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Effect of Prolactin on Galactose Cataractogenesis

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Abstract. Prolactin has been known to affect the water and electrolyte balance. Because increased lens hydration has been shown to be a common phenomenon in most, if not all types of cataracts, we have been interested in investigating a possible role of prolactin in sugar cataract induction and progression. For this study, we have used morphological and biochemical approaches. The prolactin delivery method involved intraperitoneal implantation of one or more pellets in Sprague-Dawley female rats. Following implantation of the desired number of prolactin or control (nonprolactin) pellets, animals were either fed galactose and lab chow, or lab chow diet. Gross morphological observations of whole lenses, slit-lamp examination of lenses and light microscopic analysis of lens sections showed that in the galactose-fed prolactin group, galactose associated alteration progressed faster and total opacification (mature cataract development) was achieved earlier than in the nonprolactin group. The levels of galactose and dulcitol were higher in the lenses of galactose-fed prolactin treated rats as compared to lenses from nonprolactin (control) rats. No significant difference in lens Na^+–K^+ ATPase activity between the prolactin and nonprolactin group was observed. Our results indicate that prolactin accelerates galactose-induced cataractogenesis in rats.

Introduction

Hormonal influence on lenticular abnormalities and cataract development has been postulated in both experimental animals and humans during endocrine dysfunctions [Bellows, 1944; Duke-Elder, 1949; Nordmann, 1954; Brooks, 1975]. However, concerted efforts to determine the precise role of hormones, individually or in combination, in the development of lens opacities are lacking. Several years ago during our studies involving induction of cataracts in rat fetuses [Unakar et al., 1979], we observed that during pregnancy the progression of galactose-induced opacity was slower than that

observed in the same age nonpregnant female rats. However, the rate of opacity development accelerated postpartum. These observations suggested that hormonal alterations during pregnancy and postpartum may affect the rate of progression of opacity in sugar cataracts. The serum concentration of prolactin reaches peak during postpartum when the progression of galactose-induced opacity was found by us to accelerate. Therefore, we decided first to investigate the effect of prolactin on galactose cataractogenesis. Morphological and biochemical investigations on galactose-induced cataracts in rats have been widely studied by a number of investigators [Van Heyningen, 1959; Kinoshita et al., 1962; Reddy et al., 1976; Kuwabara et al., 1969; Kinoshita, 1974; Unakar et al., 1978, 1981; Gona and Fu, 1982]. To our knowledge, except for the recent work of Gona and Fu [1982], studies to determine if prolactin plays a synergistic role to galactose in the induction of cataract have been lacking. In this report we present our preliminary results obtained from our experiments to determine the influence of prolactin on galactose cataractogenesis.

Materials and Methods

Ovine prolactin (obtained from NIADDH National Hormone and Pituitary Program) with bio potency of 30.5 IU/mg was pelletized into 5-mg pellets by Innovative Research of America (Rockville, Md.). This commercial company also prepared control pellets without prolactin. Female Sprague-Dawley rats weighing 80–100 g were used throughout this study. All rats were kept on a 12-hour light-dark cycle (0.800–20.00 h). In the initial dose-response studies, 1–5 prolactin or control pellets were implanted intraperitoneally to determine the dose of prolactin which would have a significant effect on galactose-induced alterations in the lens. As it was recognized through the dose-response studies that 3–4 pellets (15–20 mg prolactin) implantation resulted in a detectable effect on galactose-induced opacity (as compared to lenses on control pellets), in subsequent experiments only 3–4 pellets were implanted. In addition to rats implanted with control pellets, sham-operated rats without implantation of pellets were used as additional controls.

Postoperative rats were placed on regular lab chow for 2 days before switching to a galactose diet consisting of 50% galactose plus 50% powdered lab chow. The progression of opacity was monitored on a daily basis by an ophthalmologist (who had no knowledge of the treatment or diets received by the animals) with Zeiss slit-lamp biomicroscope. Diagrams of opacity observed were prepared for each lens when significant changes in the expression of opacity were detectable. Our previous morphological studies on alterations induced by galactose in the lenses served as a basis for choosing the intervals for this study. Procedures followed for morphological and biochemical studies are as follows.

Morphology

Following 3, 7, 10, 13, 17, 22, and 26 days on galactose diet, animals were sacrified and the lenses were excised. Freshly excised lenses were photographed using a Zeiss Tessovar microscope. These lenses were then fixed in 2.5% glutaraldehyde in 0.1 *M* cacodylate buffer for 24 h and then in 10% formalin for at least 24 h. Following dehydration they were embedded in JB-4 plastic medium [Datiles et al., 1982; Unakar and Tsui, 1983]. Sections of 1 μm thickness were cut and stained with 1% toluidine blue for light microscopy.

