the groups that treated with melatonin for six weeks there is significant increment between 12mg group and control (p-value=0.0017),3mg and 12mg (p=0.048) and there is no significant change between 3mg and control (p-value=0.116). while the groups that treated with melatonin for ten weeks significant changes perceive between the 3mg group and control group (p-value=0.0325),the difference between 12mg and control was significant too (p-value=0.0001). And that's observed between 3mg and 12mg groups (p-value=0.0095).

The first reference of the weight reduction caused by exogenic melatonin intake in female rat ovaries dates back to 1963 by R.J. Wurtman et al. Subsequently, numerous pieces of data emerged demonstrating the influence of the pineal gland and its primary hormone, melatonin, on reproductive function. Melatonin's primary physiological function is to increase gonadotrophin production, which results in a

larger increase in LH and FSH. Positive correlation found between melatonin and both LH and FSH. These findings support earlier research indicating melatonin raises LH and FSH levels. Another study shown that melatonin promoted the manufacture of FSH in the pituitary, which accelerated the beginning of puberty. [31]. and that by administering 15 mg/kg of melatonin (Sigma, St. Louis, MO, USA) intraperitoneally to the mice each morning at 8:00 AM.

3.2 The FSH result

The result show insignificant changes in FSH levels in six weeks period, meanwhile it shows significant change in the ten weeks groups between control and 3mg (p-value=0.0001) and between control and 12mg (p-value<0.0001). No significant change between 12mg and 3mg.

The result above proved that melatonin can affect the secretion of LH and FSH in female mice. Some studies approve the same. Yang, C. et al. study mice were chosen postnatal days Mice were given melatonin injections every morning from day 10 until the day of vaginal opening at a dose of 15 mg/kg.Reproductive hormones implicated in the hypothalamic-pituitary-ovarian axis, such as serum levels of estrogen and FSH, were elevated. [31].

3.3 The progesterone result

The level of progesterone during the 6 weeks shows significant increment between control and 3mg group (p-value 0.0046) and between control,12mg (p-value 0.0013) . No significant change between 3mg and 12mg groups.

During the 10 weeks period it shows significant change between control and 3mg group, control and 12mg group and between 3mg and 12mg with p-value <0.0001,<0.0001 and 0.0033 sequentially . Previous research has demonstrated that melatonin can encourage the ovary's synthesis of progesterone [32][33]. Melatonin is usually believed to influence reproduction at the level of the hypothalamus and pituitary gland [34]. In our result show that melatonin can effect progesterone production and the stimulatory impact might result from increased expression of Cholesterol side-chain cleavage enzyme (P450scc) and Steroidogenic Acute Regulatory protein (StAR), two crucial P4 biosynthesis pathway mediators. In the mitochondria, P450scc changes cholesterol into pregnenolone [35] [36]. Pregnenolone then diffuses out of the mitochondria and into the

smooth endoplasmic reticulum (SER), where 3beta hydroxysteroid dehydrogenase (HSD) transforms it to progesterone. LH increases the expression of 3beta HSD [37] in theca cells and luteinized granulosa cells of the ovary. Females get their plasma progesterone from their ovaries and adrenal cortex [38][39]. Meanwhile male testicles are the only source of progesterone in men.

3.4 The estrogen result

The result demonstrate that there is significant increment between control and 3mg group (p-value <0.0001) .Also, significant increment observed between control and 12mg(p-value 0.0002) ,no significant change between 3mg and 12mg groups . and that were during 6 weeks period. During the 10 weeks period no significant changes observed between groups except between control and 12mg groups that show significant increment (p-value 0.0351).

We proved that melatonin encouraged the production of FSH in the pituitary, which raised serum estrogen levels. The impact of melatonin on the female reproductive system has been demonstrated by numerous investigations. It has been established that this action is caused by directly attaching to ovarian cell receptors and via the hypothalamic/pituitary axis. Many studies proved same thesis that melatonin increase E2 levels [31] [40].

4.4 The testosterone result

During the first six weeks of melatonin treatment the result shows significant decrement between 3mg melatonin group compered to control group with p-value 0.0005. While a significant increment between 12mg and control with p-value 0.0272. Also significant increment observed between 3mg melatonin and 12mg melatonin with p-value <0.0001.

The ten weeks period shows significant increase in testosterone levels between each control,3mg melatonin and control,12mg melatonin group with p-value 0.0311 and0.0395 sequentially . It is thought that there is a bidirectional link between melatonin and testosterone, meaning that when one hormone levels up, the other does too. Furthermore, it has been demonstrated that melatonin increases the synthesis of luteinizing hormone (LH), an essential hormone for the synthesis of testosterone.

