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RESEARCH ARTICLE

Study the Effect of PG E_1 and PGF2α on Male Rat Reproductive Functions

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ARTICLE HISTORY

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Abstract: This research was performed to investigate the effects of prostaglandins on the sexual functions of albino male rats. The effects of prostaglandins on LH, FSH, testosterone secretion and semen quality of the male rats were investigated. PGE_1 induced a significant decline in the level of LH, FSH and testosterone levels. PGE_1 also induced significant decline in the testis, epididymal and seminal vesicle weights. Furthermore, PGE_1 caused significant reduction in sperm count, and significant decline in the viable and malformed sperm percent. However, $PGF_{2\alpha}$ did not affect these parameters.

Keywords: Reproduction, PGE_1 , $PGF_{2\alpha}$, male, rats, LH, FSH, testosterone.

1. INTRODUCTION

Prostaglandins are found in most tissue and organ. They are produced by almost all nucleated cells. They are synthesized in the cell from the essential fatty acids. An intermediate arachidonic acid is created from diacylglyceol *via* phosolipids-A2, then it produces prostaglandin D, E and F by cyclooxygenase (COX) [1]. Prostaglandins modulated many physiological activities including the cardiovascular, gastrointestinal, genitourinary, endocrine, respiratory, and immune response. Fertility is achieved by events that are initiated within the central nervous system and require the maturation and function of a neural network that transmits both homeostatic and external cues to the discrete hypothalamic neuronal population that releases gonadotropin-releasing hormone (GnRH) from neuroendocrine terminals within the median eminence into the pituitary portal vessels to control gonadotropins (luteinizing hormone, LH and follicle stimulating hormone, FSH) secretion [2]. The development of mice deficient in COX1 and/or COX2 has shown that COX2–null female mice are infertile. In contrast, male fertility is not affected in COX1- or COX2-mutant mice, suggesting that different PGs exert different effects on reproductive system [3]. PGE_2 injected into the third ventricle of the rat brain induced the release of LH into the general circulation and of GnRH into the pituitary portal blood vessels. PGE_2 acts at two main hypothalamic sites: the preoptic-anterior hypothalamic region in which GnRH cell bodies reside, and the tuberal region of the hypothalamus, which contains the median eminence and GnRH-releasing neuroendocrine terminals [4]. A single injection of PGE_2 dose-dependently affected a transient increase in mean LH concentration and LH pulse amplitude, while, $PGF_{2\alpha}$ did not affect LH pulsatility. However, co-administration of PGE_2 and $PGF_{2\alpha}$ induced a significant suppression of both the frequency and amplitude of LH pulses [5, 6]. PGs also affected both steroidogenesis and spermatogenesis, they adversely affected male germ cell differentiation and induced sperm structural changes in mice especially in the acrosomal apparatus and chromatin [7-9]. On the other hand,

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Table 1. Effect of Prostaglandins on LH, FSH and testosterone level when administered for 60 days in male rats.

Treatments	Hormones level		
	LH (mIU/mL)	FSH (mIU/mL)	Testosterone (ng/mL)
Control	$1.86^{a} \pm 0.009$	$0.81^{a} \pm 0.032$	$30.19^{a} \pm 1.081$
PGE_1	$1.81^{b} \pm 0.064$	$0.72^{b} \pm 0.016$	$25.49^{b} \pm 2.037$
$PGF_{2\alpha}$	$1.86^{a} \pm 0.051$	$0.75^{a} \pm 0.014$	$29.89^{a} \pm 1.380$

Similar letter means not significant, b= < 0.05 compared with control.

Table 2. Effect of Prostaglandins on relative (g/100g bw) testis, epididymis, seminal vesicle and prostate weight when administered for 60 days in male rats.