Galactose and Dulcitol Analysis

Prolactin- and nonprolactin-treated animals were sacrificed following 3, 7, 10, and 13 days on a galactose diet. A pair of freshly excised lenses from each of the 3- and 4- prolactin and control pellet groups were weighed and quickly frozen on dry ice. At least 3 rats for each of the diet periods were used for this study. All lenses were stored at −80 °C and galactose and dulcitol levels in these lenses were determined by gas liquid chromatography using the method reported by Reddy et al. [1971] with several modifications. The gas liquid chromatography of sugars and sugar alco-

hols were done on a Varian model 3700-GLC equipped with a Vista-401 data module. Detection of each solute was by flame ionization using hydrogen and air flame. Helium was the mobile phase. Separation of the sugars was done on a 6-foot coiled column packed with SE-30 on ultraphase 100–200 mesh. The oven temperature was 140 °C with the injection port temperature and the detector temperature at 250 °C.

One rat lens was homogenized in 0.5 ml of barium hydroxide (2%) and 0.5 ml of zinc sulfate (2%) and centrifuged in a Brinkman microfuge, 0.75 ml of supernatant was removed and lyophylized to dryness. The dried material was dissolved in 10 µl of pyridine and 40 µl of N,O-bis(trimethylsilyl)-trifluoroacetamide (Pierce Chemical Co.) After heating for 10 min at 37 °C, 1–2 µl of samples were injected into the GLC column.

An external standard was run containing fructose, galactose, glucose, and sorbitol or dulcitol at a concentration of 5 µ*M*/µl.

Na^+-K^+-ATPase Assays

Prolactin- and nonprolactin-treated rats were sacrificed at 2, 6, 10, 15, and 20 days on a galactose diet. Freshly excised lenses were weighed and stored at −80 °C until assayed. On the day of assay, frozen lenses were homogenized at 0–5 °C in 0.7 ml of Tris-EDTA buffer. Aliquots of 0.2 ml vol of homogenates were added to each assay medium. Total ATPase and Mg-dependent ATPase activity were determined as previously described by Bonting et al. [1963]. The Na^+-K^+-ATPase activity was obtained as ouabain-sensitive fraction of the total ATPase.

Results

Morphology

The slit-lamp biomicroscopy and observation of lenses under the dissecting microscope with a wire-mesh background indicated that in galactose-fed rats, implanted with control pellets or 1 and 2 prolactin (5–10 mg) pellets, the rate of progression of opacity and galactose-induced alterations in the lens was similar to that observed in sham-operated galactose-fed rats. However, with (3–4) prolactin pellets (15–20 mg) implantation, acceleration of galactose-induced opacity was observed. Therefore, following the initial dose-response studies, we selected implantation of 3 or 4 pellets to determine the effect of prolactin on galactose cataractogenesis. For the classification of opacity we used Sippel's chart and codes [Sippel, 1966] which grades opacity in stages 1–5 with 5 being complete opacification of the lens.

Table I. Progression of galactose cataractogenesis in rats with and without prolactin treatment

Days on galactose diet	Stage of lens opacity[1]	
	control rats	prolactin-treated rats[2]
7	1C	2
10	1C	2–3
13	2–3	4
17	3	4–5
22	4–5	5
26	4	

[1] Stages identified according to Sippel's chart.
[2] Rats implanted with 4 prolactin pellets (5 mg ovine prolactin/pellet). There were 7 rats in each group.

In galactose-fed rats, implanted with control pellets, the rate or progression of opacity was similar to that observed in sham-operated , galactose-fed rats. In galactose-fed rats with (3–4) prolactin pellets, the progression of opacity appeared to deviate from that of the nonprolactin control group (table I).

AT 7 days of galactose feeding, in lenses of rats which received no prolactin, the opacity had progressed to Sippel's stage 1C. In these lenses a small peripheral zone of the lens was opaque (fig. 1, 3). At this time in

