The Effects of Histones and Other Polycations on Cellular Energetics

III. THE SWELLING-CONTRACTION CYCLE OF MITOCHONDRIA*

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SUMMARY

Purified histone fractions were found to interact with the mitochondrial membrane system, causing a reduction in optical density as a result of swelling and aggregation. The "arginine-rich" f2a was the most active fraction; threshold concentration was approximately 1 μg per mg of mitochondrial protein.

Adenosine 5'-triphosphate slowed and guanosine 5'-triphosphate prevented the histone-induced swelling, while all other nucleoside mono-, di-, and triphosphates were without effect. Oligomycin, aurovertin, or strontium enhanced the protective action of ATP. Amytal, azide, antimycin, 2,4-dinitrophenol, and carbonyl cyanide m-chlorophenylhydrazone did not significantly affect the histone-induced changes. Octylguanidine and chlorpromazine markedly retarded the swelling process. The most active polyanionic protective compounds were gangliosides, phosphoproteins, and phosphatidylserine.

Previous communications have directed attention to the stimulatory effects of very low concentrations of histones on oxygen consumption and adenosine 5' triphosphatase activity of isolated mitochondria (1, 2). These results have been confirmed and extended recently by Utsumi and Yamamoto (3). Certain histones, derived from calf thymus and heart, used in microgram amounts, significantly increased oxygen uptake and ATPase activity while depressing the ADP-ATP exchange (1, 2). These effects occurred only in the absence of an ADP-generating system (4). Submitochondrial particles prepared with digitonin or "uncoupled" mitochondria responded to histones with an inhibition of oxygen consumption (1, 2). Data acquired during the course of these and other studies (5-7) suggested a protein-membrane interaction as a possible basis for the observed stimulatory action of the histones.

While the mechanism is still obscure, it is generally agreed that the "swelling-contraction" cycle of isolated mitochondria represents a basic membrane function probably associated in some manner with oxidative phosphorylation, ATPase activity, and ion transport (8-21). The importance of basic and acidic polyelectrolytes in membrane structure and function has been emphasized (5, 22, 23), and this provided the impetus for studying the possible effects of histones on the mitochondrial membrane system. Accordingly, fractions of histones were prepared from a variety of tissues, including neoplastic, and compared with respect to efficacy in producing swelling of mitochondria. Correlation with ATPase activities under the same conditions utilized to study swelling and contraction represented an attempt to gain further insight into the mechanism of the histone-induced swelling (24). Other basic polypeptide compounds were also included to further define specificity. For example, spermine and spermidine have been shown to "stabilize" the membrane and prevent swelling (25-27), while preliminary results obtained in this laboratory showed a marked swelling of mitochondria in the presence of specific histones, particularly the f2a fraction from rat liver (7).

The histones were compared with other agents known to cause swelling of mitochondria in order to gain information concerning possible mode of action. These included calcium, thyroxine, phosphate, and deoxycholic acid. A variety of possible anti-swelling compounds were included in the study.

MATERIALS AND METHODS

Isolation of Mitochondria—Male albino rats of either the Holtzman or Cheek-Jones strain in a weight range of from 200 to 300 g were used. The animals were anesthetized with ether and the livers were perfused through the portal vein with about 25 ml of ice-cold 0.25 M sucrose until the tissue was devoid of most of the blood. The livers were quickly removed from the animal, trimmed of adhering connective tissue and vessel remnants, and homogenized in 9 volumes of ice-cold 0.25 M sucrose. Mitochondria were isolated by the Schneider procedure (28), washed two times, suspended in 0.25 M sucrose (1 ml per g of fresh liver), and used within 5 min after preparation.

