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Ultrastructural-Morphometric Analysis of the Rat Prostate (Ventral Lobe)

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Summary. A morphometric model, which provides information on the structure of the normal gland (ventral lobe) has been developed for the rat prostate. The model consists of morphologically defined space and membrane compartments, which are used to describe the specific components of the protein and enzyme synthesizing and secreting glandular cells. The results presented are relative to a cubic centimeter of prostatic tissue, a cubic centimeter of acinar parenchyma and glandular cell cytoplasm. Special interest was given to the cell compartments which are involved in protein and enzyme synthesis.

Key words: Ventral lobe of rat prostate, stereologic procedure, morphometric model.

Abbreviations

VPL ventral prostatic lobe

IT interacinar tissue

AP acinar parenchyma

AL acinar lumen

C glandular cell

N cell nucleus

CYT cytoplasm

GS ground substance

RER rough endoplasmic reticulum

G Golgi apparatus

LY lysosomes

SG secretory granules

M mitochondrium

F fat droplets

Comp. compartment

V_V volume density

S_V surface density

N_V numerical density

SCV single cell volume

Introduction

In recent years the prostatic gland has been a subject of interest to cell biologists and pathologists, particularly with respect to the influence of various steroids on the ultrastructure and histochemistry of the various organelles of the prostatic cell. Subsequent to the initial ultrastructural studies (8, 11, 22) numerous descriptive reports on ultrastructural changes of the prostatic cell in various animal species exposed to diverse functional stimuli have been published (9, 13, 26, 27, 29). Although a considerable amount of biochemical data is now available, morphological information has been restricted mainly to descriptive findings and therefore obtained subjectively. In recent years, there have been rapid advances in stereological procedures which have made available a quantification of morphological findings (34, 45). The purpose of this paper is to report on the development of a stereological analysis of the prostatic gland, its cell and its cell compartments. This model should serve as a base line for further experimentation, using defined metabolic parameters.

Material and Methods

Animals. 200 g, male, adult, sex-mature Wistar rats, fed under rigorously standardised experimen-

tal conditions (ALTROMIN-R standard diet, water ad libitum and maintained in regular day-and-night rhythm) were used. For the morphometric analysis 5 animals were sacrificed at the same hour (08.00, morning).

Electron microscopy. One ventral lobe of the prostate from each animal was fixed in 1.33% s-collidin buffered osmium tetroxide (pH 7.4, 340 m Osm) for 2 hrs at 4° C. The other ventral lobe was fixed in phosphate-buffered formalin (pH 7.4) and embedded in paraffin. The specimens were dehydrated in increasing alcohol concentrations and propylene oxide, and embedded in Epon. Ultrathin sections were cut with the Reichert ultramicrotome OM U 2 (interference colour silver). After double staining with uranyl acetate and lead citrate they were examined with a ZEISS electron microscope EM 9 A.

Morphometric model. The model of the ventral lobe of the rat prostate is outlined in Fig. 1. It shows how the ventral lobe of prostate (VPL) was divided into morphologically defined compartments. Essentially the model has two major divisions - the interacinar tissue (IT) (including connective tissue, blood vessels, nerves and smooth muscle fibres) and the acinar parenchyma (AP) (including the lumina of the acini and the glandular epithelial cells). The latter were divided into the nuclei and the various cytoplasmic compartments.
The following primary parameters for the individual cell compartments (i) were evaluated.

1. Volume density (V_{Vi}) Volume fraction of a compartment i (cm^3) related to the unit volume (cm^3).

2. Surface density (S_{Vi}) Surface fraction of the compartment i (m^2) related to the unit volume (cm^3).

3. Numerical density (N_{Vi}) Average number of organelles i per unit volume (cm^3).

1. Volume density (V_V). The volume density was obtained by placing a point-grid with a specified number of test points (P_T) over the tissue. The number of hits (P) per cell compartment (i) was counted and the compartment's point density (P_{Pi}) was evaluated by the relationship $P_{Pi} = P_i/P_T$. According to GLAGOLEFF, the volume density (V_V) can be ascertained directly from the point density P_P.

(1) $$P_P = V_V$$

2. Surface density (S_V). This parameter was evaluated with the aid of a test lattice with a known total length of the test lines (L_T). Intersections (I) of the test lines through the cut surfaces of the cell structures (i) were counted. Since the number of these intersections into the tissue components (i) is directly proportional to the surface of these components, the following relation holds:

(2) $$S_V = \frac{2\,Ii}{L_T}$$

3. Numerical density (N_V). The numerical density (N_V) of a cell component (i) is determined by counting the number (N_A) of these components within a test area. According to the equation (3), developed by Weibel and Gomez (46), β is the form factor of the corresponding component and K the factor dependent on the distribution of the cell components.