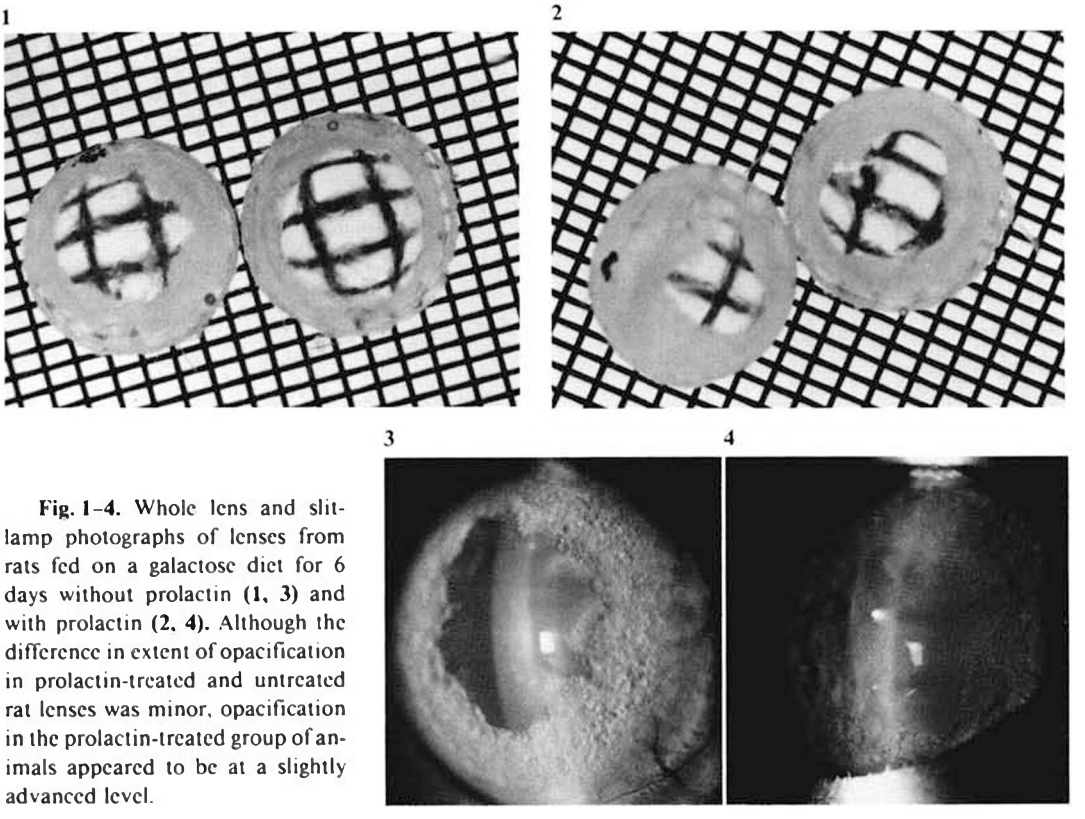

Fig. 1–4. Whole lens and slit-lamp photographs of lenses from rats fed on a galactose diet for 6 days without prolactin **(1, 3)** and with prolactin **(2, 4)**. Although the difference in extent of opacification in prolactin-treated and untreated rat lenses was minor, opacification in the prolactin-treated group of animals appeared to be at a slightly advanced level.

prolactin-treated rat lenses the opacity had progressed to stage 2 and lenses exhibited peripheral opacity which was slightly more advanced than in the control, and large vacuoles in the opaque regions were visible (fig. 2, 4). This difference in lenses from nonprolactin and prolactin groups increased with continuation of galactose diet. At 10 days, lenses from prolactin-treated rats exhibited stage 2–3 opacity while lenses of control rats were still of stage 1C. At 13 days in rats from the nonprolactin group, the extent of lens opacity could be classified as stage 2–3 (fig. 5), while in the prolactin group the opacity had progressed to stage 4 with the presence of vacuoles often distributed over the entire lens and the beginning of nuclear opacity (fig. 6). At 17 days on galactose diet the lens opacity in the nonprolactin group was equivalent to stage 3, and in prolactin-treated animals lenses were completely opaque and similar to Sippel's stages 4–5. At 22 days, lenses from nonprolactin group of rats indicated that the opacity had progressed considerably towards complete opacification with a few small remaining clear spots (fig. 7). At this stage of galactose feeding the prolactin-treated rats had completely opaque lenses with stage 5 opacity (fig. 8). Except for a probable few small clear areas in the lenses of the nonprolactin group the differences between the extent of opacification between the two groups, at this stage of galactose feeding, was very difficult to recog-