Determination of "Swelling"—Swelling was estimated by measuring the decrease in optical density at 520 μm of a suitably
buffered mitochondrial suspension (10). The incubation medium (pH 7.4) consisted of 107 mM KCl and 17 mM Tris HCl, final concentrations, in a total volume of 3.5 ml. The medium and various agents were placed in cuvettes. The mitochondria (0.1 ml) were added and mixed by inversion, and the optical density was read in a Coleman junior spectrophotometer at various time intervals. The tubes were mixed before each reading. In some experiments the mitochondria were preincubated with various compounds before addition of the swelling-inducing agent. The experiments were carried out at room temperature (20-24°C). The total mitochondrial protein in the reaction mixture ranged from 1.9 to 2.5 mg, with an average of 2.2. This concentration (0.63 mg per ml) gave an initial optical density which averaged 0.54 in the Coleman junior spectrophotometer. The geometry of the Coleman junior is slightly different from that of the Beckman DU-2 or DB and Bausch and Lomb Spectronic-20 spectrophotometers. Consequently, about 3 to 4 times more protein is necessary to produce an optical density in the Coleman equivalent to that found with the Beckman or Bausch and Lomb instruments. Many of the experiments were repeated with a Beckman DU-2 spectrophotometer, at the same wave length, but with one-third to one-fourth of the protein concentration. The changes were similar in magnitude to those measured in a Coleman junior spectrophotometer.

Microscopy—Samples of suspensions were examined under phase contrast in a Nikon photomicroscope.

Histone Fractions—The various fractions were isolated and characterized according to their amino acid content and electrophoretic mobility on starch gel, as described previously (29, 30). The designations and amino acid characteristics are listed in Table I.

Commercial Histone Preparations—Lysine-rich and arginine-rich histones were purchased from Worthington. A whole histone (Type II from calf thymus) and an arginine-rich histone (Type IV from calf thymus) were purchased from Sigma. The histones were dissolved in water or in a medium consisting of 125 mM KCl and 20 mM Tris-hydrochloride (pH 7.4) and stored at -20°C.

Nucleotides—ATP, ADP, AMP, ITP, and GTP were purchased from Sigma; they were dissolved either in water or the above buffer solution. Stock solutions of the nucleotides were stored at -20°C.

Polypeptides—Chondroitin sulfate (Grade III), gangliosides (Type II), L-phosphatidylserine (Fraction III), O-phospho-L-serine, dl-α-lecithin (synthetic), phosphatidylethanolamine (Fraction V), O-phosphorylethanolamine, N-acetylneuraminic acid (Type III, from egg, or Type IV, synthetic), phosphatidylinositol (Fraction I), RNA (yeast, Type XI), DNA (calf thymus, Type I), and phytic acid (Type V) were purchased from Sigma. Phosvitin was purchased from Calbiochem. Cerebral phosphoprotein “residue” was isolated by the method of Matsui et al. (31). The polyethylene sulfonates were gifts from Upjohn. Protamine sulfate, poly-L-lysine (low and high molecular weights), spermine, spermidine, and putrescine were purchased from Sigma.

Other Chemicals—Carbonyl cyanide m-chlorophenylhydrazone was a gift from Dr. P. G. Heytler of du Pont. The Pittman-Moore Company of Indianapolis, through Dr. II. A. Nash and C. L. Baldwin, generously made available a small quantity of highly purified aurovertin. Oligomycin was purchased from the Wisconsin Alumni Research Foundation, Madison. Both antibiotics were dissolved as stock solutions (1 mg per ml) in absolute ethanol and stored at -20°C. They were appropriately diluted with water before use. Antimycin A, 2,4-dinitrophenol, p-hydroxymercuribenzoate (sodium salt), and L-thyroxine were purchased from Sigma. Chlorpromazine and chlorpromazine sulfoxide were gifts from Smith Kline and French Laboratories. They were dissolved in water and stored at -20°C. Various alkylguanidines were generously donated by Dr. B. C. Pressman (Johnson Research Foundation) and prepared as stock solutions either in 50% ethanol or in water. All other salts and compounds were of reagent grade. Deionized, glass-distilled water was used throughout.