(3) $$N_{Vi} = \frac{K}{\beta}\sqrt{\frac{N_{Ai}^3}{V_{Vi}}}$$

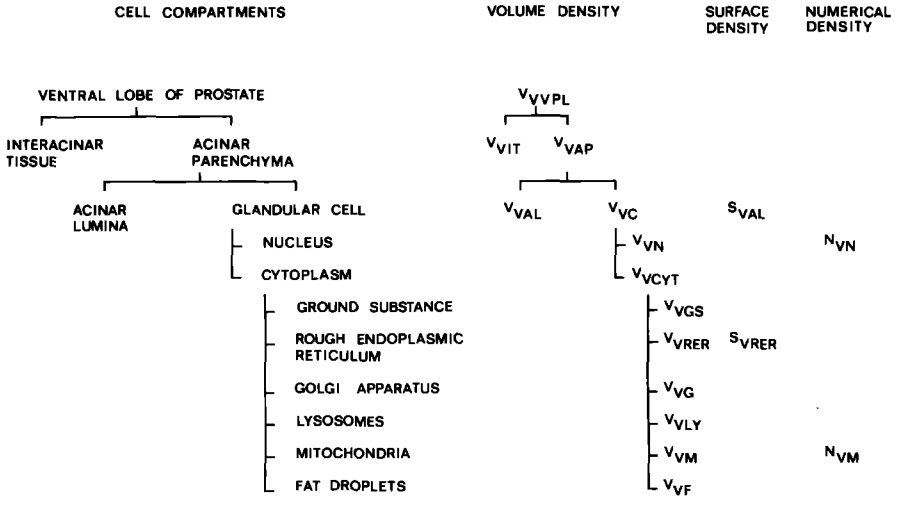

Fig. 1. Stereological model of the ventral prostatic lobe

Morphometric procedure. The morphometric evaluation of ventral prostatic lobe was done at 3 different stages of magnification:

Stage I (90 x). This stage affords a survey of various acini and the interacinar tissue. The H. E. stained paraffin sections of the ventral lobe of prostate were projected on a double lattice test system (121 heavy and 1089 fine test points). The following structures were determined:

P_C : points over the acinar cells

P_{AL} : points over the acinar lumina

P_{IT} : points over the interacinar tissue

Stage II (1300 x). Morphometric evaluation of ultrathin sections is done with the multipurpose test system (100 test points) according to Weibel (45). The following data can be determined:

$P_{IT'}$: points over the interacinar tissue

$P_{AL'}$: points over the acinar lumina

$P_{N'}$: points over the glandular cell nuclei

The number of the nuclei (N_{AN}) was counted separately.

Stage III (4100 x). While the evaluation of the glandular cell nuclei, the interacinar tissue and rough endoplasmic reticulum was done with a test system of 121 heavy points, the compartments of Golgi-apparatus, mitochondria, lysosomes, fat and ground substance were determined with a test system of 1089 fine points. The following compartments were counted:

$P_{IT''} + P_{AL''}$: points over the interacinar tissue and acinar lumina

$P_{N''}$: points over the glandular cell nuclei

$P_{RER''}$: points over the rough endoplasmic reticulum

$P_{G''}$: points over the Golgi-apparatus

$P_{LY''}$: points over the lysosomes

$P_{M''}$: points over the mitochondria

$P_{F''}$: points over the fat droplets

The number of the mitochondria (N_{AM}) was determined separately.

Sampling. 10 sections were selected from each animal for light microscopic-morphometric evaluation (staining: H. E.). Only those sections that included various acini and a portion of interacinar tissue were chosen. The morphometric evaluation was done with the Wild multistage sampling microscope (Wild, AG, Heerbrugg, Switzerland) at a magnification of 90 x (= stage I).

Ultrathin sections were made from at least 3 blocks per animal for sampling with the electron microscope using a 1 300 magnification in stage II and 4 100 magnification in stage III. 6 photographs were made per block according to strict criteria of randomisation. The electron-microscopic negatives together with the corresponding test systems were subsequently enlarged and evaluated.