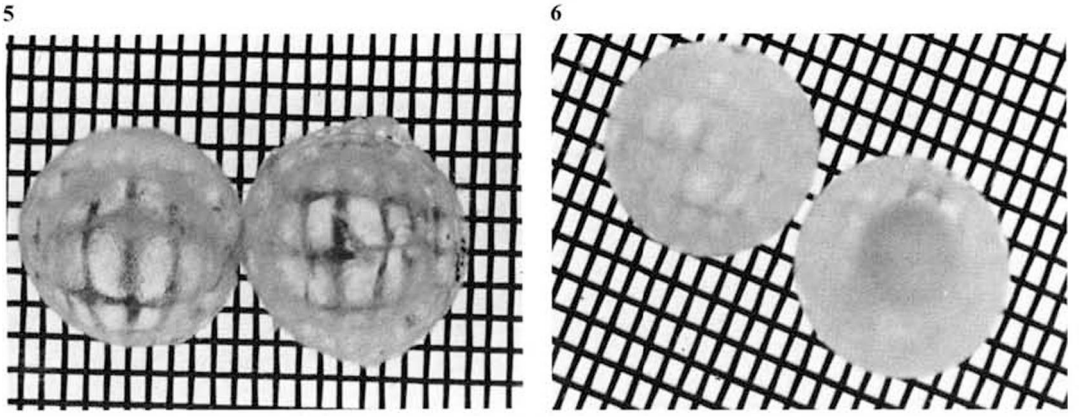

Fig. 5, 6. Whole lens photographs of lenses from rats fed galactose for 13 days without **(5)** and with **(6)** prolactin. At this stage of experimentation in the nonprolactin group, opacity had advanced to stage 2–3 of Sippel. Vacuoles in the peripheral regions of the lens were visible. In the prolactin-treated group of animals, opacity appeared to be similar to Sippel's stage 4 with the beginning of nuclear opacification.

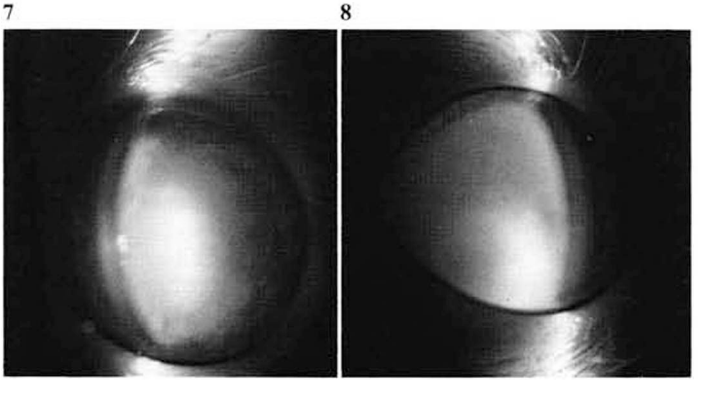

Fig. 7, 8. Slit-lamp photographs of lenses from rats fed galactose for 22 days without **(7)** and with **(8)** prolactin. The difference in extent of opacification between these two groups was less obvious. However, the lenses of prolactin-treated rats appear to have slightly advanced stage of cataract development.

nize. Comparatively, it took the lenses of nonprolactin control rats 26 or more days to reach stage 5 opacities.

The light microscopic analysis of 1-μm thick sections confirmed the alterations observed with slit-lamp or whole lens microscopy. At 3 days of galactose feedings, lenses from rats implanted with 4–5 control pellets exhibited vacuolation and distortion which was localized in cortical fibers in the equatorial region (fig. 9, 10). This vacuolation was more pronounced and occupied larger areas in the lenses of rats with 3–4 prolactin pellet implants (fig. 11). Damage to epithelial cells in these lenses was also visible (fig. 12).

Following 10–16 days of galactose feeding, lenses from the prolactin-treated rats not only exhibited more advanced stages of damage, but there were also differences in the extent of damage between rats implanted with 3 versus 4 prolactin pellets. At 10 days, the lenses in 3-pellet prolactin groups exhib-

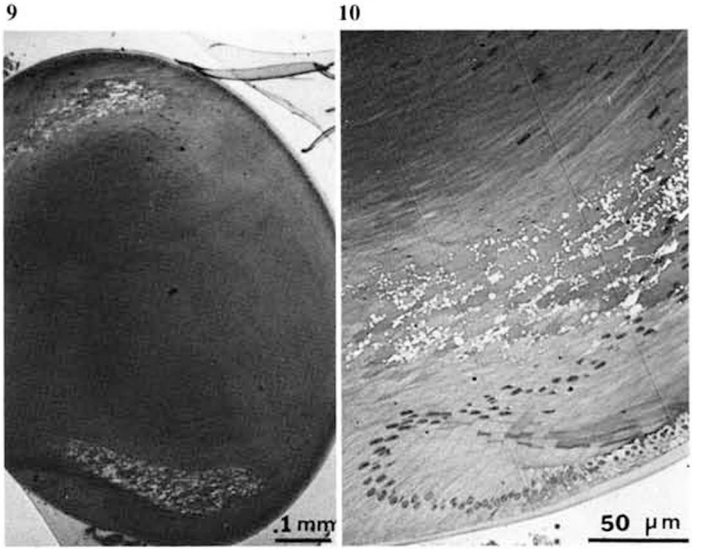

Fig. 9, 10. Micrographs of 1 µm thick sections of lenses. These are lens sections from rats in the control nonprolactin group which were fed a galactose diet for 3 days. Note the presence of vacuoles and distortion of cortical fiber cell organization in the equatorial region. **9** × 77; **10** × 307.