TABLE I

Amino acid content of histone fractions

<table>
<thead>
<tr>
<th>Histone fraction</th>
<th>Lysine</th>
<th>Arginine</th>
<th>Histidine</th>
<th>Glutamic acid</th>
<th>Aspartic acid</th>
<th>Amino acid ratio (basic to acidic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>f1 (lysine-rich)</td>
<td>25</td>
<td>3</td>
<td>0.4</td>
<td>6</td>
<td>3</td>
<td>3.1</td>
</tr>
<tr>
<td>f2a (moderately lysine-rich)</td>
<td>10</td>
<td>12</td>
<td>2.2</td>
<td>8</td>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>f2b (moderately lysine-rich)</td>
<td>15</td>
<td>7</td>
<td>2.5</td>
<td>9</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>f3 (arginine-rich)</td>
<td>9</td>
<td>12</td>
<td>2.0</td>
<td>13</td>
<td>6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Results

Nature of Changes in Optical Density Induced by Histones—Phase micrographs indicated the formation of aggregated mitochondria 5 to 10 min after histone addition. However, when very low concentrations of histone were used, an early significant fall in optical density (within 1 min) was observed before aggregation occurred. Similar results were obtained by light scattering measurements. The histone-mitochondria interaction therefore results in two phases, (a) initial swelling and (b) subsequent aggregation. Both phases produce changes in optical density.

Effect of Age of Mitochondria, pH, and Medium on Histone-induced Changes—The ability of the histones to produce swelling diminished with increasing age of the mitochondria. Thus, 24 hours after preparation, the mitochondria showed approximately a 40% reduction in swelling response to the histone, in spite of the fact that the initial optical density readings were unchanged during this period.

The histone-induced swelling was somewhat dependent upon pH. Maximal effects were noted between pH 7.0 and 8.5 (Fig. 1).

The swelling induced by histones was qualitatively similar in different types of media. For example, significant swelling occurred in a medium containing 20 mM Tris (pH 7.4), 80 mM NaCl, 10 mM MgCl₂, and 20 mM β-hydroxybutyrate. Differences in ATPase activity were noted, however, and will be discussed in a forthcoming paper (24).

Specificity of Histone-Mitochondria Interaction—The histones are basic nuclear proteins which are divided into several types of fractions, as shown in Table I. These types are based mainly upon the elution patterns obtained after chromatography on

carboxymethyl cellulose. They are further classified according to amino acid content. Distinct differences were found among these purified fractions with regard to swelling efficacy. Regardless of the tissue source, the f2a histone was the most active, while f1 was almost inactive (Fig. 2). The evidence further suggests that the f2a histones from liver and Walker tumor are more active than f2a from calf thymus. The arginine-rich f3 appears to be second in activity. Thus, the histone fractions with a relatively high content of arginine (f2a and f3) are the most effective in inducing mitochondrial swelling.

Fig. 1. Effect of pH on histone-induced swelling. ---, control (i); ----, 50 µg of f2a (ii). The incubation medium and procedure are defined in the text; mitochondrial protein, 2.3 mg. Each point represents a separate tube, read rapidly at the 8-min interval. Unless otherwise specified, the histones in this and subsequent figures were isolated from calf thymus. The medium and procedure are the same for all figures.

Fig. 2. Comparison of effects of purified histone fractions isolated from rat liver. a, control; b, 50 µg of f1; c, 50 µg of f2b; d, 50 µg of f3; e, 50 µg of f2a; mitochondrial protein, 2.4 mg.
Half-maximal stimulation of swelling is produced by 35 μg of f2a per mg of mitochondrial protein. Threshold concentration is about 1 μg per ml of protein.

A number of commercially prepared basic polyelectrolytes were tested. The lysine-rich histone from Worthington, which is probably comparable to f1, produced no significant mitochondrial swelling, while the swelling induced by arginine-rich histones obtained from Sigma or Worthington was qualitatively similar to that produced by f2a or f3. Neither poly-L-lysine nor protamine produced significant swelling except in concentrations above 125 μg per mg of mitochondrial protein. Spermine, spermidine, and putrescine were inactive.