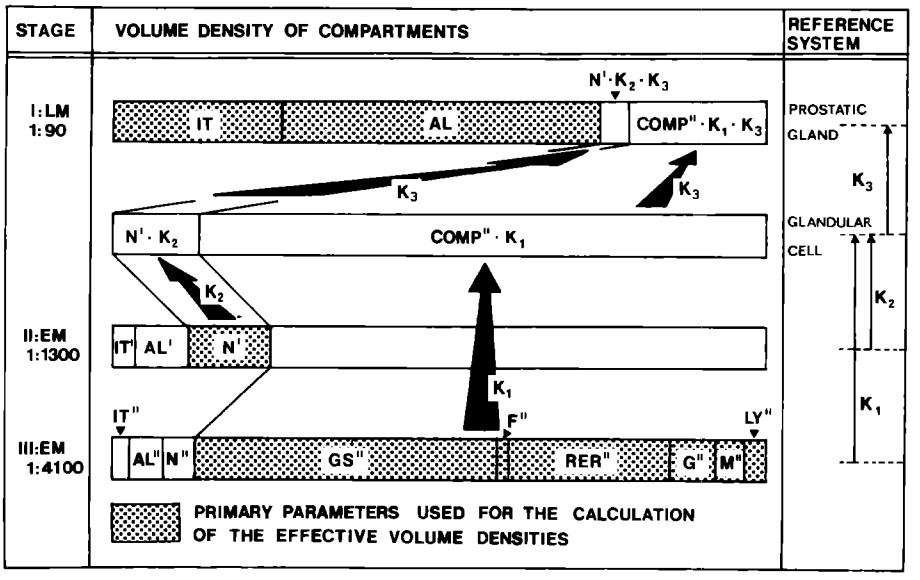

Fig. 2. Elaboration of the correction factors for the various morphometric stages

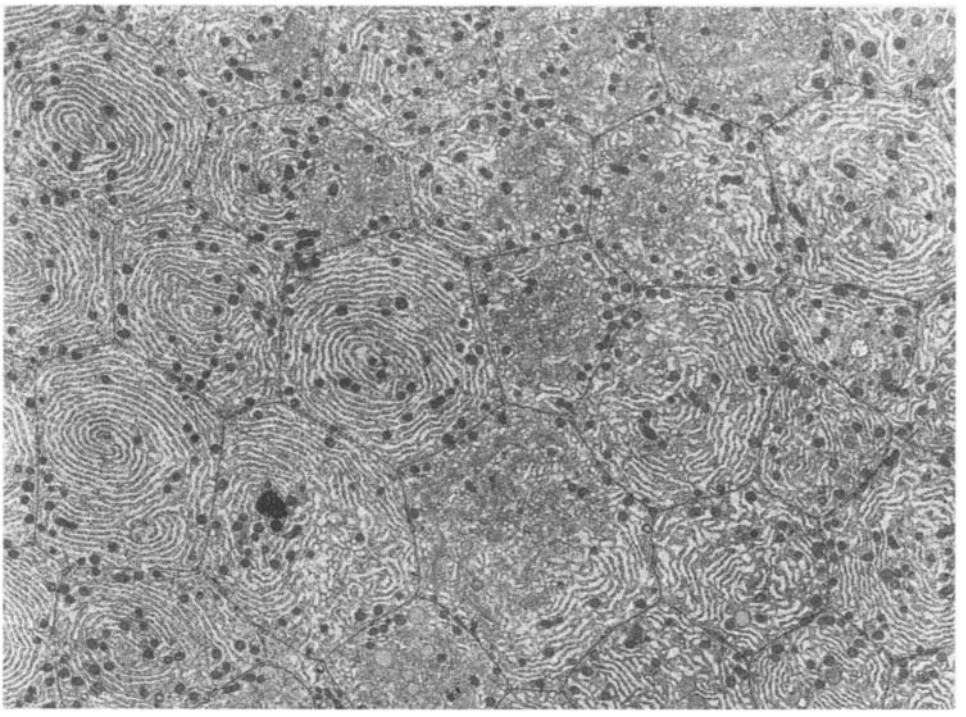

Fig. 3. Low power electron micrograph of glandular cells (tangential section) primary magnification 1300 x.