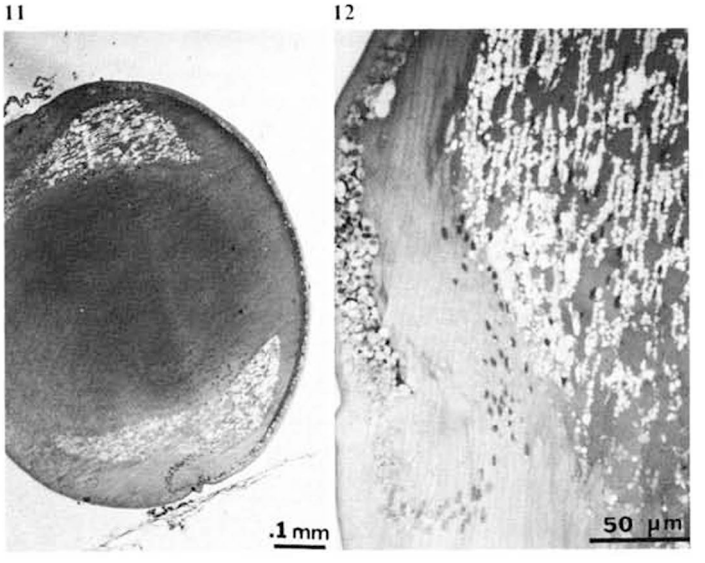

Fig. 11, 12. Micrographs of 1 µm thick sections of lenses. These are lens sections from rats in the prolactin group which were fed a galactose diet for 3 days. The extent of vacuolation and fiber swelling in the equatorial region was more pronounced. In some lenses, epithelial cells also appeared to be damaged (compare with figures 9 and 10). **11** × 77; **12** × 307.

ited considerable swelling of fibres throughout the lens giving it a 'foamy' appearance (fig. 13). At higher magnification, however, fiber boundaries appeared intact (fig. 14). With 4 prolactin pellets, at the same stage of galactose feeding (10 days), swollen fibers were found to be localized mainly in the superficial cortex and the rest of the lens appeared homogenous and liquefied areas were visible (fig. 15, 16). When rats were kept for 16 days on galactose in 3-pellet prolactin groups, patchy areas of liquefied fibers with loss of fiber integrity in these areas were observed (fig. 17). With 4 prolactin pellets, the lens damage was more extensive. Except for the equatorial zone, where some lens

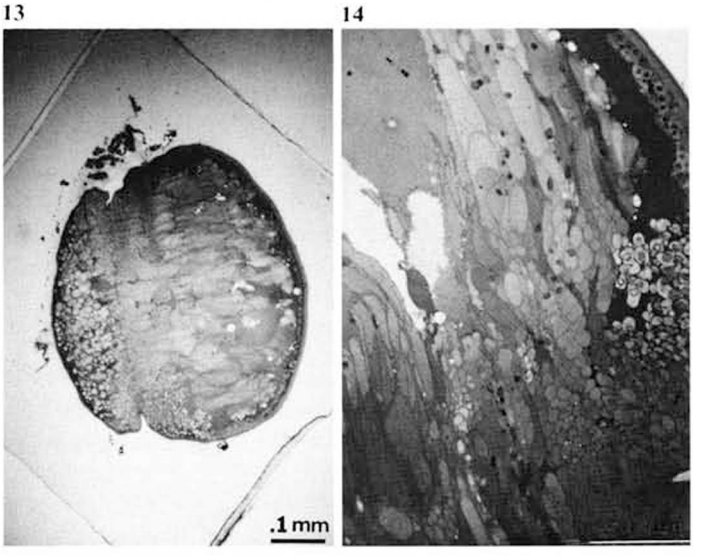

Fig. 13, 14. Micrographs of 1 μm thick sections of lenses. At 10 days of galactose feeding in rats implanted with 3 prolactin pellets, damage to lens fibers in all regions is observed. However, fiber membranes are still intact. **13** × 77; **14** × 307.

