The Effect of Medroxyprogesterone on Cells of the Pituitary Pars Distalis[1] (36458)

B. L. BAKER, T. A. ESKIN[2] AND H. W. CLAPP

Department of Anatomy, The University of Michigan Medical School, Ann Arbor, Michigan 48104

Considerable disagreement exists regarding the action of progestins on cells of the pituitary pars distalis. Their response to medroxyprogesterone [6α-methyl-17α-hydroxyprogesterone (MAP)] is of special interest because it is one of the most potent progestational compounds available (1–3) and is used as a contraceptive agent (Provera, Provest). Glenn, Richardson, and Bowman (4) found that medroxyprogesterone decreases the weight of rat adrenal glands and ovaries, these effects being attributed to suppressed secretion of tropic hormones by the hypophysis.

The structural effects elicited in the hypophysis by administration of MAP have not been clearly defined. As compared with controls, rats treated for 110 days beginning soon after birth are reported to have lighter pituitaries with smaller chromophobes, an absence of gonadotropic cells, and unchanged acidophils and thyrotropic cells (5). On the contrary, Ectors, Pasteels, and Herlant (6) found that MAP stimulates prolactin cells (a subclass of acidophils) in a "spectacular manner" and causes accumulation of cytoplasmic granulation in luteinizing hormone (LH)-secreting basophils.

Much of the difficulty in determining the structural response of the hypophysis to progestins stems from limitations inherent in histologic staining procedures and electron microscopy for delineation of the various pituitary cell types. Immunochemical staining permits accurate identification of most of these cell types and was employed in this study in conjunction with histologic staining to reveal the action of MAP on the hypophysis.

Methods. MAP[3] was suspended in Upjohn Vehicle 98 (carboxymethylcellulose, polysorbate and propylparaben), diluted 1:2 with 0.9% NaCl, and injected subcutaneously, morning and evening, into young female rats (Table I) at daily doses ranging from 0.5 to 1.5 mg/100 g body weight. Treatment was usually continued for 14 to 28 days although some rats were treated for longer periods. Comparable volumes of the vehicle were given to the controls. Pituitary glands were fixed, sectioned, stained with aldehyde fuchsin and Masson, and differential cell counts were carried out as previously described (8). Data are presented only for one of the cell types that could be identified accurately in both vehicle- and MAP-treated groups.

For immunochemical staining of single sections from various regions of the gland the peroxidase-labeled antibody procedure of Nakane and Pierce (7) was used with rabbit antisera to the following hormones: rat prolactin (anti-RP), human growth hormone (anti-HGH), porcine corticotropin (anti-PC), and human chorionic gonadotropin (anti-HCG). Information regarding specificity of the procedure has been published previously for prolactin and growth hormone cells (9) and corticotropic cells (10, 11). Because of questionable specificity of anti-HCG (12) for LH, the cells demonstrated with it are designated gonadotropic cells.

Observations. In confirmation of the findings of Logothetopoulos, Sharma, and Kraicer (5) MAP had no effect on weight of the body or thyroid glands but reduced the

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TABLE I. Effect of MAP on Body and Organ Weights.

Treatment	Duration treatment (days)	No. of rats	Daily dose (mg/100 g body wt)	Mean body wt (g)		Mean final organ wt (mg)				
				Initial	Final	Hypophysis	Adrenals	Ovaries	Uterus	Thyroid
MAP	28	13	1.5	127 ± 10[a]	199 ± 9					
Vehicle		14		124 ± 10	197 ± 8					
MAP	21	8	1.5	100 ± 4	176 ± 3	5.6 ± 0.3	15 ± 1	28 ± 3	158 ± 11	9.8 ± 0.4
Vehicle		8		107 ± 3	171 ± 6	7.2 ± 0.5	50 ± 2	53 ± 3	268 ± 27	10.8 ± 0.5
MAP	14	8	1.5	104 ± 3	151 ± 3	5.4 ± 0.3	20 ± 2	28 ± 4	177 ± 25	9.6 ± 0.6
Vehicle		8		107 ± 2	155 ± 2	6.7 ± 0.4	44 ± 2	48 ± 2	239 ± 19	9.4 ± 0.4
MAP	28	4	1.0	104 ± 2	190 ± 5	6.5 ± 0.3	17 ± 1	33 ± 3	150 ± 9	9.3 ± 0.2
Vehicle		4		101 ± 2	195 ± 2	9.2 ± 0.1	52 ± 3	55 ± 4	238 ± 3	9.4 ± 0.5
MAP	28	10	0.5	135 ± 13	220 ± 11					
Vehicle		10		131 ± 13	203 ± 11					