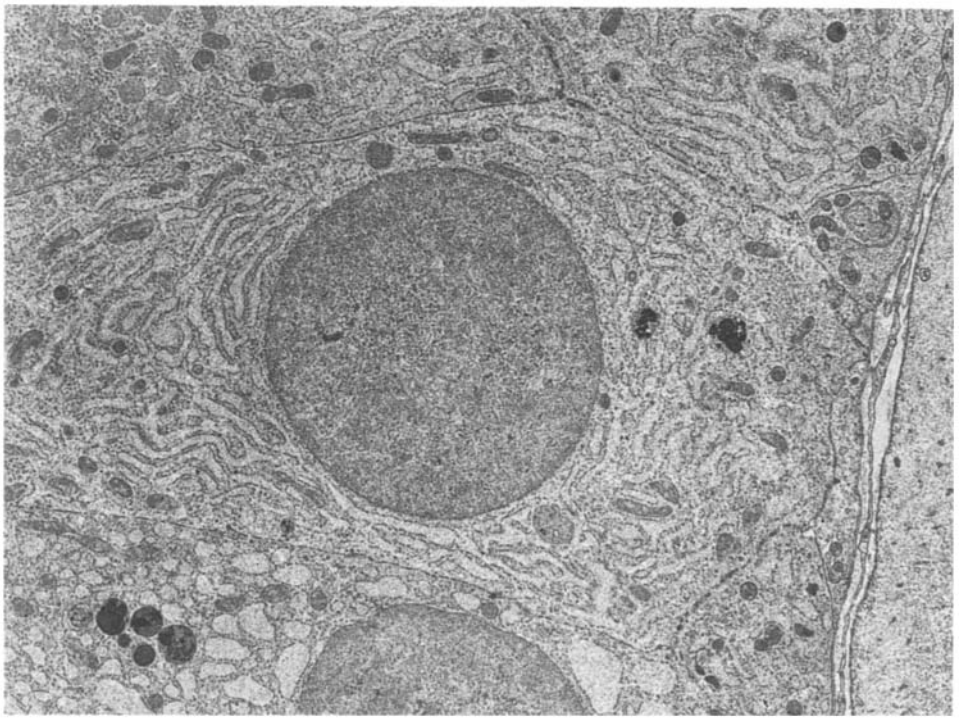

Fig. 4. Low power electron micrograph of glandular cell (cross section) primary magnification 1300 x.

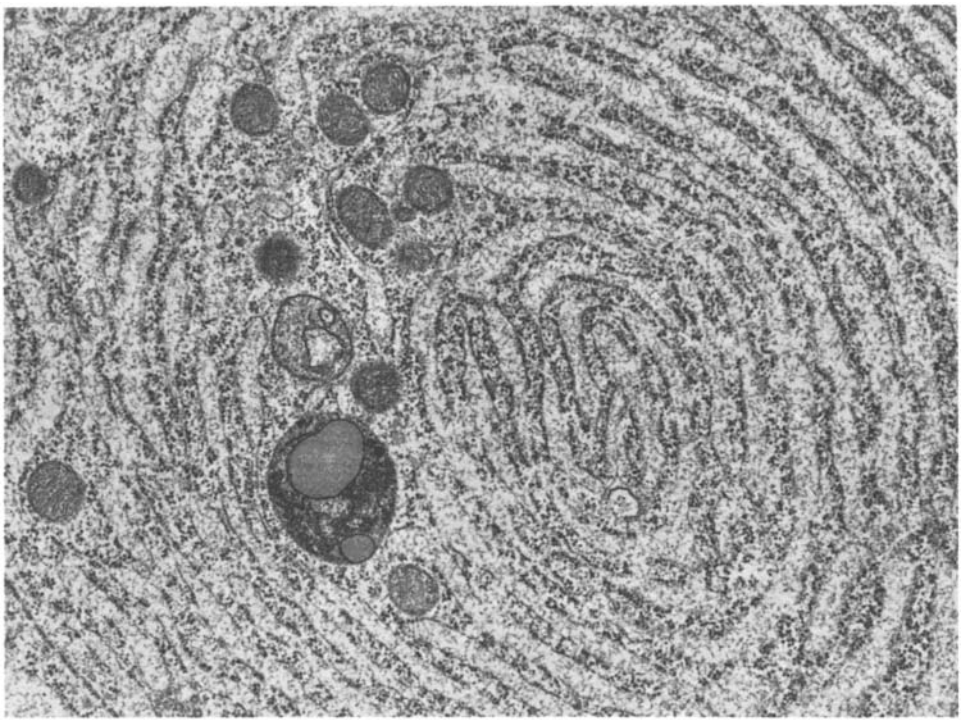

Fig. 5. Rough endoplasmic reticulum, mitochondria and lysosomes; primary magnification 4100 x.