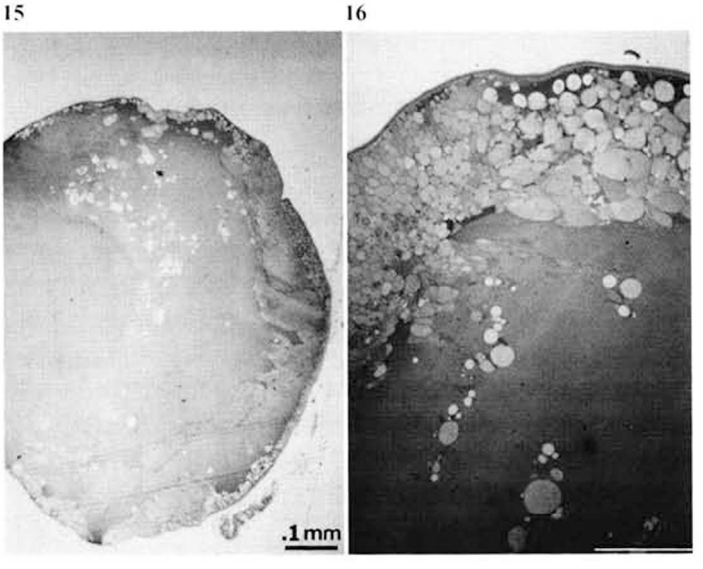

Fig. 15, 16. Micrographs of 1 μm thick sections of lenses. These lens sections are from rats at 10 days of galactose feeding implanted with 4 prolactin pellets. The extent of damage to lens components was more advanced than that seen in the 3-pellet group. Fiber membranes were damaged and most of the lens area was occupied by homogeneous material. **15** × 77; **16** × 307.

fibers and epithelium appeared intact, the rest of the lens was liquefied and contained aggregates of membrane debris (fig. 18).

Galactose and Dulcitol Analysis

The levels of galactose and dulcitol in the lenses were determined with GLC. Table II presents a GLC analysis of the galactose content in μmol/g dry weight of lenses in three different groups of rats. Lenses from all three groups of rats (control pellet group and 3- and 4-prolactin pellet groups) show similar patterns but different magnitude in the galactose level over a period of 15 days. The control rats had the lowest level of galactose in their lenses while the rats on 4 prolactin

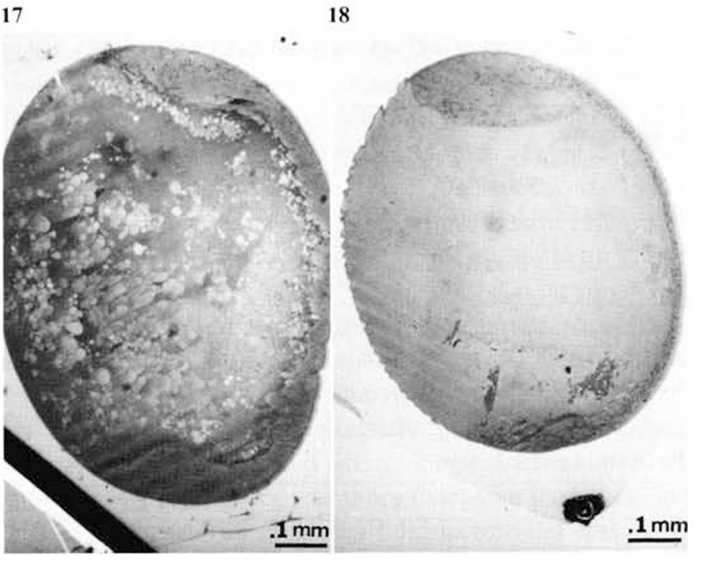

Fig. 17, 18. Micrographs of 1 µm thick sections of lenses. These micrographs are of lens sections from prolactin-treated rats fed a galactose diet for 16 days. Damage to lens in both 3-prolactin **(17)** and 4-prolactin **(18)** pellet groups is shown. In the 3-prolactin group, patchy areas of liquefied fibres were observable, while in the 4-prolactin pellet group this damage was more extreme. **17** × 77; **18** × 77.

Table II. Galactose content (µmol/g dry weight) of lenses from galactose-fed rats with and without prolactin treatment

Days on galactose diet	Treatment		
	control pellets	3 prolactin pellets[1]	4 prolactin pellets[1]
3	11.05	10.36	7.55
6	11.84	19.13	24.03
10	21.97	30.59	47.71
13	14.00	27.92	60.52
15	6.90	–	40.38

[1] Each pellet contained 5 mg of ovine prolactin.