Fig. 3. Effect of ATP concentration on histone-induced swelling. a, control; b, f2a plus 22.8 mM ATP; c, f2a plus 11.4 mM ATP; d, f2a plus 5.7 mM ATP; e, f2a plus 2.85 mM ATP; f, f2a. Mitochondrial protein, 2.3 mg; f2a, 50 μg.

Fig. 4. Comparison of effectiveness of ATP, GTP, and ITP on inhibition of histone-induced swelling. a, control or ITP or GTP; b, ATP; c, f2a plus GTP; d, f2a plus ITP; e, f2a; f, f2a plus ATP. Mitochondrial protein, 1.94 mg; ATP, GTP, ITP, 2.85 mM; f2a, 50 μg.
Attempts to Prevent Swelling with Nucleotides—Mitochondria swollen by phosphate, calcium, or thyroxine can generally be “contracted” by the addition of ATP (17). This is not the case, however, with regard to histone-induced swelling. Pretreatment of the mitochondria with certain concentrations of ATP significantly retarded the swelling process. Fig. 3 summarizes these observations. Concentrations of ATP from 5.7 to 22.8 mM inhibited the histone-induced swelling. The effects of low ATP (2.85 to 5.7 mM) are noteworthy. An initial protection was followed by an increase in swelling. This “cross-over” phenomenon resembles the swelling induced by ATP plus inorganic phosphate at slightly acidic pH values, reported recently (32). Various concentrations of ATP comparable to those used above were mixed with histones in the absence of mitochondria. No precipitation or change in optical density at 260 or 280 nm was found.

To further examine the protective effect of ATP, all known nucleoside mono-, di-, and triphosphates were used. ITP, essentially a deaminated ATP, had no effect and is typical of the results obtained with all tested nucleosides and nucleotides except GTP. The latter was more effective in preventing histone-induced swelling than ATP, and did not produce a cross-over even in very low concentrations (Fig. 4).

Effects of Acidic Polyelectrolytes—It is conceivable that the histones produce membrane changes by interacting with polyanionic groups present in the mitochondrial membrane system. Consequently, a number of compounds which are normally found in membranes were tested. Gangliosides were particularly effective in preventing histone-induced swelling than ATP, and did not produce a cross-over even in very low concentrations (Fig. 5). Half-maximal inhibition of swelling was elicited by approximately 0.5 µg of whole ganglioside per µg of f2a. The polyanion itself produced no mitochondrial changes even in concentrations above 50 µg per ml. The hydrolyzed molecule, as well as N-acetylneuraminic acid, was completely ineffective in preventing histone-induced swelling. No observable precipitation occurred when the required low concentrations of ganglioside and histone were mixed. Phosvitin and phosphatidylserine were more effective inhibitors of histone-induced mitochondrial swelling than gangliosides. Half-maximal inhibition occurred at 0.13 µg and 0.2 µg per µg of f2a, respectively. The inhibition appeared to be of the competitive type and no visible precipitation took place under the defined experimental conditions. A fraction rich in phosphoprotein from cerebral tissues was found to be as effective as phosvitin. A number of other polyanions were used in efforts to duplicate the ganglioside and phosphoprotein effects. These are summarized in Table II. Those that were effective, however, also precipitated the histone. Phosphoserine, in contrast to phosphatidylserine, was without effect on the histone-induced swelling.

Effects of Various Respiratory Inhibitors, Uncoupling, and Other Agents—Chlorpromazine, a “membrane stabilizer” (33), was a potent inhibitor of histone-induced swelling (Fig. 6). However, the metabolite, chlorpromazine sulfonamide, was inactive. Strontium ion, which effectively prevents calcium-induced swelling (34), was inactive alone, but when it was combined with ATP it increased the protective effect of ATP.

Oligomycin and aurovertin presumably interact with an energy intermediate which may be required for the swelling-contraction process (16, 32). With the use of these antibiotics the histone-induced swelling, the results were unusual in that no effect was elicited when the agents were used in the absence of ATP (Table III). However, when combined with low concentrations of ATP, oligomycin or aurovertin abolished the crossover and enhanced the protective effect of ATP (Fig. 7).

