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Mini Review

Can Oxytocin be used as a Treatment for Sub/Infertility of Males of Seasonal Breeders?

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ABSTRACT

Oxytocin (OXT) is a critical endocrine, paracrine and autocrine factor in male reproductive system. In seasonal breeders, the expression of OXT and its receptor (OXTR) were observed in germ cells, Sertoli cells, Leydig cells, and the membrane of the seminiferous tubules, indicating that OXT plays roles in spermatogenesis and steroidogenesis. OXT and OXTR were expressed in epithelial cells and smooth muscle cells in the epididymis as well as the epithelial cells in ductus deferens, suggesting that OXT is involved in the sperm transportation. The intensity of OXT and OXTR expression was significantly higher in the breeding season than in the non-breeding season. Several studies demonstrated that the size of reproductive organs and the rate of sperm production vary depending on the season. These results implied that OXT and OXTR systems appear to be important factors for promoting and maintaining reproductive functions in breeding season. Changes in the expression level of OXT and OXTR, along with the seasonal variation of reproductive functions, indicate that OXT system plays important roles in reproductive functions in seasonal breeders. Therefore, treatment with OXT may improve the male reproductive functions of infertile/sub fertile seasonal breeders.

Keywords: Oxytocin; Oxytocin receptor; Spermatogenesis; Seasonal breeders; Therapeutics

INTRODUCTION

The reproductive status of seasonal breeders is regulated by photoperiodic. As a basic mechanism for the photoperiod system, mammals receive the photoperiodic information into the retina, and the photoperiodic information is transmitted to the pineal gland to control the secretion of melatonin [1]. Melatonin indirectly participates in the secretion of Gonadotropin-Releasing Hormone (GnRH) to promote or inhibit the secretion of Luteinizing Hormone (LH) and Follicle Stimulation Hormone (FSH) in the pituitary gland. The LH and FSH regulate the secretion of sex steroid hormone in the gonads, and this mechanism determines the breeding and non-breeding seasons [1]. The efficiency of reproductive functions dramatically changes depending on the season in male seasonal breeders. Sperm production reduction and reproductive organ size reduction occur during the non-breeding season. In stallions, the number of sperm decreases by half, and the testis length is reduced by approximately 28% during non-breeding season [2]. The process of seasonal changes of testes is similar to that of testicular degeneration, which is the main cause of sub/infertility of stallions [3]. Therefore, by observing hormones and growth factors that change following the season, the cause of sub/infertility can be identified, and treatment methods can be derived. Oxytocin (OXT) comprises six cyclic amino acid structures with a tail of three amino acids [4]. The OXT is produced by the magnocellular neurons within the paraventricular nucleus and supraoptic nucleus of the hypothalamus. The OXT is released from the magnocellular neurons into the posterior pituitary [5]. OXT effects on the reproductive system as endocrine and paracrine factors. Salehi and coworkers demonstrated that the OXT treatment increased the GnRH expression in hypothalamus tissues of rats [6]. Also, OXT administration induced the increase of peripheral LH and FSH levels in this species [7]. The OXT and oxytocin receptor (OXTR) were expressed in the testis and reproductive tract of seasonal breeders. Several studies demonstrated that the expression level of OXT and OXTR also changes with the season [4,8,9]. With these concepts, we hypothesized that OXT and OXTR are essential factors influencing the male reproductive system of seasonal breeders. In this review, the seasonal modification of expression level and functions of OXT and OXTR in seasonal breeders were

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discussed. This information may be used to develop a therapeutic approach for subfertility or infertility of the males of seasonal breeders.

LITERATURE REVIEW

The expression of OXT and OXTR in the reproductive systems and their functions in the male of seasonal breeders

The expression of OXT and OXTR in the testis: The OXTR expression was observed in the cytoplasm of spermatogonia, round, elongating, elongated spermatids, and fully elongated spermatids of stallions [4]. In rams, OXTR was expressed in the cytoplasm of spermatogonia, Pachytene spermatocytes, and elongating spermatids [10] (Table 1). The expression of OXTR in germ cells indicates that OXT is involved in the process of spermatogenesis. The effects of OXT on inducing spermatogenesis were revealed in several studies. A long-term OXT treatment induced the proliferation of spermatogonia, spermatocytes, and spermatids, followed by the increased sperm output in rabbits [11]. Whittington and coworkers demonstrated that OXT treatment increased the population of spermatozoa in the rete testis fluid compared with the treatment with saline and OXT antagonist in rams [10]. Also, sperm cells were shed earlier in bovine OXT transgene mice than in the wild-type as well as the OXT knockout mice [12]. These results support the fact that OXT is a key modulator for spermatogenesis. There was an expression of OXTR in the Leydig cells of the stallions [4]. Also, OXT and OXTR were observed in the rams [10,13]. In bucks, OXT was observed in the interstitial tissues, including the Leydig cells (Table 1) [14]. Several studies suggested that OXT affects the secretion of testosterone and dihydrotestosterone as well as the activation of 5α-reductase in Leydig cells. These results suggest that OXT plays a vital role in steroidogenesis in Leydig cells, but its function depends on the species, developmental stages, and treatment periods. In the Sertoli cells of stallions, OXTR was not expressed [4]. However, the OXT and OXTR expression was detected in Sertoli cells of rams [10,13]. OXT was also observed in Sertoli cells of bucks (Table 1) [14]. So far, no study indicates the direct function of OXT in Sertoli cells. The fact that the expression of OXTR in Sertoli cells suggests that OXT supports spermatogenesis *via* Sertoli cells regulation. The OXTR was expressed in the basal membrane of the seminiferous tubule in stallions and rams (Table 1) [4,10]. The basal membrane was involved in the contractility of seminiferous tubules. OXT treatment induced a significant increase of seminiferous tubule contractility from stage VII to stage VIII in rats [15]. Following these results, we suggested that the OXT and OXTR systems may be associated with the spermiation process, which involves the movement of spermatids to the lumen of the seminiferous tubule.