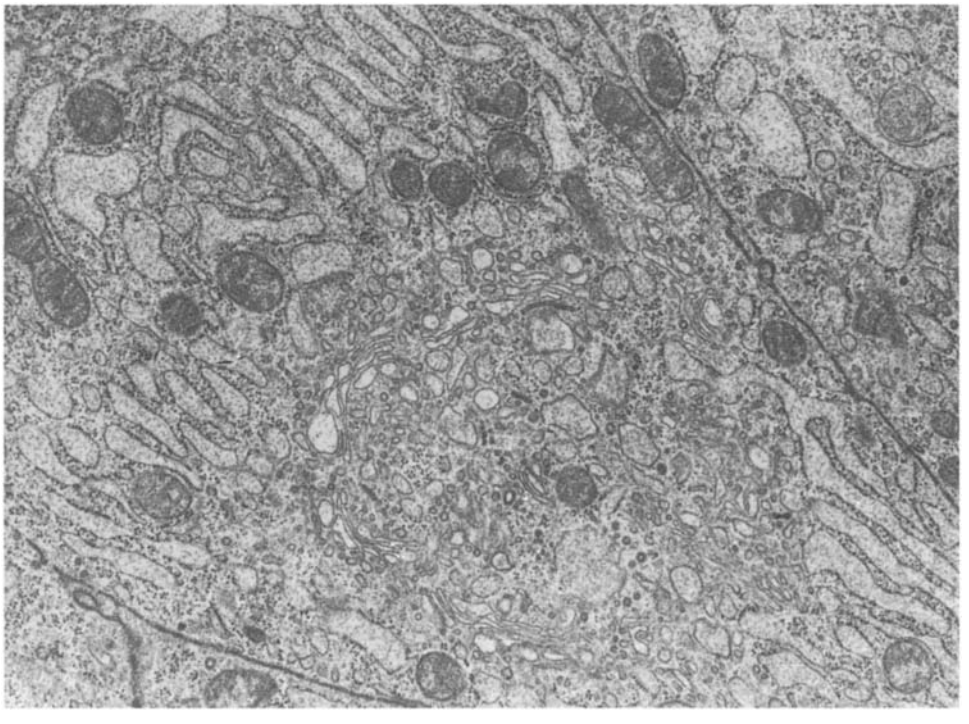

Fig. 6. Golgi apparatus, including saccules vesicles and vacuoles; below which lie secretory granules, rough endoplasmic reticulum and mitochondria; primary magnification 4100 x.

Conversion factors. The calculation of the conversion factors $K_1 - K_3$ is shown in Fig. 2. The primary parameters used for the evaluation of the effective volume densities are shaded. The sum of all volume densities in each morphometric stage represents 1 (= 100%). The primary parameters, obtained from the various morphometric stages (stage 1 - 3) must be multiplied by conversion factors that correspond to the effective values of the reference systems.

The following reference systems are used:

Ventral lobe of prostate (VPL)
Glandular cell (C)

The following formulae are used:

$$K_1 \cdot \left[1 - (V_{VIT''} + V_{VAL''} + V_{VN''})\right] = 1 - V_{VN'} \cdot K_2$$

$$K_2 \cdot \left[1 - (V_{VIT'} + V_{VAL'})\right] = 1$$

$$K_3 = 1 - (V_{VIT} + V_{VAL})$$

Secondary parameters. Results of the primary parameters always refer to 1 cm^3 of prostatic gland (VPL) tissue. The functional interpretation of a cell however requires relative and absolute values. In order to facilitate a comparison of quantitative morphological data with biochemical findings, the following secondary parameters are used:

1. Parameters related to the unit volume of the ventral lobe prostatic tissue.
2. Parameters related to the unit volume of the acinar parenchyma.
3. Parameters related to the unit volume of cytoplasm.
4. Absolute values of the different compartments.

Data Processing. Calculation of data obtained from the different stages of magnification in evaluating the primary and secondary parameters was done with an OLIVETTI Programma 602 desk computer connected with the magnetic tape unit MLU 600. A programme permitted fully automated evaluation following initial manual input of data. The evaluation was done in several steps as follows:

1. Print-out of the primary parameters: mean (m), standard deviation (s. d.) and standard error (s. e.) of parameters for each animal.
2. Comparison of the primary parameters of each animal with the Student t-test.
3. Print-out of the secondary parameters for each animal.
4. Summarisation of the values of each animal into groups and recalculation of the values in 1. -3. given above.