[a] Standard error of the mean.

weight of the hypophysis, adrenals, ovaries and uterus (Table I). Treatment with MAP for 4 weeks or longer caused marked degranulation and reduction in size of prolactin cells when compared with vehicle-treated controls (Fig. 1A, B). In general, the 0.5 mg/100 g body weight dose was as effective as 1.5 mg although in some cases the higher dose appeared to induce a greater change. In contrast, growth hormone cells were enlarged in many rats that received MAP, the change being more profound at the 1.5 mg than at the 0.5 mg dose level (Fig. 1C, D). Also, growth hormone cells become more closely arranged, partly due to the general reduction in size of the intervening prolactin cells. Differential cell counts carried out on Masson-stained preparations, in which growth hormone cells can be identified readily (9), showed that their relative number was increased by MAP, the mean percentage at the 1.5 mg dose given for 4 weeks being 39.0 ± 1.04[4] for rats receiving MAP and 24.3 ± 3.0 for the controls, the difference being significant ($p < .01$, Student's t test).

The influence of MAP on gonadotropic cells was less clear and varied from rat to rat. The number of gonadotropic cells was reduced somewhat especially in the central and medial areas of the lateral lobes. On the other hand the numerous remaining gonadotropic cells were enlarged and more intensely stained than those in the control glands (Fig. 2A, B).

Corticotropic cells could be identified accurately only with immunochemical staining; they were not affected by MAP (Fig. 2C, D).

Discussion. Our finding of a reduction in size of prolactin cells in female rats observed after treatment with MAP contrasts with the enlargement and cytological evidence of activation observed by Ectors, Pasteels, and Herlant (6) in erythrosinophils (regarded by them as prolactin cells) and the report of Pasteels (13) that progesterone simulates estrogen in its action on prolactin cells. On the other hand, using electron microscopy, Kurosumi (14) found an accumulation of secretory granules and regression of rough endoplas-

[4] Standard error of the mean.