Conclusions

It's becoming steadily more obvious that melatonin and sex steroid hormones interact, often in a reciprocal manner in which the sex steroids influence melatonin's actions while melatonin is also influenced by them. Age, tissue, hormonal state, melatonin levels, and environmental factors all affect this transmission. Moreover, this relationship is highly complex due to the direct or indirect mechanistic pathways involved.Our data result shows the levels of female sexual hormones under the melatonin treatment.Each sex hormone (FSH, LH, estrogen, progesterone and testosterone) affect with the treatment of melatonin.

References

- Kratz, E. M., & Piwowar, A. (2017). Melatonin, advanced oxidation protein products and total antioxidant capacity as seminal parameters of prooxidant-antioxidant balance and their connection with expression of metalloproteinases in context of male fertility. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society, 68(5), 659–668.
- Huang, B., Qian, C., Ding, C., Meng, Q., Zou, Q., & Li, H. (2019). Fetal liver mesenchymal stem cells restore ovarian function in premature ovarian insufficiency by targeting MT1. Stem cell research & therapy, 10(1), 362. https://doi.org/10.1186/s13287-019-1490-8
- Elokil, A. A., Bhuiyan, A. A., Liu, H. Z., Hussein, M. N., Ahmed, H. I., Azmal, S. A., Yang, L., & Li, S. (2019). The capability of L-carnitine-mediated antioxidant on cock during aging: evidence for the improved semen quality and enhanced testicular expressions of GnRH1, GnRHR, and melatonin receptors MT 1/2. Poultry science, 98(9), 4172–4181. https://doi.org/10.3382/ps/pez201
- Espino, J., Macedo, M., Lozano, G., Ortiz, Á., Rodríguez, C., Rodríguez, A. B., & Bejarano, I. (2019). Impact of Melatonin Supplementation in Women with Unexplained Infertility Undergoing Fertility Treatment. Antioxidants (Basel, Switzerland), 8(9), 338. https://doi.org/10.3390/antiox8090338
- Nehme, P. A., Amaral, F., Lowden, A., Skene, D. J., Cipolla-Neto, J., & Moreno, C. R. C. (2019). Reduced melatonin synthesis in pregnant

night workers: Metabolic implications for offspring. Medical hypotheses, 132, 109353. https://doi.org/10.1016/j.mehy.2019.109353

- Harter, C. J. L., Kavanagh, G. S., & Smith, J. T. (2018). The role of kisspeptin neurons in reproduction and metabolism. The Journal of endocrinology, 238(3), R173–R183. https://doi.org/10.1530/JOE-18-0108
- Yeo, S. H., & Colledge, W. H. (2018). The Role of Kiss1 Neurons As Integrators of Endocrine, Metabolic, and Environmental Factors in the Hypothalamic-Pituitary-Gonadal Axis. Frontiers in endocrinology, 9, 188. https://doi.org/10.3389/fendo.2018.00188
- Irwig, M. S., Fraley, G. S., Smith, J. T., Acohido, B. V., Popa, S. M., Cunningham, M. J., Gottsch, M. L., Clifton, D. K., & Steiner, R. A. (2004). Kisspeptin activation of gonadotropin releasing hormone neurons and regulation of KiSS-1 mRNA in the male rat. Neuroendocrinology, 80(4), 264–272. https://doi.org/10.1159/000083140
- Messager, S., Chatzidaki, E. E., Ma, D., Hendrick, A. G., Zahn, D., Dixon, J., Thresher, R. R., Malinge, I., Lomet, D., Carlton, M. B., Colledge, W. H., Caraty, A., & Aparicio, S. A. (2005). Kisspeptin directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54. Proceedings of the National Academy of Sciences of the United States of America, 102(5), 1761–1766. https://doi.org/10.1073/pnas.0409330102
- Goh, H. H., & Ratnam, S. S. (1988). The LH surge in humans: its mechanism and sex difference. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology, 2(2), 165–182. https://doi.org/10.3109/09513598809023624
- Kobayashi, M., Watanabe, K., Matsumura, R., Anayama, N., Miyamoto, A., Miyazaki, H., Miyazaki, K., Shimizu, T., & Akashi, M. (2018). Involvement of the luteinizing hormone surge in the regulation of ovary and oviduct clock gene expression in mice. Genes to cells : devoted to molecular & cellular mechanisms, 10.1111/gtc.12605. Advance online publication. https://doi.org/10.1111/gtc.12605
- Morselli, E., Santos, R. S., Criollo, A., Nelson, M. D., Palmer, B. F.,