Table III. Dulcitol content (µmol/g dry weight) of lenses from galactose-fed rats with and without prolactin treatment

Days on galactose diet	Treatment		
	control pellets	3 prolactin pellets[1]	4 prolactin pellets[1]
3	297.43	370.06	246.81
6	379.94	505.81	357.48
10	303.63	598.92	412.55
13	237.16	438.08	594.40
15	166.64	–	267.55

[1] Each pellet contained 5 mg of ovine prolactin.

pellets had the highest, and rats with 3 prolactin pellets had galactose values at an intermediate level. The peak of galactose level in the lenses was reached at 10 days in control rats (21.97 µmol/g dry wt of lens) and 3-pellet groups (30.59 µmol/g dry wt of lens). At 10 days the galactose level in lenses of the 4-pellet groups of rat was much higher (47.71 µmol/g dry wt of lens) than in the other two groups and reached a peak of 60.52 µmol/g dry wt of lens on the 13th day. In all groups, following the peak levels there was a drop in lens galactose.

Changes somewhat similar to those observed for lens galactose levels were observed for lens dulcitol (table III). In the con-

Table IV. Activity of ATPase in whole lenses from prolactin- and nonprolactin treated rats fed on galactose diet (μmol Pi/lens/h ± SD)

Galactose diet	n	ATPase activity		
		total	Mg	Na/K
Control				
2	4	0.942 ± 0.219	0.595 ± 0.139	0.348 ± 0.082
6	5	0.863 ± 0.112	0.557 ± 0.060	0.307 ± 0.096
10	5	0.763 ± 0.107	0.483 ± 0.037	0.280 ± 0.072
15	5	0.419 ± 0.114	0.333 ± 0.062	0.087 ± 0.071
20	6	0.284 ± 0.051	0.247 ± 0.023	0.037 ± 0.033
Prolactin (4 pellets)				
2	8	1.003 ± 0.328	0.612 ± 0.162	0.391 ± 0.200
6	10	0.791 ± 0.172	0.506 ± 0.076	0.285 ± 0.103
10	10	0.703 ± 0.124	0.492 ± 0.068	0.234 ± 0.081
15	10	0.495 ± 0.229	0.358 ± 0.116	0.141 ± 0.119
20	8	0.296 ± 0.083	0.243 ± 0.062	0.054 ± 0.049

n = Number of lenses.

trol group of rats the peak for dulcitol was reached at 6 days and was 379.94 μmol/g dry wt of lens. In 3- and 4-pellet prolactin groups the peak dulcitol level was similar (598.92 μmol in the 3-pellet group and 594.40 in the 4-pellet group) but the peak value in the 3-pellet group was reached at 10 days compared to 13 days in the 4-pellet group. There was a rapid and significant drop in lens dulcitol levels following the peak levels.

Na^+-K^+-ATPase Assay

The effect of prolactin and galactose feeding on ATPase activities in lenses of rats is shown in table IV. The control rats for this study received galactose diet alone while the experimental animals received the same diet but with 4-pellet prolactin implants. Na^+-K^+-ATPase activity was calculated as the difference between total ATPase and Mg-ATPase acitivity. In both control and prolactin groups, all ATPase activity (including total, Mg + Na^+/K^+) seemed to decline with increasing duration on galactose diet. Nevertheless, there was no significant difference at the 5% level in all ATPase activity between the control and the prolactin group at any given point of the experimentation.

Discussion

Hormones have shown to have influence on the development of cataracts [Bellows, 1944; Duke-Elder, 1949; Nordmann, 1954; Brooks, 1975]. However, the exact mecha-

nism of their action still remains speculative. Cotlier [1962] reported acceleration of the development of lens opacity in galactose-fed hypophysectomized rats. The effect of pituitary hormones on cataract development has been suggested by Cotlier to be indirect. Hypophysectomy and influence of hormones on mitosis in lens epithelium have been the subject of many investigations. As alterations in miotic activity in lens epithelium of galactose-fed rats have been observed [von Sallmann, 1957; Grimes and von Sallmann, 1961], influence of hormones on galactose cataractogenesis through their action on mitosis cannot be ruled out. Pesch et al. [1960] demonstrated that progesterone delays galactose-induced cataracts in rats. Recently, Gona and Fu [1982], based on their gross observation of the lens, showed that prolactin accelerated galactose cataractogenesis in female rats. The results presented in this report using morphological and biochemical parameters demonstrate acceleration of galactose cataractogenesis in female rats administered high levels of prolactin. Moreover, our investigation involving up to 4 prolactin pellet implantations suggests that this acceleration is dose-dependent and that maximum effect of prolactin on the rate of cataract development is obtained with 15- to 20-mg implants. Although serum prolactin levels were not monitored, previous investigations from other laboratories have shown that administration of prolactin does inhibit prolactin secretion from the pituitary [Treiguerras et al., 1981]. Therefore, a lower number of prolactin pellets does not elevate serum prolactin level sufficiently to effect cataractogenesis.