Results

Data for the whole ventral prostatic lobe, the acinar parenchyma, the glandular cell and its various compartments are given in the tables 1-4 and Figs. 7-9. In table 1 the mean values of all components are related to the unit volume of prostatic tissue. Table 2 refers to the unit volume of acinar parenchyma; Table 3 is related to the unit volume of the glandular cell cytoplasm. The absolute data for the cell components are shown in Table 4. Means and standard errors (s. e.) are indicated in all 4 tables.
Figs. 7 and 8 show the percentage amounts of cell components per unit volume of prostatic tissue, glandular cell and cytoplasm. Figure 9 represents the absolute volume of the glandular cell, its nucleus, cytoplasm and cytoplasmic compartments.

Ventral prostatic lobe. As shown in Fig. 7 the acinar parenchyma (defined as the sum of acinar lumina and glandular cells) contributes 75% to the whole lobe. Whereas the acinar lumina represent 51.9% of the prostatic gland, the glandular cells volume was calculated as 22.8%. The interacinar tissue makes up 25% of the whole gland volume.

Glandular cell. Fig. 7 shows the percentage amount of cytoplasm and cell nuclei per unit volume of prostatic tissue.
The average single cell volume is calculated to be 1946 μ^3 (Fig. 9, Table 4); while the average volume of the cell nuclei is about 216 μ^3, the cytoplasm amounts 1729 μ^3.

Cell compartments. As shown in Fig. 8 the rough endoplasmic reticulum represents 31% of the unit volume of cytoplasm; the absolute value of the volume is about 564 μ^3 (Table 4). The Golgi-apparatus has an absolute volume of 118 μ^3 and amounts to 7.5% of the unit volume of cytoplasm (Fig. 8, 9, Tabele 3, 4). The ground substance accounts for 54% of the cytoplasm. The average number of mitochondria per cell is about 547 (Table 4). The compartment of lysosomes is defined to contain primary lysosomes and acid phosphatase positive mature secretory granules; in most cases it was not possible to decide between these two cell structures using the criteria of descriptive electron microscopy (Fig. 7, 8, 9, Tables 1, 3 and 4). Fat droplets were found to be less than 1% of cytoplasm.

Discussion

Our findings indicated that a quantitative analysis of the ventral lobe of prostate, acinar parenchyma, glandular cell and cell compartments was successful. A comparison of our data with that of the literature was not possible since there are no quantitative data currently available for the prostatic gland.

The light microscopic analysis showed clearly the so-called 'hollow organ' prostatic gland. The ventral lobe of rat prostate (related to the unit

volume of prostatic tissue = 100%) consisted of 75% acini and 25% interacinar tissue. Dividing the acini into its two components (acinar lumina and glandular cells) clearly indicated that the acinar lumina comprised more than half the volume (52%) of the whole gland, whereas the functional parenchyma (sum of all glandular cells) was only about 23%.

The dimension of an average glandular cell (1946 μ^3) was smaller than that of a hepatocyte (5000 μ^3, 34), but closer to that of an exocrine pancreatic cell (1060 μ^3). The average volume of the nucleus was about 216 μ^3.

The great volume density of the rough endoplasmic reticulum (absolute value 564 μ^3, 31% of the volume of cytoplasm) indicates the main function - protein and enzyme synthesis - of the glandular cell.

Prostatic glands depend on androgen stimulation for the maintenance of their structural and func-

Table 1. Values per unit volume of prostatic gland tissue

Compartment	Parameter	Symbol	Unit	Mean	s.e.
Acinar parenchyma	Volume	V_{VAP}	cm^3/cm^3	0.747	0.048
Acinar Lumina	Volume	V_{VAL}	cm^3/cm^3	0.519	0.038
Interacinar tissue	Volume	V_{VIT}	cm^3/cm^3	0.253	0.048
Glandular cells	Volume	V_{VC}	cm^3/cm^3	0.228	0.011
Nucleus	Volume	V_{VN}	cm^3/cm^3	0.029	0.005
Cytoplasm	Volume	V_{VCYT}	cm^3/cm^3	0.208	0.018
Nucleus	Number	N_{VN}	cm^{-3}	$0.132 \cdot 10^9$	$0.032 \cdot 10.9$
Rough endoplm. reticulum	Volume	V_{VRER}	cm^3/cm^3	0.061	0.005
Golgi apparatus	Volume	V_{VG}	cm^3/cm^3	0.014	0.001
Lysosomes	Volume	V_{VIY}	cm^3/cm^3	0.004	0.001
Ground substance	Volume	V_{VGS}	cm^3/cm^3	0.106	0.006
Mitochondria	Volume	V_{VM}	cm^3/cm^3	0.009	0.001