& Clegg, D. J. (2017). The effects of oestrogens and their receptors on cardiometabolic health. Nature reviews. Endocrinology, 13(6), 352–364. https://doi.org/10.1038/nrendo.2017.12

- Laisk, T., Tšuiko, O., Jatsenko, T., Hõrak, P., Otala, M., Lahdenperä, M., Lummaa, V., Tuuri, T., Salumets, A., & Tapanainen, J. S. (2019). Demographic and evolutionary trends in ovarian function and aging. Human reproduction update, 25(1), 34–50. https://doi.org/10.1093/humupd/dmy031
- Faltas, C. L., LeBron, K. A., & Holz, M. K. (2020). Unconventional Estrogen Signaling in Health and Disease. Endocrinology, 161(4), bqaa030. https://doi.org/10.1210/endocr/bqaa030
- Rahman, S. A., Grant, L. K., Gooley, J. J., Rajaratnam, S. M. W., Czeisler, C. A., & Lockley, S. W. (2019). Endogenous Circadian Regulation of Female Reproductive Hormones. The Journal of clinical endocrinology and metabolism, 104(12), 6049–6059. https://doi.org/10.1210/jc.2019-00803
- Henderson V. W. (2018). Progesterone and human cognition. Climacteric : the journal of the International Menopause Society, 21(4), 333–340. https://doi.org/10.1080/13697137.2018.1476484
- Piette P. (2018). The history of natural progesterone, the never-ending story. Climacteric : the journal of the International Menopause Society, 21(4), 308–314. https://doi.org/10.1080/13697137.2018.1462792
- Taraborrelli S. (2015). Physiology, production and action of progesterone. Acta obstetricia et gynecologica Scandinavica, 94 Suppl 161, 8–16. https://doi.org/10.1111/aogs.12771
- Nagy, B., Szekeres-Barthó, J., Kovács, G. L., Sulyok, E., Farkas, B., Várnagy, Á., Vértes, V., Kovács, K., & Bódis, J. (2021). Key to Life: Physiological Role and Clinical Implications of Progesterone. International journal of molecular sciences, 22(20), 11039. https://doi.org/10.3390/ijms222011039
- Mesen, T. B., & Young, S. L. (2015). Progesterone and the luteal phase: a requisite to reproduction. Obstetrics and gynecology clinics of North America, 42(1), 135–151. https://doi.org/10.1016/j.ogc.2014.10.003
- Casarini, L., & Crépieux, P. (2019).

Molecular Mechanisms of Action of FSH. Frontiers in endocrinology, 10, 305. https://doi.org/10.3389/fendo.2019.00305

- Sun, L., Zhang, Z., Zhu, L. L., Peng, Y., Liu, X., Li, J., Agrawal, M., Robinson, L. J., Iqbal, J., Blair, H. C., & Zaidi, M. (2010). Further evidence for direct pro-resorptive actions of FSH. Biochemical and biophysical research communications, 394(1), 6–11. https://doi.org/10.1016/j.bbrc.2010.02.113
- Liu, P., Ji, Y., Yuen, T., Rendina-Ruedy, E., DeMambro, V. E., Dhawan, S., Abu-Amer, W., Izadmehr, S., Zhou, B., Shin, A. C., Latif, R., Thangeswaran, P., Gupta, A., Li, J., Shnayder, V., Robinson, S. T., Yu, Y. E., Zhang, X., Yang, F., Lu, P., … Zaidi, M. (2017). Blocking FSH induces thermogenic adipose tissue and reduces body fat. Nature, 546(7656), 107–112. https://doi.org/10.1038/nature22342
- Laven J. S. E. (2019). Follicle Stimulating Hormone Receptor (FSHR) Polymorphisms and Polycystic Ovary Syndrome (PCOS). Frontiers in endocrinology, 10, 23. https://doi.org/10.3389/fendo.2019.00023
- Kumar, P., & Sait, S. F. (2011). Luteinizing hormone and its dilemma in ovulation induction. Journal of human reproductive sciences, 4(1), 2–7. https://doi.org/10.4103/0974-1208.82351
- Malpaux, B., Migaud, M., Tricoire, H., & Chemineau, P. (2001). Biology of mammalian photoperiodism and the critical role of the pineal gland and melatonin. Journal of biological rhythms, 16(4), 336–347. https://doi.org/10.1177/074873001129002051
- Romeu, L. R. G., da Motta, E. L. A., Maganhin, C. C., Oshima, C. T., Fonseca, M. C., Barrueco, K. F., ... & Soares-Junior, J. M. (2011). Effects of melatonin on histomorphology and on the expression of steroid receptors, VEGF, and PCNA in ovaries of pinealectomized female rats. Fertility and sterility, 95(4), 1379-1384.
- Cipolla-Neto, J., Amaral, F. G., Soares, J. M., Jr, Gallo, C. C., Furtado, A., Cavaco, J. E., Gonçalves, I., Santos, C. R. A., & Quintela, T. (2022). The Crosstalk between Melatonin and Sex Steroid Hormones. Neuroendocrinology, 112(2), 115–129. https://doi.org/10.1159/000516148