Fig. 5. A reciprocal plot of the inhibition of histone-induced swelling with gangliosides. a, no gangliosides; b, 25 µg of gangliosides; c, 50 µg of gangliosides; d, 75 µg of gangliosides; mitochondrial protein, 2.3 mg. ΔO.D. 520, the difference between the optical density readings of the experimental tube and a control tube containing no histone 20 min after swelling was initiated. ΔO.D. 520 therefore represents extent of optical density change and not rate of change. CT, calf thymus.
The character of the histone-induced swelling was compared with several known inducers of swelling, including phosphate, calcium, and thyroxine, and with a surface-active agent, deoxycholic acid. Deoxycholic acid was chosen since the swelling-inducing effects of the histones might be attributed to a surface action. In all cases, oligomycin, but not aurovertin, reversed or prevented ATP-induced inhibition of swelling. These results are in contrast to the effects of histones described above. The observations concerning deoxycholate should be emphasized.

ATP (2.85 mM) prevented or reversed the swelling induced by 10.8 x 10^{-3} M deoxycholic acid, and oligomycin inhibited the ATP effect. Phase microscopy further showed that deoxycholate produced significant swelling which was reversible upon addi-

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect</th>
<th>Precipitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosvitin</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Phosphatidylserine</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Phosphatidylinositide</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gangliosides</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Polyethylene sulfonates</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phytic acid (hexaphosphoinositol)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Casein</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lecithin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phosphoserine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phosphothanolamine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>γ-Glutamyl polypeptides</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phosphoprotein &quot;residue&quot; from</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNA or DNA</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

a, prevention of histone-induced swelling; b, no effect or increased swelling.

+ and - refer to presence or absence of a visible precipitate, respectively.

**TABLE III**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-Dinitrophenol (up to 10^{-4} M)</td>
<td>Slight inhibition (10 to 20%)</td>
</tr>
<tr>
<td>Oligomycin (no ATP)</td>
<td>No effect</td>
</tr>
<tr>
<td>Arylamine (no ATP)</td>
<td>Enhancement of ATP inhibition</td>
</tr>
<tr>
<td>Oligomycin (with ATP)^{a}</td>
<td>(see &quot;Results&quot;)</td>
</tr>
<tr>
<td>Aurovertin (with ATP)^{a}</td>
<td>Enhancement of ATP inhibition</td>
</tr>
<tr>
<td>Antimycin A (3 μg/ml)</td>
<td>No effect</td>
</tr>
<tr>
<td>KCN (1 to 3 mM)</td>
<td>Slight inhibition (10 to 20%)</td>
</tr>
<tr>
<td>Azide (8 mM)</td>
<td>No effect</td>
</tr>
<tr>
<td>Amytal (4 mM)</td>
<td>No effect</td>
</tr>
<tr>
<td>p-Hydroxymercuribenzoate (3 x 10^{-4} M)</td>
<td>No effect (causes swelling)</td>
</tr>
<tr>
<td>NaF (20 mM)</td>
<td>No effect</td>
</tr>
<tr>
<td>Carbonyl cyanide m-chloro-phenylhydrazone (3 x 10^{-4} M)</td>
<td>Inhibition (up to 50%)</td>
</tr>
<tr>
<td>Arsenate (0.5 mM)</td>
<td>No effect (causes swelling)</td>
</tr>
</tbody>
</table>

Oligomycin and aurovertin were used in the same concentrations as in Fig. 7.

![Image](http://www.jbc.org/)
tion of ATP. Furthermore, chlorpromazine was unable to prevent the swelling induced by deoxycholate under the conditions used in this study.

Most of the known respiratory chain inhibitors were used, and their more important effects are listed in Table III. Dinitrophenol and cyanide prevented histone-induced swelling, but only minimally. Azide, Amytal, and antimycin were without effect, as were combinations of these agents with oligomycin or aurovertin. Octylguanidine was the only inhibitor that produced significant inhibition.

