AN UPDATE ON COAGULATING GLAND RENIN-ANGIOTENSIN-PROSTAGLANDIN SYSTEM: A NEW HYPOTHESIS ON ITS RENIN FUNCTION

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ABSTRACT

After a proper description of reproductive functions of rodent anterior prostate, coagulating gland (CG), by Moore and Gallagher in 1930, numerous papers have been published on this gland and its function in male fertility. It has also been known that it has a local renin-angiotensin system. However, the actual function of this system is not very clear, and even nowadays, this gland is getting ignored in reproductive physiology research. Thus, this review article attempts to unearth the reproductive functions of this gland, with a hypothetical mechanism of CG renin function. We have reviewed the available literature published on this gland and correlated the fragmented information to unveil its importance. We have proposed a hypothetical mechanism (aided by self-designed schemes) of CG renin function along with its functional and structural aspects in reproductive physiology. Despite being ignored in modern research, CG has a very significant function in rodent reproduction and breeding. It has also a very significant role in the regulation of local homeostasis by the renin-angiotensin-prostaglandin system.

Keywords: Laboratory rat, Mice, Accessory sex organs, Coagulating gland, Renin.

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INTRODUCTION

Moore and Gallagher, in 1930, during their experimentation had found that after mating of male and female rats, a coagulum had formed in vagina of female rat, which they named as vaginal plug. On investigation, they found that a male accessory sex gland, anterior prostate, is responsible for the formation of this plug, which on electrical stimulation also forms coagulum. They named this accessory sex gland as coagulating gland (CG) [1]. It is one of the most essential accessory sex glands in rodents and monkeys for their normal reproductive functions including fertility [2,3]. Average sized CG has been found in most of the rodents, including plains' mouse, western chestnut mouse, desert short-tailed mouse, fawn hopping mouse, spinifex hopping mouse, giant white-tailed rat, fawn-footed melomys, water rat, water mouse, guinea pig, rabbit, and all other rats and mice used for experimental purposes [4]. Like other male accessory sex organs, it is also androgen dependent [3,5].

Numerous research articles have already described the structure as well as the functions of this gland in male reproduction [6,7]. It is well known that it also secretes renin, like renal tissues [6]. However, a proper function of CG-renin is still not very clear. Thus, this review makes an attempt to clarify those facts, after detailed scrutinization of the available information regarding CG and proposes a mechanism of CG renin function, along with a brief description of the structural aspects of this male accessory sex gland.

HISTOLOGICAL AND HISTOCHEMICAL STRUCTURE OF CG: AN UPDATE

In mice and rats, CG, with a translucent color, is located adjacent to the medial concave surface of seminal vesicles (SV). However, a recent research has revealed that there are some differences in locations of CG in animals. They have reported that in mice, rat, and great African rat, the gland lies along almost the entire length of vesicular glands while in Viscacha it is located in the upper part of prostate [8]. With light microscopy, the CGs can be differentiated from the SV by paler eosin staining and slight dilation of the lumen which is composed of single columnar or cuboidal epithelium surrounded by connective tissue and smooth muscle. The cell membranes of adjacent cells are separated by a narrow layer of structureless material of low density. The epithelial height varies somewhat within the gland. Secretory activity is heterogeneous along the length of the duct: Certain regions are distended with secretion and had few in folding’s (Fig. 1) [9], other regions have extensive folds (mucosal plicae). Plications of the cell membrane are visible at the lateral aspects and the base of the cells [1,9]. Recent ultrastructural and immunohistochemical studies on greater cane rats also indicated the presence of some blebbing on the apical part of the epithelial cells [8]. According to Badia et al., the presence of abundant in-foldings (microvilli) and coated vesicles have been associated with the absorptive activity in the SV. These microvilli have also been reported to have an apocrine mode of secretion and extruding soluble and membrane-bound proteins [10]. These features also tend to suggest a robust protein synthesis with the packaged secretory products released through the merocrine mechanism [8,10]. Recent studies have reported the presence of transglutaminase type IV, kinesin and other soluble proteins which may be concerned with vesicle trafficking and secretion of proteins from CG [11]. As the structure of the CG, in mice and rats, is ductal rather than acinar, the large dilated tubules are located near the SV and longitudinally along the SV that are identified as main duct, whereas the small tubules that are crossed or obliquely located along the SV and distributed to peripheral areas of the gland are identified as terminal ducts. Each single elongated main duct remains joined to the posterior cranial portion of the urethra. Each main duct is differentiated into 40-50 terminal ducts whose tips were distended with eosinophilic secretion [9].