Table 2. Values per unit volume of acinar parenchyma

Compartment	Parameter	Symbol	Unit	Mean	s.e.
Cytoplasm	Volume	V_{VCYT}	cm^3/cm^3	0.868	0.027
Nucleus	Volume	V_{VN}	cm^3/cm^3	0.130	0.027
Nucleus	Number	N_{VN}	cm^{-3}	$0.618 \cdot 10^9$	$0.155 \cdot 10^9$

tional integrity (47). Biochemical studies suggest that RNA synthesis and the synthesis and secretion of prostatic fluid is stimulated and controlled not directly by testosterone but by two major metabolites of testosterone. In vitro incubations of rat prostate slices (1), ventral prostate homogenates (12) and ventral prostate organ culture (2) have confirmed that androstanolone (5 α-dihydrotestosterone = DHT) and androsterone are the two major metabolites of testosterone. The conversion of testosterone by 5 α-reductase to 5 α-dihydrotestosterone was performed in isolated ventral prostate nuclei (12); however, there is also evidence for the presence of 5 α-reductase activity in prostate mi-

Table 3. Values per unit volume of glandular cell cytoplasm

Compartment	Parameter	Symbol	Unit	Mean	s.e.
Rough endoplm. reticulum	Volume	V_{VRER}	cm^3/cm^3	0.310	0.024
Golgi apparatus	Volume	V_{VG}	cm^3/cm^3	0.075	0.010
Lysosomes	Volume	V_{VLY}	cm^3/cm^3	0.021	0.003
Ground substance	Volume	V_{VGS}	cm^3/cm^3	0.541	0.013
Mitochondria	Volume	V_{VM}	cm^3/cm^3	0.050	0.003
Mitochondria	Number	N_{VM}	cm^{-3}	$0.347 \cdot 10^{12}$	$0.045 \cdot 10^{12}$

Table 4. Absolute values per single glandular cell

Compartment	Parameter	Unit	Mean	s.e.
Glandular cell (average single cell volume, SVC)	Volume	μ^3	1946	357
Nucleus	Volume	μ^3	216	14
Cytoplasm	Volume	μ^3	1729	351
Rough endoplm. reticulum	Volume	μ^3	564	143
Golgi apparatus	Volume	μ^3	118	24
Lysosomes	Volume	μ^3	38	8
Ground substance	Volume	μ^3	923	175
Mitochondria	Volume	μ^3	84	14
Mitochondrium (average single volume)	Volume	μ^3	0.142	0.009
Mitochondria	Number	-	547	76

crosomal fractions of the rat (33). There is still some discussion as to whether 5 α-dihydrotestosterone controls the tissue growth and androsterone influences the secretion of the prostatic fluid. It has been demonstrated that testosterone and 5 α-dihydrotestosterone stimulate RNA-synthesis, when injected in vivo. Bashirelahi and Villee (3) investigated the effect of these androgens on RNA synthesis in nuclei isolated from prostate of orchidectomised rats and found that 5 α-dihydrotestosterone increased the incorporation of uridine, while testosterone had no stimulatory effect on RNA synthesis. Before entering the nucleus, 5 α-dihydrotestosterone, as well as testosterone must be bound to a cytoplasmic receptor, which can be recovered from the cytosol fraction (48). In addition there is some evidence that oestradiol, progesterone and cyproterone have been found to be competitors of androstanolone binding (4).

The high volume density of the Golgi apparatus (absolute volume 118 μ^3; 7.5% of the whole cytoplasm) can be interpreted as an expression of a high rate of membrane synthesis. Helminen and Erikson (24, 25) demonstrated that acid phosphatase, the marker enzyme of the prostatic fluid, is packed within the Golgi apparatus into condensing vacuoles and secretory granules. The inability to demonstrate acid phosphatase histochemically over