Treatments	Testis Weight	Epididymis Weight	Seminal Vesicle Weight	Prostate Weight
Control	0.012 ± 0.42^{a}	0.004 ± 0.20^{a}	0.050 ± 0.35^{a}	0.014 ± 0.015^{a}
PGE_1	0.001 ± 0.30^{b}	0.002 ± 0.16^{b}	0.010 ± 0.21^{b}	0.001 ± 0.013^{b}
$PGF_{2\alpha}$	0.021 ± 0.42^{a}	0.005 ± 0.17^{a}	0.051 ± 0.26^{b}	0.003 ± 0.013^{b}

Similar letter means not significant, b= < 0.05 compared with control.

nonsteroidal anti-inflammatory drugs which inhibit the synthesis of all PGs *via* inhibition of cyclooxygenase (COX) enzyme, showed antiandrogen effects and decreased the sperm count and motility and also induced seminiferous tubules damage, suggesting that some of PGs are essential for normal reproductive functions [10-13]. However, although, prostaglandins regulated several reproductive processes in the female, including ovulation, fertilization, mediating LH-induced progesterone synthesis, uteolysis, uterine contraction and parturition [14], but, their roles in the male reproductive system, are poorly defined and still controversial. This study was designed to investigate the effects of different prostaglandins on male rat reproductive performance.

2. MATERIAL AND METHODS

Thirty six male rats were used in this experiments, they were taken from lab animal house in the college of science, university of Thi qar. They were 9-10 wks old and weighing 170-180 gm. They were housed for 2 wks before the experiment to be adapted on the experiment environment. Water and diet were offered *ad. libtum*. The temperature of the housing room was adapted to 25±3 C, with 12 hr day/12 hr darkness. Males were divided into 3 groups. The 2nd and 3rd groups were given PGE_1 12.5 µg / kg and $PGF_{2\alpha}$ 50 µg /kg bw respectively as a single daily dose for 60 days. The first group was given the vehicle for the same period to serve as a control. The volume of dose is adjusted to 0.2 ml/rat. After the treatment periods, males in each group were anesthetized with ether, blood samples were collected by cardiac puncture, scrotum was open, the right testis epididymis as well as seminal vesicle and prostate were isolated from each animal. After weighting of these organs, the number of sperms / mg in the left epididymal head were counted according to the method of Sakamoto and Hashimoto [15]. Viable sperm count and sperm malformation ratio were determined by routine lab tests [16]. Serum was isolated from blood sample and used for the determination of LH, FSH and testosterone levels by ELISA. Statistical package of social sciences (SPSS) was used to determine the significance among groups.

3. RESULTS

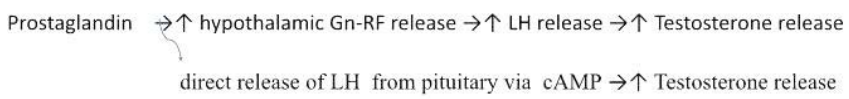
As shown in Table **1**, PGE_1 induced a significant decline in the level of LH, FSH and testosterone, while $PGF_{2\alpha}$ did not induce significant changes in serum level of these hormones.

PGE_1 induced significant decline the relative testis, seminal vesicle, epididymal and prostate weights (g/ 100g bw) (Table **2**). It also caused significant reducted sperm count and viable sperm percent and significantly increased malformed sperm percent (Table **3**). However, PGF2α did not induce significant changes in the weights of sexual

Table 3. Effect of Prostaglandins on semen parameters when administered for 60 days in male rats.

Treatments	Semen analysis (Mean± SE)		
	Sperm count × 10^6 Sperm/mg of Epididymal Head	Viable Sperm %	Sperm Malformation Ratio %
Control	46.58^a ± 0.55	79.50^a ± 0.763	9.00^a ± 0.577
PGE_1	20.85^c ± 0.67	52.50^c ± 0.921	18.00^b ± 0.966
$PGF_{2\alpha}$	44.48^a ± 0.94	68.00^a ± 1.751	11.50^a ± 0.763

Similar letter means not significant, b= < 0.05, c = < 0.001 compared with control.



Possible interaction between prostaglandins at and hypothalamic-pituitary- gonads axis.