Cytoplasmic matrix of epithelial cells contains structureless material of medium density which shows a number of small discrete dense particles. Due to the intense dilation of the cavities of the endoplasmic reticulum (ER), the cytoplasmic matrix in between appears reduced to narrow strands or either oval or circular profiles. The exception to this is in the region of the Golgi complex where the various components of this organelle lie in a broader zone of the cytoplasmic matrix [12]. The most striking feature of epithelial cells is the pronounced dilation of the various cisternae of the ER. The content of the dilated cavities
is homogeneous and less dense than the cytoplasmic matrix and it does not appear to come into contact with the cell membrane at any point of its extension.

It is well known that this gland expresses androgen receptors (AR) in cytoplasmic matrix and nucleus [13]. As we know from the previous reports, only distribution of estrogen receptors (ER) varies in cell types and species, but ARs are commonly found in epithelial cells and stromal cells in reproductive organs [13]. Adebayo et al. (2015), with histomorphochemical studies, showed immune expression of ER-α and ER-β on the surface of epithelial cells of CG. They have showed an extensive expression of ER-α in the nucleus and in the apical bleb or cytoplasm of the secretory epithelium in rat CG. They have indicated that this kind of immunoreactivity is not common in all rodents [8]. As reported by Prins and Korach [14], ER-α is basically localized in stroma cells with consequent cell death. The equilibrium between connective and epithelial and connective tissue elements does not occur part pass. Therefore, it can be concluded that degenerative changes in the CG are not connected with the process of lumen formation. Since the changes occur during the prepubertal and pubertal periods, they must be associated with the structural and functional maturation of the gland. Cell deaths occurring at this time fall into the category of “histiogenetic degenerations” [12], and they may be caused either by a failure or by a change of the differentiating impulse. In the prepubertal male, androgen is the main stimulus to differentiation of the accessory reproductive organs, and failure in its production obviously does not occur at this age. Androgens are not the only substances capable of influencing the development of the reproductive system; estrogens may act synergistically with androgens to produce full development of the accessory organs. In this cooperative function, as discussed earlier, androgens stimulate the epithelium and estrogens the connective tissue through ER-α [8]. It is well known that estrogens may cause water-retention in the reproductive organs, and this fact may account for the edema observed in the SV and to a lesser extent in the CG, which indicates the estrogen-dependent development of SV and CG [13,14].

In CG, cell deaths may be seen with no concomitant edema, and the following hypothesis is advanced to meet the observed facts. With the rapid increase in gonadal hormone production which occurs before and at puberty it is conceivable that temporary variations may arise in the proportions of androgens to estrogens, with the result that growth of epithelial and connective tissue elements does not occur part pass. Connective tissue overgrowth due to a preponderance of estrogen may therefore lead to a strangulation of the blood supply to epithelial cells with consequent cell death. The equilibrium between connective tissue and epithelium would only be established when androgen and estrogen production became stabilized at the time of sexual maturity [17]. Ortiz et al. with a photomicrograph of CG containing large intraluminal masses in the lateral prostate of a 10-day-old guinea pig claimed such masses being the evidence of secretion although they contained distinct cellular elements [18]. In the CG, edema is seen much less frequently, and although it is a possible cause of cell death, other etiological factors must be considered [18]. Since the process of canalization of the acini of the gland occurs shortly before cell deaths are observed (between the 10th and 17th days in these investigations), the presence of masses of cells in acini might be explained on this basis, especially since the usual theory of the formation of Lumina in solid rods of cells involves the death of cells in the centre of the rod, the peripheral cells surviving [18].

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**COAGULATING GLAND AND ANIMAL REPRODUCTION**

It is well known that in certain animals, particularly rodents, a firm coagulated mass forms in the vagina after copulation. It was called a vaginal plug or copulation plug by Moore and Gallagher (1930) who first described the anterior lobes of the prostate as the source of the coagulating enzyme and called these “coagulating glands” [1]. This anterior portion differs physiologically and histologically from the middle and posterior lobes. Scott and Dzunc (1959) during their experiment with rats first noticed that CG is a major obstacle to electro-ejaculation since the plug blocks the urethra and causes death from uremic poisoning. Then, they removed the SVs and the attached CGs and easily obtained samples of semen relatively free from the
Table 1: Postnatal changes in the histology of coagulating gland in rat