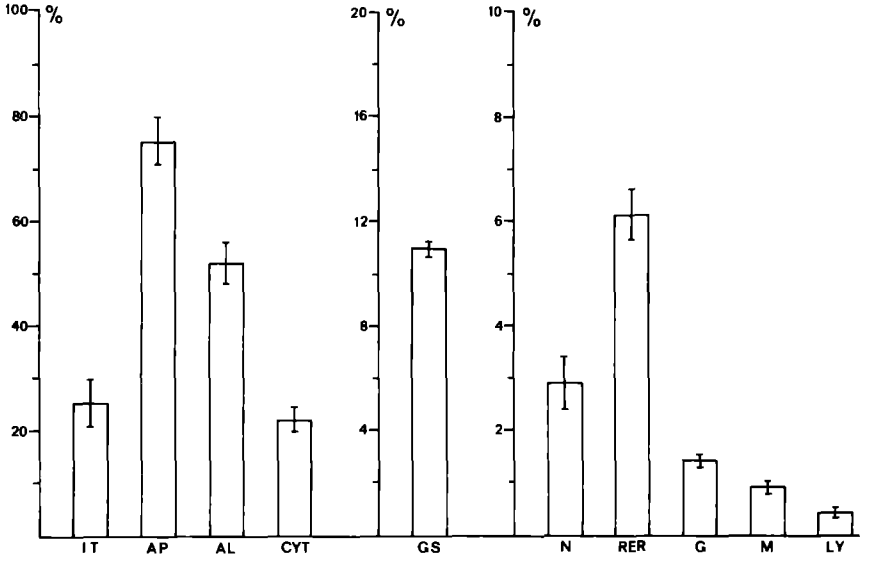

Fig. 7. Tissue components and glandular cell compartments of the ventral prostatic lobe are expressed as a percent of the total prostatic gland volume (± Standard errors of the mean)

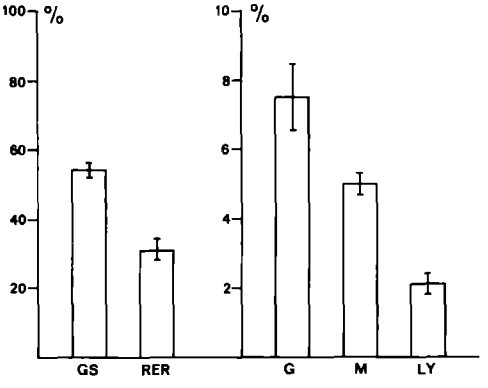

Fig. 8. Volumes of the glandular cell compartments are expressed as a percent of total glandular cell cytoplasm volume (± Standard errors of the mean)

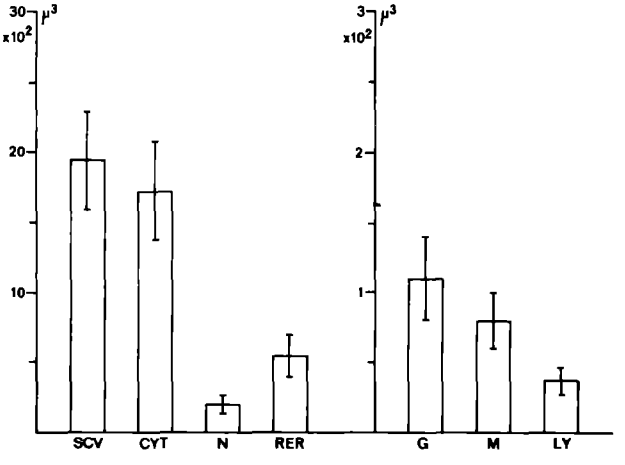

Fig. 9. Absolute volumes of the glandular cell and its compartments. (± Standard errors of the mean)

the rough endoplasmic reticulum and the presence of apparent high activity over the Golgi apparatus (25) may be explained either by a low concentration of acid phosphatase in the rough endoplasmic reticulum, or by a stimulating effect of the Golgi apparatus on the acid phosphatase. Furthermore it is evident that the Golgi apparatus is implicated in the formation of lysosomes (15). Vanha-Pertulla et al. (44) showed that acid phosphatase could be divided into 2 types - the secretory and the lysosomal form. If we assume, that the Golgi apparatus is able to recognise these two forms because of their molecular weight and structure, he may be responsible for packing these two types into two different particles - lysosomes and secretory granules. Specific zones of the Golgi apparatus could then be anticipated as the sites of secretory granule and lysosome formation - so explaining the high volume density of the Golgi apparatus in the glandular cell of the prostatic glands.

This morphometric model represents an improvement over descriptive morphology. It provides quantitative information on the volumes, surfaces and numbers of cell components. In attempting to relate morphological and biochemical data, a morphometric analysis of the various cellular compartments involved in the prostatic fluid synthesis and secretion should be useful. Such base line data contain considerable information for the biochemists. They permit, for instance, the determination of the relative amounts of individual membranes within a membrane compartment from intact tissue. Thus, a microsomal fraction of rat prostatic tissue containing rough endoplasmic reticulum and Golgi apparatus would be expected to contain 80% rough and 20% smooth surfaced membranes; similar comparisons could be made from other cell compartments (6).

This stereological analysis should serve as base line for studying the influence of various sex steroids on the ventral lobe of the prostate gland; it is hoped that this approach will provide a better insight into morphology and physiology of the prostate gland.

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