Fig. (1).

and secondary sexual organs and seminal quality parameters (Tables **2** and **3**).

4. DISCUSSION

Prostaglandins E series decreased LH and FSH levels by inhibition of the binding of gonadotropin releasing hormone with G-protein coupled receptor in pituitary gland through competition on receptors of this hormone [17], the decreased in the level of FSH could be occurred either by direct effect on pituitary gland or by increasing of inhibin release from Sertoli cells which subsequently suppress FSH [18, 19], while inhibition of testosterone level could be attributed to the declined LH level [21, 22]. On the other hand, previous studies also showed that the impact of PGE series on hormonal secretion was more than that of PGF2α. This could be attributed to the type of prostaglandins receptors distributed on in the median eminence, hypothalamus and pituitary glands [23]. A single injection of PGE_2 dose-dependently affected LH concentration and LH pulse amplitude, $PGF_{2\alpha}$ did not affect LH pulsatility. However, co-administration of PGE_2 and $PGF_{2\alpha}$ induced a significant suppression of both the frequency and amplitude of LH pulses [5, 6].

The decline in the weight of sexual and secondary sexual organs by PGE_2, could be attributed to the decline in the level of testosterone and the inhibition of secondary sexual organs response to testosterone [24, 25].

The decline in the sperm count with an increase of dead and malformed sperm percent could be attributed to the decrease in spermatogenesis as a result of decline in the levels of LH, FSH and testosterone. In addition, PG adversely affected male germ cell differentiation and induced sperm structural changes in mice especially in the acrosomal apparatus and chromatin [7-9].

CONCLUSION

According to these results, it appeared that Prostaglandins E1 played an important effects on the reproductive system. It adversely affected hormonal status, sexual and secondary sexual organs weights and semen quality.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

REFERENCES

[1] Preethi, R.; Pavithra, I. and Sethu, G. (2017). Role of prostaglandin in reproductive physiology. *Intern., J., of Sci., and Res.* 6(5): 378-379.

[2] Donato, J. Jr.; Cravo, R. M.; Frazao, R. and Elias, C. F. (2011). Hypothalamic sites of leptin action linking metabolism and reproduction. *Neuroendocrinology*, 93: 1809–1810.

[3] Frungieri, M. B.; Gonzalez-Calvar, S. I.; Matzkin, M. E.; Mayerhofer, A. and Calandra, R.S. (2007). Sources and functions of prostaglandins in the testis: evidence for their relevance in male infertility. *Anim., Reprod.,* 4(3):63-69.

[4] Clasadonte, J.; Sharif, A.; Baroncini, A. and Prevot V. (2011). Gliotransmission by prostaglandin E_2: A prerequisite for GnRH neuronal function? *Front., Endocrinol.,* (Lausanne). 2: 91.

[5] Matsuwaki, T.; Komatsuda, M.;, Fujisawa, A.; Doke, M.; Yamanouchi, K. and Nishihara, M. (2017). Molecular species of prostaglandins involved in modulating luteinising hormone pulses of female rats under infectious stress conditions. *J., Neuroendocrinol.,* 29(7). doi: 10.1111/jne.12490.

[6] Diether, N. and Dyck, M.K. (2017). Male fertility evaluation using biomarkers in livestock. *JSM., Biomar.,* 3(1): 1011.

[7] Sava, A.; Motoc, A.G. and Stan, C. I. (2015). Electron microscopic aspects of the effects of certain prostaglandin analogs on mouse testes. *Rom., J., Morphol., Embryol.,* 56(2 Suppl):771-775.

[8] Rossitto, M.; Ujjan, S.; Poulat, F. and Boizet-Bonhoure, B. (2016). Multiple roles of the prostaglandin D2 signaling pathway in reproduction. *Reproduction.,* 149(1): R49-58.

[9] Moniot, B.; Ujjan, S.; Champagne, J.; Hirai, H.; Aritake, K.; Nagata, K.; Dubois, E.; Nidelet, S.; Nakamura, M.; Urade, Y.; Poulat, F. and Boizet-Bonhoure, B. (2014). Prostaglandin D2 acts through the Dp2 receptor to influence male germ cell differentiation in the foetal mouse testis. *Development.,* 141(18):3561-3571.