- Simonneaux, V., Bahougne, T., & Angelopoulou, E. (2017). Daily rhythms count for female fertility. Best practice & research. Clinical endocrinology & metabolism, 31(5), 505–519. https://doi.org/10.1016/j.beem.2017.10.012
- Chu, A., Zhu, L., Blum, I. D., Mai, O., Leliavski, A., Fahrenkrug, J., Oster, H., Boehm, U., & Storch, K. F. (2013). Global but not gonadotrope-specific disruption of Bmal1 abolishes the luteinizing hormone surge without affecting ovulation. Endocrinology, 154(8), 2924–2935. https://doi.org/10.1210/en.2013-1080
- Yang, C., Ran, Z., Liu, G., Hou, R., He, C., Liu, Q., Chen, Y., Liu, Y., Wang, X., Ling, C., Fang, F., & Li, X. (2021). Melatonin Administration Accelerates Puberty Onset in Mice by Promoting FSH Synthesis. Molecules (Basel, Switzerland), 26(5), 1474. https://doi.org/10.3390/molecules26051474
- Wang, S., Liu, W., Pang, X., Dai, S., & Liu, G. (2018). The Mechanism of Melatonin and Its Receptor MT2 Involved in the Development of Bovine Granulosa Cells. International journal of molecular sciences, 19(7), 2028. https://doi.org/10.3390/ijms19072028
- Wang, S. J., Liu, W. J., Wu, C. J., Ma, F. H., Ahmad, S., Liu, B. R., Han, L., Jiang, X. P., Zhang, S. J., & Yang, L. G. (2012). Melatonin suppresses apoptosis and stimulates progesterone production by bovine granulosa cells via its receptors (MT1 and MT2). Theriogenology, 78(7), 1517–1526. https://doi.org/10.1016/j.theriogenology.2012.06.019
- Venugopal S. P. (2019). Effect of melatonin on the onset of puberty in male juvenile rats. Anatomy & cell biology, 52(3), 286–295. https://doi.org/10.5115/acb.18.122
- Chu, P. W., Yang, Z. J., Huang, H. H., Chang, A. A., Cheng, Y. C., Wu, G. J., & Lan, H. C. (2018). Low-dose bisphenol A activates the ERK signaling pathway and attenuates steroidogenic gene expression in human placental cells. Biology of reproduction, 98(2), 250–258. https://doi.org/10.1093/biolre/iox162
- Xie, W., Tang, Z., Xu, L., Zhong, J., Zhang, H., Han, Y., Yuan, Z., & Weng, Q. (2020). Seasonal expressions of SF-1, StAR and P450scc

in the scent glands of the muskrats (Ondatra zibethicus). The Journal of steroid biochemistry and molecular biology, 204, 105766. https://doi.org/10.1016/j.jsbmb.2020.105766

- Chapman, J. C., Polanco, J. R., Min, S., & Michael, S. D. (2005). Mitochondrial 3 beta-hydroxysteroid dehydrogenase (HSD) is essential for the synthesis of progesterone by corpora lutea: an hypothesis. Reproductive biology and endocrinology : RB&E, 3, 11. https://doi.org/10.1186/1477-7827-3-11
- Duan, L., Yang, Y., Gu, Y., Zhang, X., Mao, Q., Pan, B., Deng, C., Pan, H., & Zhu, H. (2019). The utility of adrenal and ovarian venous sampling in a progesterone-producing adrenal tumor and review of the literature. Endocrine, 66(2), 319–325. https://doi.org/10.1007/s12020-019-02007-7
- Aickareth, J., Hawwar, M., Sanchez, N., Gnanasekaran, R., & Zhang, J. (2023). Membrane Progesterone Receptors (mPRs/PAQRs) Are Going beyond Its Initial Definitions. Membranes, 13(3), 260. https://doi.org/10.3390/membranes13030260
- Cipolla-Neto, J., Amaral, F. G., Soares Jr, J. M., Gallo, C. C., Furtado, A., Cavaco, J. E., ... & Quintela, T. (2022). The crosstalk between melatonin and sex steroid hormones. Neuroendocrinology, 112(2), 115-129.