

The Prominent Role of Pituitary Adenylate Cyclase-Activating Polypeptide in Spermatogenesis and Function of Spermatozoa: A Mini Review

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ABSTRACT

Spermatogenesis is a great, complex, and long process. This process take place in the tubulus seminiferus of the testis and consists of three phases i.e. proliferation, meiosis, and spermiogenesis. In proliferation phase, the number of cells were multiplied, while in the meiosis occurs the completion of cleavage to form haploid cells. In the spermiogenesis, the cells perform a morphological change to form the mature gamet that is spermatozoa. Spermatogenesis involves the role of hormones and many molecules resulting the functional spermatozoa which crucial to induce the process of fertilization. Pituitary adenylate cyclase-activating polypeptide (PACAP) is an elderly and multifunctional molecule that necessary in spermatogenesis and the quality of spermatozoa. Many results revealed that PACAP molecule is responsible for male reproduction and fertility. The main objective of this review is to describe the prominent role of PACAP in spermatogenesis and the spermatozoa function.

Keywords: *pituitary adenylate cyclase-activating polypeptide, reproduction, spermatogenesis, male fertility*

1. INTRODUCTION

Spermatogenesis is a complicated and long process [1] involves a division and differentiation of spermatogonial stem cells (SCCs) in producing the billions of haploid spermatozoa cells daily [2,3,4] which occurs within tubulus seminiferus of the male testis [5]. SCCs are germinal stem cell which has an important key in maintaining the spermatogenesis a long lifetime of the male [6]. Disturbance in spermatogenesis results a low-quality of spermatozoa [7] that caused the male infertility [8].

The important role of hormonal factors in spermatogenesis has been shown previously [9,10]. *Luteinizing hormone* (LH) or testosterone (T) dan *follicle stimulating hormone* (FSH) are indispensable in regulating the function of testicular/spermatogenesis [11]. LH induces Leydig cells to produce T hormone [10,12]; while within Sertoli cells, FSH cooperate in good-synergy with T to arrange many signals (molecules) and nutrients needed during spermatogenesis [10]. Therefore, FSH and T hormone regulate the spermatogenesis indirectly [10]. Dun *et al.* [13] stated that the several molecules are required in spermatogenesis.

Pituitary adenylate cyclase-activating polypeptide (PACAP) is one of molecule has a key role in regulation of gonadotropin secretion [14,15], system of reproductive [16] spermatogenesis and steroidogenesis [17,18]. Data

revealed that some organs particularly brain, testis, and also spermatid cells are rich in the content of PACAP [19,20]. PACAP also required in development and function of spermatozoa [21] and also involved in secretion of T in the culture of Leydig cells [22]. Moreover, Agnese *et al.* [17] stated that PACAP is a molecule which has a vital role for reproduction.

2. PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE (PACAP)

PACAP is neuropeptide molecule [23,24,25] which expressed extensively in many tissue of the body [26]. PACAP and its receptor is not only express in hypothalamus, however it also expressed in more of the other peripheral organ [27]. Biologically, there are two form of PACAP active such as PACAP 38 dan PACAP 27 [28]. PACAP 27 is originated from the maturation cleavage of PACAP 38 [29] while PACAP 38 is a main form of PACAP which can be found in various tissue of the organ [30]. Agnes *et al.* [17] stated that there were three receptors of PACAP in many tissues: PAC1, significantly binds with PACAP; VPAC1 and VPAC2, the bond with PACAP and vasoactive intestinal peptide.

PACAP is synthesized as a preprohormone and processed by prohormone convertases such as PC1, PC2, and PC4. PC4 only expressed in testis and ovary, while PC1 and PC2 are not express in these organs [19]. Data revealed that hypothalamus is the organ with a high

concentration of PACAP, whereas PACAP mRNA discovered in the some organ, including testis [28].

Initially, PACAP isolated from the brain [21]. However, a high concentration of PACAP has been found in the testis [30] and also expressed significantly in the spermatids of rats [19] as well as in the acrosome of spermatozoa. This indicated that PACAP have a critical role in the growth and function of spermatozoa [21], and assumed to have the role in mediating the interaction between spermatozoa and cumulus cells in supporting the fertilization process [31].

PACAP involving spermatogenesis in four phases: (i) Expressed in immature of the spermatozoa, (ii) Involved in the late of spermiogenesis, (iii) Induce the activity in supporting the Sertoli cells, and (iv) Regulate the Leydig cells in secretion of T [22]. Chun_Mei *et al.* [32] reported that PACAP mRNA was expressed in the testis and epididymis of the rats. In the testis, particularly in spermatocyte and round spermatid cells, the expression of PACAP mRNA was observed on day 20 after birth and then increase rapidly until maximum level on day 60. Meanwhile in epididymis, expression of PACAP mRNA was visible on day 10 after birth and increase in a high level from day 40 [32]. Moreover, in the normal testes, immunoreactivity of PACAP has been found in the cells of spermatogonia and spermatid [33].