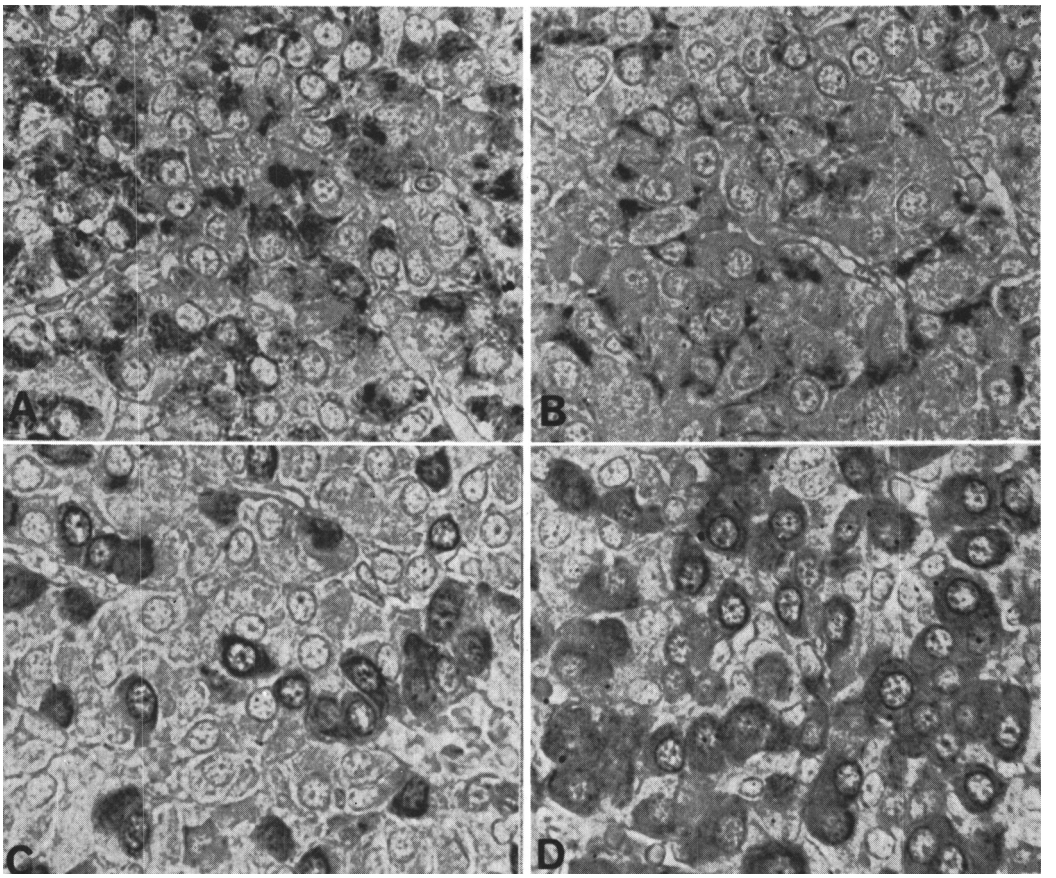

FIG. 1. All photomicrographs are of the pituitary pars distalis. The sections illustrated in (A) and (B) are stained for prolactin cells and those in (C) and (D) for growth hormone cells, ×600. (A) Vehicle-treated rat; (B) rat treated daily with 0.5 mg MAP/100 g body weight for 28 days. Prolactin cells are reduced in size. (C) Vehicle-treated rat; (D) rat treated daily with 1.5 mg MAP/100 g body weight for 28 days. Growth hormone cells are enlarged and more densely arranged than in (C).

mic reticulum in mammotropes (prolactin cells) under the influence of progesterone; these cytological alterations were considered indicative of atrophy.

The lack of agreement between our conclusions and those of Ectors, Pasteels, and Herlant (6) may have resulted from different cell types being identified as prolactin cells. A more likely reason is the probable difference in the amount of progestational activity exerted by the compounds used. Although estrogen elevates pituitary prolactin content over a wide range of doses (15, 16), progesterone reduces prolactin content at low doses and raises it only when extremely high doses are employed (16). The regression of prolactin cells reported here accounts primarily for the reduced pituitary weight brought about by MAP and is consonant with a reduction in prolactin content in the gland. Indeed, Ectors, Pasteels, ad Herlant (6) found that treatment of female rats with MAP reduces the amount of prolactin in the hypophysis.

The various progestational agents used as contraceptive agents differ widely in their action on prolactin cells. Thus, norethynodrel, the major component of Enovid, stimulates prolactin cells (17) and increases the prolactin content of the hypophysis (18) in contrast to the inhibitory action of MAP report-