The expression of OXT and OXTR in the epididymis: Several studies demonstrated that OXT and OXTR were expressed in epididymis cells of seasonal breeders. In stallions, OXT was expressed in epithelial cells and smooth muscle layers, and OXTR was expressed in principal cells and basal cells [4,16]. In rams, OXT

Table 1: OXT and OXTR expression in male reproductive tract of seasonal breeder.

Tissue	Species	Method	OXT	OXTR
Testis	Stallion [4,16]	IHC	(+) Interstitial cell, tail of spermatozoa -Seminiferous tubule	(+) Spermatogonia, spermatid, seminiferous tubule membrane, Leydig cell
		WB		(+)
		RT-PCR		(+)
	Ram [10,13]	IHC	(+) Leydig cell	(+) Spermatogonia
		ICC	+ Sertoli cell	pachytene spermatocyte, early spermatid, late spermatid, Sertoli cell, seminiferous tubule membrane, Leydig cell - Myoid cell layer
		WB	(+)	(+) Spermatogonia, pachytene spermatocyte, early spermatid, late spermatid
	Buck [14]	IHC	(+) Sertoli cell	
			+ Interstitial tissue	
		RT-PCR	(+)	
Epididymis	Stallion [4,16]	IHC	(+) Epithelial cell, smooth muscle layer	(+) Principal cell, basal cell
	Ram [10,13]	IHC	(+) Principal cell	(+) Epithelial cell
		ICC		+ Peritubular smooth muscle layer (not expressed in caput)
		WB	(+)	(+) Spermatogonia (not expressed in caput), pachytene spermatocyte, early spermatid, late spermatid
	Muskrat [8]	IHC	(+) Epithelial cell, smooth muscle cell	(+) Epithelial cell, smooth muscle cell
		RT-PCR	(+)	(+)
	Ground squirrel [9]	IHC	(+) Epithelial cell, smooth muscle cell	(+) Epithelial cell, smooth muscle cell
		RT-PCR		(+)
Ductus deferens	Ram [10]	IHC		(+) Epithelial cell, circular smooth muscle layer - Longitudinal smooth muscle

Note: (+): Detected, +: Weak detection, -: Not detected.
IHC: Immunohistochemistry, ICC: Immunocytochemistry, WB: Western blot, RT-PCR: Reverse transcription-polymerase chain reaction.

expression was found in principal cells, and OXTR expression was noticed in epithelial cells [10,13]. Muskrats and ground squirrels, OXT and OXTR were expressed in both epithelial cells and smooth muscle cells (Table 1) [8,9]. Nicholson and coworkers demonstrated the effect of OXT treatment in sperm transport of rams [17]. In this study, the fluid output and the population of spermatozoa increased in the OXT injected groups (10 and 100 μg), but these parameters decreased in the OXT antagonist injected group. The results suggest that OXT may regulate the function of epididymis cells.

The expression of OXTR in the ductus deferens: The OXTR expression was detected in epithelial cells in the seminiferous tubules of rams (Table 1) [10]. Knight demonstrated that the OXT treatment promoted the contraction and tonus in ductus deferens of rams [18]. Following these results, OXT may induce sperm transport in ductus deferens.

The seasonal effect on the reproductive system and OXT and OXTR expression in seasonal breeders

Seasonal changes of the reproductive system in seasonal breeders: Dramatic changes occur in the male reproductive system of seasonal breeders. In stallions, the parenchymal weight of testis, volume and population of germ cells, daily sperm production rate, and germ cell degeneration significantly increase during the breeding season [2]. Also, the volume of Leydig cells and nuclei as well as the population of Leydig cells significantly increases during the breeding season [19]. In muskrats and ground squirrels, the weight and length of the epididymis were significantly larger than the non-breeding season during the breeding season [8,9], and in these species, there was a significant increase in epithelial thickness, lumen diameter, and population of mature spermatozoa during the breeding season.

Seasonal changes of OXT and OXTR expression of the reproductive system in seasonal breeders: Several studies observed that OXT and OXTR expression were higher during the breeding season compared with the non-breeding season. In testicular tissues of stallions [4], there was an intensive expression of OXTR protein during the breeding season. In epididymis tissues of ground squirrels, the same results were indicated [9]. The immunoreactivity of OXT and OXTR were higher in the epididymis of muskrats and ground squirrels castrated in the breeding season [8,9]. Additionally, the mRNA level of OXT and OXTR was significantly higher in the breeding season of these species. OXT level in the testis and epididymis was significantly higher in the breeding season than in the non-breeding season in ground squirrels [9]. In muskrats, the OXT concentration was also significantly higher in the epididymis of the breeding season and vice versa [8]. The intensity of OXTR protein increased as the breeding season approached [4]. In muskrats during the breeding season, as the epididymis weight increases, the expression level of OXT and OXTR mRNA increases [8]. In ground squirrels, the expression level of OXTR mRNA and protein changed with epididymis weight in the same way during seasonal changes [9]. The results of these studies suggest that the expression level of the OXT system in the reproductive organs changes along with the seasonal dependent reproductive functions in seasonal breeders [20].

CONCLUSION

In previous studies, OXT and OXTR were expressed in the reproductive system of seasonal breeders. Also, changes in the expression level of OXT and OXTR, along with the seasonal variation of reproductive functions, indicate that OXT system plays important roles in reproductive functions in seasonal breeders. Therefore, treatment with OXT may improve the male reproductive functions of infertile/sub fertile seasonal breeders.

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CONFLICT OF INTEREST

None declared.

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