| Day   | Developmental changes                                                                                      |
|-------|------------------------------------------------------------------------------------------------------------|
| 1     | The anlage of the coagulating gland is present as a solid rod of cells ventrolateral to the mesonephric and |
|       | paramesonephric ducts. It penetrates the mesenchyme to only a short distance from the urogenital sinus. Its  |
|       | diameter averages 85 µ. In both organs mitoses are numerous                                                |
| 3     | The anlage of the coagulating gland has penetrated further in a dorsolateral direction, and its free end has |
|       | expanded somewhat. Its average diameter has increased to 45 µ. There are numerous mitoses in both organs.    |
| 5     | In the coagulating gland, dorsolateral extension has continued and the diameter has increased to 75 µ.       |
|       | A lumen is visible in that part destined to become the duct of the gland. Mitoses are numerous               |
| 7     | The diameter remains approximately the same, and the process of canalization is extending towards the secretory |
|       | part of the gland. Mitoses are frequent                                                                    |
| 17    | About half the acini are now patent. Their diameters vary between 40 and 60 µ and they are usually lined by  |
|       | single layers of cells, whose average height is 11 µ.                                                    |
|       | Most acini contain a structureless substance, which is rather more eosinophilic than the cytoplasm of the   |
|       | epithelial cells. A few acini contain collections of necrotic epithelial cells                             |
| 21    | About two-thirds of the acini are patent, and occasional convolutions of the lining epithelium may be seen.  |
|       | The cell height is rather variable, averaging 15 µ.                                                      |
|       | The acinar diameters vary between 40 and 60 µ. Most acini are lined by a single layer of cells; occasionally  |
|       | a second layer may be seen. The nuclei are vesicular and basal, with a markedly eosinophilic cytoplasm.      |
|       | Mitoses are frequent.                                    About a quarter of the acini contain debris consisting of |
|       | aggregations of cells with deeply basophilic homogeneous nuclei and very eosinophilic cytoplasm. Cells      |
|       | possessing similar characteristics may be seen in the walls of some acini, where they stand out prominently  |
|       | by comparison with their neighbouring, less deeply stained cells.                                          |
| 28-30 | All the acini are patent. They average 90 µ in diameter, and the cell heights 14 µ. The cells differ little  |
|       | in appearance from those seen at 21 days. In addition to necrotic cells in the acinar walls and cellular      |
|       | debris in lumina, areas of epithelium may be seen to be shed into acini. This is only an occasional finding,  |
|       | and even then, it is localized to only a part of an acinus. In such regions, the wall of the acinus consists of |
|       | the connective tissue and muscular sheath of the gland, together with the Membrana propria. Occasional epithelial |
|       | cells may remain adherent. Although less generalized, the appearances are similar to those produced by       |
|       | interruption of the arterial supply to the gland                                                         |
| 35-37 | The findings resemble those at the previous age, although degenerative phenomena are not so frequently seen.  |
|       | The acini average 130 µ, in diameter, and the cell height averages 14 µ                                   |
| 41-44 | The average diameter of the acini is the same as at the previous age, but the epithelium is rather lower,    |
|       | averaging 11 µ. Many of the cells show the basal vacuolation characteristic of maturity, and the nucleus     |
|       | lies in the mid-zone of the cell. Degenerative changes of all three types may be seen, but they are less      |
|       | widespread than at previous stages                                                                       |
| 48-55 | This presents an appearance of maturity. A few acini contain masses of secretion, which are almost completely |
|       | acellular                                                                                                  |

accessory fluids [19]. Afterward, in 1961, Birnbaum and Hall showed by using low voltage current, semen can be collected from rat CG. They have used 30 cycles/second and collected coagulum-free, small volume, seminal fluid free semen from rats. They also reported after the experiment, CGs regenerated readily, but they have not provided any data [20]. Several other studies have reported the importance of CG in rat breeding and formation of coagulum [21,22]. In the rat, coagulation is due to the action of enzyme "vesiculase" secreted by CG on a coagulable protein secreted by SV [21]. Similar reaction was also described between a coagulogen secreted by the CG of male rat and a coagulating factor present in the uterine fluid of the female rat [22].

Following the classical studies, numerous studies have been carried out to demonstrate the functional significance of CG in animal reproduction. Several ablation studies [23] and endocrine disruptor exposure studies [3,24-29] have confirmed that this is an essential male accessory sex organ. In this review article, through our hypothesis, we have also tried to focus its role in spermatogenesis and expulsion of mature spermatozoa from the epididymis.