**DISCUSSION**

Mitochondrial swelling was first observed by Cleland (8) and by Raaflaub (9). Raaflaub described the phenomenon in detail, establishing the ionic requirements and the optical density and morphological changes. Subsequently, a number of publications have appeared, directing particular attention to various means of measuring swelling (18-20, 34-36), including the most frequently used optical density and light scattering methods. The dangers inherent in these procedures have been adequately discussed by Spirtes and Guth (33).

Regardless of the exact nature of the process, it seems clear that the swelling phenomenon is often linked in some way to mitochondrial activity. The determination of the physiological significance of swelling is complicated by the paucity of knowledge concerning structural correlates. The mitochondrion, according to Palade and others, consists of three compartments bordered by membranes: an outer, an inner or matrix, and an intercrystal (37). Hackenbrock and Brandt, in a combined biochemical and morphological study (38), reported a correlation between the foldings of the inner membrane and state of mitochondrial activity. The basic proteins probably interact with some component in this membrane system. This interaction results in a marked morphological change. The question of the relationship of this alteration to functional changes previously described (1, 2) is incompletely answered, although the present findings suggest a possible answer. The results described in this study clearly show that the same concentrations which cause an increase in oxygen consumption and ATPase activity also produce a swelling of the mitochondria. It is of interest that the histone fraction most active on all the measured parameters is f2a, a relatively arginine-rich protein. A similar fraction, extracted from calf thymus, was recently reported to effect an increase in light scattering as well as concomitant increases in oxygen consumption and ATPase activity of liver mitochondria, in the same concentrations used in the present study (3). Ryser and Hancock (23) recently reported that concentrations of histone as low as $10^{-10} \text{m}$ produced a marked increase in albumin uptake into monolayers of Sarcoma 180 cells. Again, the arginine-rich histones were much more active than crude histones, and the lysine-rich histone fraction was essentially inactive. These investigators postulated, in agreement with the suggestions from this laboratory (1, 2, 5), that some type of membrane action is involved and that the histones should be considered “as highly potent membrane agents.” In the present study, the lysine-rich histone fraction f1, used in the same concentrations as f2a or f3, was found to be almost inactive. Apparently, both the basic nature of the histone and its molecular structure are of importance in the membrane effects. This is further exemplified by the inactivity of spermine.

It should be emphasized that the histones represent heterogeneous structures. Consequently, it is difficult to speculate on the molecular requirements. Work is presently in progress in this laboratory on subfractionation and purification of histone fractions from a variety of tissues.

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**FIG. 7.** Effect of aurovertin and oligomycin on histone-induced swelling. a, control or ATP; b, f2a plus ATP plus aurovertin or oligomycin; c, f2a or f2a plus aurovertin or oligomycin; d, f2a plus ATP. Mitochondrial protein, 1.9 mg; f2a, 75 μg; ATP, 5.7 mM; oligomycin and aurovertin, 5 μg.
Maximum histone effects were always noted on fresh mitochondrial preparations, which is in agreement with the observations of Hunter et al. (14) and other investigators who have observed that after 2 or more hours the mitochondria become less sensitive to swelling-inducing agents. The nature of this phenomenon is unknown, although a loss of a substance required for the swelling process, possibly phosphatidylinositol, has been suggested (39). It is of interest in this respect that the compounds most active in preventing the histone-induced mitochondrial changes are phosphatidylserine and phosphoproteins.

It is well known that mitochondrial swelling of large amplitude is effectively prevented in most instances by ATP (9, 16, 17, 40, 41). The complexity of the swelling-contraction cycle is exemplified by the effects of ATP on the histone-induced changes particularly the increase in swelling caused by low concentrations of the nucleotides. The nature of the oligomycin or aurovertin enhancement of the ATP antiswelling effect and abolition of the cross-over is not clear. The concentrations of Hunter et al. (14) and other investigators who have suggested (39). It is of interest in this respect that the compounds most active in preventing the histone-induced mitochondrial changes are phosphatidylserine and phosphoproteins.

REFERENCES

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