[10] Uzun, B.; Atli, O.; Perk, B.O.; Burukoglu, D. and Ilgin, S. (2015). Evaluation of the reproductive toxicity of naproxen sodium and meloxicam in male rats. *Hum., Exp., Toxicol.,* 34(4):415-229.

[11] Kristensen, D.M., Desdoits-Lethimonier, C.; Mackey, A.L.; *et al*. (2017). Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism. *Proc., Natl., Acad., Sci.; USA.* 115(4): E715-E724.

[12] Al-Snafi AE, Al- Kasab TM. and Al-Azzawi SS. (1997). Effect of prostaglandin F2α on male mice reproductive function. *J. Coll. Edu.,* (1): 1-8.

[13] Reid, G.; Wielinga,P.; Zelcer, N.; Heijden, I.V.; Kuli, A.and Haas, M.(2003). The human multidrug resistance protein MRP4 function as a Prostaglandin efflux transporter and is inhibited by nonsteroidal antiinflammatory drugs. *Proc. Natl. Acad. Sci. USA*, 100(16): 9244-9249.

[14] Preethi, R,; Pavithra, I. and Sethu, G. (2017). Role of prostaglandin in reproductive physiology. *Intern., J., of Sci., and Res.* 6(5): 378-379.

[15] Al-Snafi AE, Kubba MA, Al-Tahan FJ, Al-Janabi AS. (1993). Effect of chronic diazepam treatment on the reproductive performance of male rats. *Iraqi J. Biol. Science*, 11: 82-92.

[16] Al-Tahan FJ, Al- Janabi AS and Al-Snafi AE. (1993). Effect of chronic diazepam treatment on fertility and sexual ability of male rats. *Dirasat*, 20(4): 151-158.

[17] Narumiya, S. and FitzGerald, G.A. (2001). Genetic and pharmalogical analysis of prostanoid receptor function. *J. Clin. Invest.,* 108(1): 25-30.

[18] Romanelli, F.; Valenca, M.; Conte, D.; Isidori, A. and Negro-Vilar, A.(1995). Arachidonic acid and its metabolites effects on testosterone production by rat Leydig cells. *J Endocrinol Invest.,* 18:186-193.

[19] Lin, T.; Galkins, J. and Morris, P. (1989). Regulation of leydig cells function in primary culture by inhibin and activin. *Endocrinol*., 125: 2134-2140.

[20] Bearden, H.J. and Fuquay, J.W. (1992). Semen collection. In: Bearden, H.J. (Eds.), Applied Animal Reproduction. Prentice-Hall International, London, 72-73.

[21] Vermouth, N.T. and Deis, R.P. (1974). Prolactin release induced by prostaglandin F2α . *Acta physiol. latinoam*. 24, 101-102.

[22] Bartke, A.; Goldman, B.; Bex, F.; Kelch, R.; Smith, M.; Dalterio, S. and Doherty, P. (1981) Effectsof prolactin on testicular regression and recrudescence in the golden hamster. *Endocrin.*, 106(1): 167-72 .

[23] Lubicz-Anwrocki CM, Saksena SK and Chang MC. The effect of prostaglandins E and F2a on the fertilizing ability of hamster spermatozoa. J Rep Fert 1973; 35: 557-559.

[24] Joseph, M.M. and Siwela, A.A. (1976). Effect of prostaglandin $F_{2\alpha}$ and indomethacin on the response of the accessory sex glands of male rats to testosterone. *J. Reprod. Fert*., 47: 93-94.

[25] Jacqueson, A.; Semont, H.; Thevenin, M.; Warnet, J.M.; Prost, R. and Claude, J.R. (1984). Effects of daily high doses of paracetamol given oraly during spermatogenesis in the rat testes. *Arch. Toxicol*., Suppl. 7:164-166.