CG RENIN-ANGIOTENSIN-PROSTAGLANDIN SYSTEM: A HYPOTHESIS

It is well documented that in systemic circulation, the aspartyl protease renin catalyzes the cleavage of the polypeptide precursor or angiotensinogen to form the decapeptide angiotensin I, which is subsequently hydrolyzed by a tissue-protease (angiotensin I converting enzyme, ACE) to form the peptide hormone angiotensin II that functions to increase blood pressure and blood volume [6].

Although the primary source of circulating renin is the juxtaglomerular cells of the kidney [6], renin mRNA and protein have also been detected in several extra-renal tissues [30]. A subset of the extra-renal sites includes the submandibular glands and reproductive organs of males and females. In females, prorenin (the biosynthetic precursor of renin) is reported to be secreted by the ovary and placenta [12]. In males, all the components of the renin-angiotensin system (RAS) have been detected in the testis, epididymis, SV and CG. Furthermore, in males, angiotensin II has been found to bind to specific receptors in the epididymis and stimulate the expulsion of spermatozoa [12].

Expression of renin in CG

The function of renin from the CG in rats and mice is not very clear. However, it has been emphasized that the CG renin is significant because large amounts of both renin mRNA and protein can be detected in this organ [12]. Immunoreactive deposits of renin are localized in many granules of epithelial cells of the CG, as well as in the surface membrane and luminal extracts. Immunohistochemically, renin-positive cells are observed in the epithelial lining of the CGs of C57BL/6 mice. The immunoreactivities displayed a dot-like shape of varying diameter in the lateral and basal regions of epithelial cells. However, in light microscopic examination, immunoreactivities of renin are detected in the apical portion of epithelial cells and in some luminal products as well as in the basolateral granules [21].

Production of murine renin is basically controlled by two types of genes, Ren-1 and Ren-2. Although Ren-1 and Ren-2 were found to be co-expressed in kidney of mice in two renin loci, Ren-1 gene is known to be related to renal expression of renin, while Ren-2 is concerned with renin expression in submandibular tissues. It has also been detected that in inbred mice (having only Ren-1 gene) that Ren-1 is concerned with expression of renin mRNA in male sex accessory gland tissue (SV, epididymis and CG) [12]. In an experiment, it has been shown that inbred strains of mice that harbor a different Ren-1c produced more renin. It may be due to the differences in the cis-acting DNA regulatory elements associated with the inbred renin genes [31]. Expression of
renin in the sex accessory gland, therefore, differs from the expression of the mouse renin genes in the kidney, where all three renin genes (Ren-1c, Ren-1d, and Ren-2) are expressed at equal levels (Table 2). It has also been known that CG is the origin of the Ren-C mRNA to produce more renin [12,31].

Exocrine function of renin in CG

In immunoelectron microscopic observation, two types of secretory pathways of renin are proposed. The first type is general exocrine pathway, in which renin protein is targeted with other materials into apical exocrine granules. The other type is lysosome-dependent pathway, in which renin is targeted to lysosomal granules (Fig. 1). Renin proteins produced by CGs are stored in electron-dense granules, which include crystalline structures located in the basalolateral region [12]. Esposito et al. (2001) have reported that rat CG is androgen dependent and concerned with the secretion of several soluble proteins. They have reported the presence of type IV Tangle, kinesin superfamily proteins (kinesin, kif5c) and proteins with GTPase activity. They have also suggested that these proteins are concerned with protein processing, vesicle trafficking and other secretory mechanisms [11]. Although the secretory pathway is not very clear, it can be assumed that these CG proteins play a key role in the above-mentioned pathways [11].

Because renin is secreted first toward the seminiferous lumen, the secretory style of CG renin is classified as an exocrine function, while that in the kidney is an endocrine or paracrine function secreted toward the intercellular spaces, blood or lymphatic circulation. The granular convoluted tubule cells of the mouse submandibular glands also produce renin, as well as epidermal growth factor, nerve growth factor, kallikrein, proteinase-A and tonin [12]. In particular, because it has been reported that renal/pancreatic kallikrein of the submandibular gland is secreted from both the basalolateral and apical surfaces [31], the possibility of bipolar secretory pathways for CG renin cannot be ignored. CG renin released by an exocrine mechanism performs certain functions for the male urogenital or the female genital organ. Renin protein, but not detectable mRNA, is observed in the epithelial cell lines of the uterus at the 1st day after mating, suggesting that CG renin is transferred into the female uterus by this process [22]. In addition, the signal for angiotensinogen mRNA is detected in the epithelial cells of the uterus by hybridohistochemistry after mating. The function of angiotensin II cleaved from angiotensinogen is the production of prostaglandin in several organs as well as the control of blood pressure and the water-mineral balance [12]. Moreover, prostaglandin has been shown to stimulate steroidogenesis in the adrenal gland [32], and renin release in association with β-adrenergic receptors [12]. It is possible that CG renin also plays a role in the production of the angiotensin series, and functions in association with prostaglandin. These findings suggest that the renin-angiotensin-prostaglandin system is dependent on male sexual maturation and affects certain aspects of female reproduction as well, working in local feedback and local enhancing mechanisms [12].