3. THE ROLE OF PACAP

PACAP is a multifunctional molecule that is required to stimulate cyclic adenosine monophosphate (cAMP) production in anterior of pituitary cells [34], while cAMP itself is a compound which is needed to activate the steroidogenesis [35] and a good regulator in induction of Leydig cells function [36]. Although PACAP was ineffective in stimulating the cAMP production in Sertoli cells compared to FSH [37], PACAP showed the ability to substitute FSH to induce the level cAMP that was required in spermatogenesis [26].

Spermatozoa motility in the human male is influenced by PACAP and involving the growth and functional of spermatozoa. Lack in PACAP concentration causes bad-effects on motility and morphology of the spermatozoa [21]. Study on male rats revealed that PACAP is a molecule that responsibility to the decrease of the male mice fertility [16]. Nakamura *et al.* [33] showed that in human, PACAP have a significant role in spermatogenesis and the growth of testicular germ cell tumor.

The scientists have found a signaling pathway in describing the role of PACAP in spermatogenesis. Binding PACAP to its receptor (PAC1) will activate the enhancement intracellular concentration of PACAP which caused the activation of protein kinase A (PKA). Ser/Thr phosphatase (PP2A) arranged the phosphorylation of downstream PKA target reversibly.

PP2A can induce the dephosphorylation of Sox9 transcription factor until it be able to modify the expression or activation of Sox10. On the other hand, PKA can regulate the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2) that followed by p38 activation. The main target of Sox9 transcription factor is collagen type IV and collagen type IV or testatin. All of these are responsible in phosphorylation some the event that regulate proliferation, motility, and establishment of the blood-testis barrier [16]. The results showed that PKA needed in capacitation of mammalian spermatozoa [38], while ERK pathway involved in the functional of human spermatozoa [39] and it also required in the regulation of capacitation and acrosome reaction on the mammalian spermatozoa [40]. In addition, the facts showed that in human, expression of collagen type IV causes the thickening of basic membrane of tubules seminiferous testes which relating with spermatogenesis [41]. The study also showed that defect in *testatin* expression on mice relating with the development disorder of fetal Sertoli cells [42].

The previous study showed that administration of epididymis extract which in rich concentration of PACAP have potency in the increase of T concentration [43], FSH, LH, and follicle stimulating hormone-receptor expression [44], estrogen [45], dihydrotestosterone [46] and capable to increase the quality of spermatozoa in male local goat [47]. Furthermore, the study in male chicken showed that administration of epididymis and testicular extract combination influence the concentration of androgen receptor, protein kinase A [48], PACAP, protamine 1 and increase significantly the concentration of T [49]. Protamine has a vital role as a check point spermatogenesis [50], in which protamine 1 affects the quality of spermatozoa in the bull [51] and mice [52], while protamine 2 is required in inducing spermatogenesis and spermatozoa quality in the male rats [7]. Furthermore, both protamine 1 dan 2 plays important role in functional and quality of the human spermatozoa [53]. Generally, the role of PACAP in spermatogenesis and spermatozoa function is presented in Figure 1.

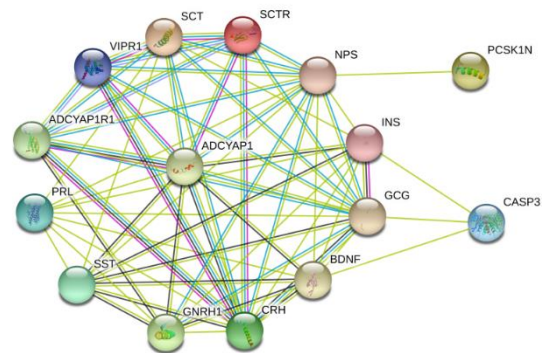


Figure 1 PACAP Protein Network

PACAP protein has linkage to many proteins in involving the spermatogenesis and spermatozoa function. Figure 1 which was obtained from STRING-DB showed that the interaction of PACAP (ADCYAP1) to its receptor and some of the other molecules involve the expression of PACAP (up-regulation and down-regulation). Lines of interaction with colors showed that some type of interaction which gained and proved from several of literature source. The numbers of line interaction between protein indicated the confidence score of a high interaction. However, the scoring did not show the strength or interaction of specificity.

PACAP protein have the multifunctional role as a hormone, neurotransmitter, neuromodulator, vasodilator and neurotropic factor caused it affect and influenced by many molecules protein as shown in the picture. ADCYAP1 (pituitary adenylate cyclase-activating polypeptide), ADCYAP1R1 (pituitary adenylate cyclase-activating polypeptide type 1 receptor), VIPR1 (vasoactive intestinal polypeptide receptor 1), SCT (secretin), SCTR (secretin receptor), NPS (neuropeptide), INS (Insulin), GCG (glucagon), BDNF (brain-derived neurotrophic factor), CRH (corticotropin-releasing hormone), GNRH1 (Gonadotropin-releasing hormone-1), SST (somatostatin), PRL (prolactin) PCSK1N (ProSAAS), CASP3 (Caspase-3). Data was obtained from String-DB.

4. CONCLUSION

PACAP is an elderly and multifunctional molecule which express in many tissue of the body particularly in the brain and testis. This molecule has a significant role in spermatogenesis and function of spermatozoa that essential for fertilization process.

AUTHORS' CONTRIBUTIONS

MA, Z, G, TZH, and S, are equally contributed to this article.

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