Morphological and some biochemical alterations, such as alterations in lens galactose and dulcitol level and the level of Na^+-K^+-ATPase activity, associated with galactose cataractogenesis have been well elucidated through previous studies from this and other laboratories [Unakar et al., 1978, 1979, Unakar and Tsui, 1980a, b, 1981; Reddy et al., 1976; Kinoshita, 1974]. However, data on the effect of prolactin on galactose-induced changes had been lacking. Our results presented in this report show that with the administration of 15–20 mg of prolactin (3–4 pellets), at any given stage of galactose feeding, the progression of galactose-induced morphological alterations in rat lenses was more extensive than that observed in lenses of galactose-fed rats with control nonprolactin pellet implants. Moreover, our preliminary investigation suggests that, under similar conditions, rats implanted with these prolactin pellets may accumulate larger amounts of galactose and dulcitol in their lenses during the regimen of galactose diet as compared to those control groups.

The effect of prolactin on galactose and dulcitol accumulation in the lens was found to be dose-dependent. Rats implanted with 4 prolactin (20 mg) pellets did show higher levels of galactose in lenses as compared to those from rats with 3 prolactin pellets. There are several questions which remain unanswered at this stage of our observations. The lens galactose level appears to rise faster in the 4-pellet prolactin groups and reached the peak slower than the 3-pellet prolactin groups. In comparison, the lens dulcitol values rose more rapidly and reached the peak faster in the 3-pellet groups. The reason for these changes needs to be explored. The drop in the lens galactose and dulcitol levels following the peak values in all groups is probably due to their rapid diffusion out of the lens at the advanced stages of opacity.

Prolactin does not appear to exert any significant effect on the acitivity of Mg^{++} and Na^{+}-K^{+}-ATPase activity. The total Mg^{++} and Na^{+}-K^{+}-ATPase activity in the lens decreases with increase in the duration of galactose diet, and there is no significant difference in these enzyme values in both control and prolactin groups.

The present studies show that prolactin accelerates the morphological alteration and increases the dulcitol and galactose levels in the lenses of galactose-fed rats. However, the exact mechanism of prolactin action still remains speculative. Prolactin has been shown to have a diverse array of actions in vertebrates which includes an increase in intestinal fluid and an increase in ion, sugar and amino acid transport [Nicoll, 1981; Bern, 1975; Ensor, 1978; Mattheij et al., 1980; Bisbee, 1981; Pang, 1981; Mainoya, 1975]. In mammals, prolactin has been proposed to be a modulator rather than a primary controlling factor of fluid and electrolyte metabolism. As alterations in ion, sugar and amino acid transport and hydration of lens have been known to play an important role in galactose cataractogenesis [Kinoshita, 1974], prolactin could be facilitating the transport of these important elements into the lens and thus cause an acceleration of the development of lens opacity. In this sense, prolactin probably has an enhancing effect on galactose-induced alterations observed during the course of cataract development, particularly with regard to increases in galactose and dulcitol levels. As prolactin does not appear to have any significant effect on the level of Na^{+}-K^{+}-ATPase activity, which decreased during galactose cataractogenesis, its direct role in acceleration of galactose cataractogenesis through causing an increase in the rate of Na^{+} and K^{+} ion imbalance in the lens does not appear to be a primary factor for its action on galactose cataract development. Precise evaluation of the role of prolactin on cataractogenesis is obviously complicated in view of its known influence on endocrine modulations. It is, therefore, possible that the observed effect of prolactin on galactose cataractogenesis is mediated through other factors such as other hormones.

In conclusion, our morphological and biochemical studies presented in this report show that prolactin accelerates galactose-induced alterations in the lens and progression and establishment of lens opacity. Development of galactose cataract progressed more rapidly when prolactin was administered to galactose-fed rats. Damage to lens morphology was more extensive and accumulation of galactose and dulcitol was more rapid in the lenses of prolactin-treated rats as compared to nonprolactin control rats. Although the exact mechanism of action of prolactin on galactose cataractogenesis still remains to be elucidated, it is possible that it accelerates cataractogenesis through facilitating transport via altering permeability of the lens to ions, amino acid and galactose leading to rapid increase in lens galactose and dulcitol levels and hydration of the lens. These preliminary results suggest that further studies be conducted to investigate hormonal influence on cataractogenesis and to examine if there is any direct involvement of prolactin in this process.The long-term objective of the study is to also explore involvement of other hormones in the process of cataractogenesis, with particular reference to those whose levels undergo dramatic alterations during pregnancy and parturition, and those that are regulated by altering levels of prolactin.

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