Correlation of renin expression in CG and testosterone

It is known that the renin found in Leydig cells of testis and the ACE (of male reproductive tract), part of RAS, are dependent on pituitary hormones. In the uterus of mice and rats, the renin concentrations vary with the ovarian cycle, peaking during estrous and reaching the lowest level during the proestrous phase. In the ovary of rabbit, estradiol in perfusion pressure, more renin and angiotensin-II are secreted, which produces preprorenin in rough ER (rER). This preprorenin is converted to prorenin by signal peptidase in Golgi apparatus, and then to renin in terminal ducts of the CG, whereas weak renin immunoreactivity is still observed in the main duct [12]. After testosterone administration to castrated mice, large numbers of RC cells can be detected. It appears that the expression of CG renin is mainly regulated by the testes, especially by testosterone. It has also been proposed that the expression of renin mRNA in CG is very similar to that in submandibular gland which is also androgen-sensitive. Both tissues, after testosterone administration, start transcription at similar series in upstream start sites. Tronik et al. reported the presence of a 500-bp transposable element residing at position - 80 of the mouse renin genes (not present in rat or human renin genes) and it is totally species-specific [3-4]. A comparative study of CG renin expression in C57Bl/6 and Balb/c mice on testosterone exposure showed C57Bl/6 mice express Ren-1c genes more than Balb/c [12]. These reports suggest, in the presence of testosterone, CG renin gene (Ren-1c) is expressed causing synthesis of Ren-C mRNA which produces prorenin in rough ER (rER). This prorenin is converted to prorenin by signal peptidase in Golgi apparatus, and then it is converted to active renin (by lysosomal cathepsin-B or kallikrein). It has been reported by Kon et al. that immunoelectron microscopical observation showed renin-positive granules both in Golgi apparatus and in lysomes [12].

CG RAS: A hypothesis

The overall function of renin secreted from CG (anterior prostate) is not very clear. However, the findings of numerous studies have showed a positive-feedback of renin-angiotensin-prostaglandin that regulates blood pressure, electrolyte balance and related local homeostasis of CG. In addition, an acute reduction in renal perfusion pressure increases release of prostaglandins [12]. Prostaglandin also reported to increase steroidogenesis in adrenal gland [32]. It has been reported that the main regulator of RAS, angiotensin-II stimulates prostaglandin synthesis as well as local blood flow and blood pressure [6]. On the other hand, arachidonic acid, precursor of prostaglandin stimulates CG renin secretion [12,33].

Hence, from these reports if we correlate the renin-angiotensin-prostaglandin system, it can be predicted that during an acute reduction in perfusion pressure, more renin and angiotensin-II are secreted, which causes increased prostaglandin secretion. Prostaglandin, again, stimulates adrenal steroidogenesis to secrete more testosterone. Testosterone and DHT, in turn, increases CG renin expression which causes expulsion of mature spermatozoa from epididymis. This positive feedback regulates local perfusion pressure which is important for hormonal functioning, as well as it helps in production and release of mature spermatozoa to maintain normal reproductive functions (Fig. 2).

| Organ          | Ren 1c | Ren 1d | Ren 2 | Rat | Human |
|----------------|--------|--------|-------|-----|-------|
| Submandibular gland | A      | -      | A     | ND  |       |
| Kidney          | A, F   | A, F   | A, F  | A   | F     |
| Adrenal gland   | F      | F      | F     | A   | A     |
| Coagulating gland | A     | -      | -     | ND  |       |
| Testes          | A, F   | A, F   | A, F  | F   | ND    |
| Ovary           | A      | A      | A     | ND  |       |
| Subcutaneous gland | F     | F      | F     | ND  |       |
| Chorion         | ND     | ND     | ND    | ND  | Positive |

A: Adult, F: Fetus, ND: Not determined
CONCLUSION

The present review attempts to concisely update and synchronize the available information regarding the structure-function correlation of CG with special reference to its significance in animal reproduction. In this review, we have proposed a hypothesis of CG renin-angiotensin-prostaglandin system and its role in the maintenance of local homeostasis and regulation of male reproductive functions.

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