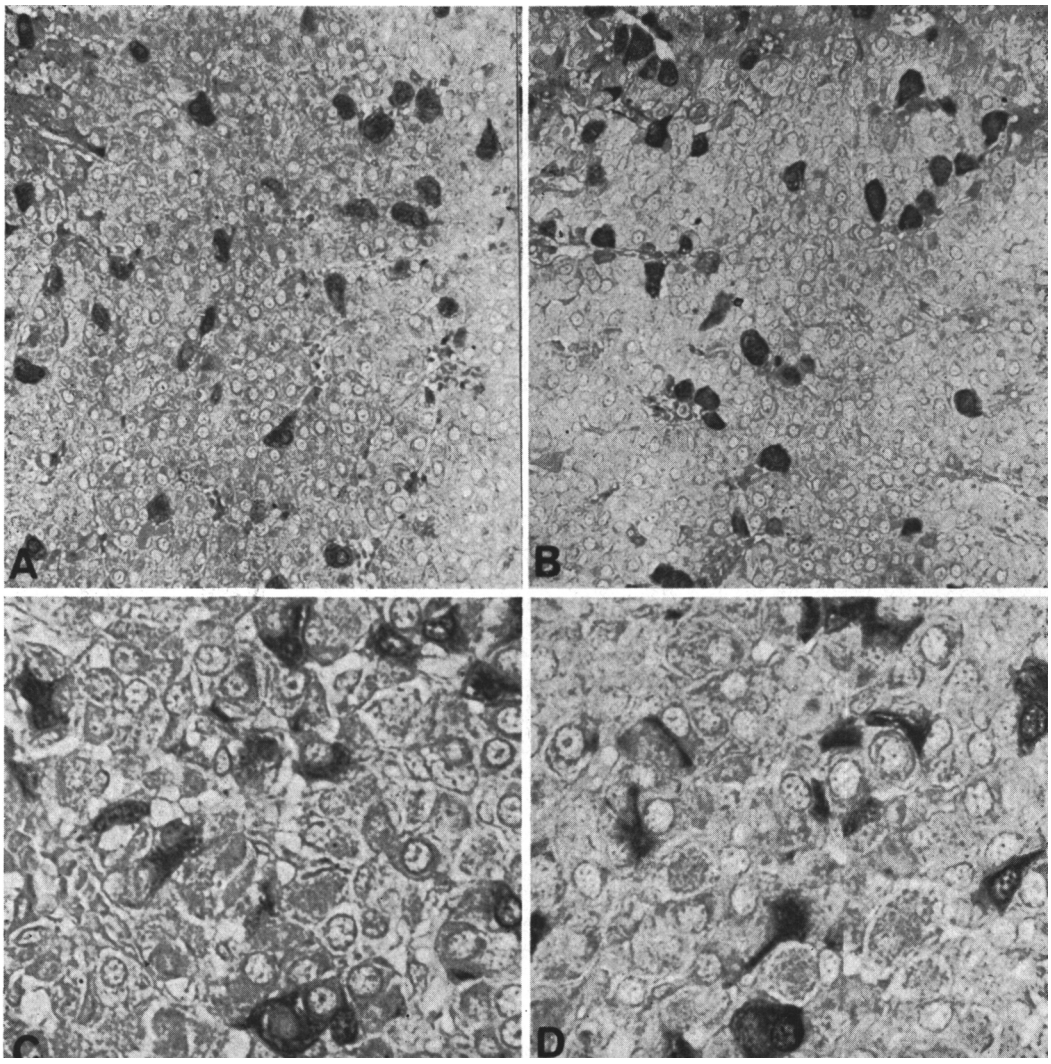

FIG. 2. All photomicrographs are of the hypophyseal pars distalis. (A) and (B) are lateral areas stained for gonadotropic cells, ×250; (C) and (D) are stained for corticotropic cells, ×600. (A) Vehicle-treated rat; (B) rat treated daily with 1.5 mg MAP/100 g body weight for 5 weeks; compared with (A) some gonadotropic cells are somewhat enlarged and stain more intensely. (C) Vehicle-treated rat; (D) rat treated with 0.5 mg MAP daily for 4 weeks. Corticotropic cells are not changed from those in (C).

ed herein. Also unlike MAP, norethynodrel does not alter pituitary weight in intact female rats.

No information is available regarding the effect of MAP on the pituitary level of growth hormone although the existence of such an influence is suggested by the high plasma levels observed in diabetic patients receiving MAP (19). The enlargement and increased relative number of growth hormone cells observed by us indicate that at least the concentration of growth hormone in hypophyses of female rats is increased by MAP. Both Wolfe (20) and Herlant (21) reported acidophils to be more numerous after treatment of female rats with progesterone.

Information on the action of progestins on

the gonadotropin content of the hypophysis is inconclusive. In general, progesterone has little effect (22) although treatment for a few days may increase the LH content (23). Administration of MAP to immature female rats for 5 weeks causes a decline in both the concentration and total amount of LH in the gland (24). The capacity of MAP to suppress pituitary secretion of at least a part of the gonadotropic complex is clearly indicated by the marked fall in ovarian and uterine weights. The variable alteration in structure of gonadotropic cells observed here does not permit a close correlation with reported changes in gonadotropin content. However, the cytological modifications seem to resemble those reported by Herlant and Ectors (25) in hypophyses of sows treated with MAP.

Because MAP causes adrenocortical atrophy in rats and reduces pituitary corticotropin content (26) the absence of regressive changes in corticotropic cells is unexpected. An explanation is not apparent although Holub, Katz, and Jailer (26) found that MAP can induce some adrenocortical atrophy independently of pituitary mediation. Corticotropic cells are small in normal rats and more intensive inhibition may be required to elicit cytological evidence of suppression; loss of staining capacity does follow prolonged treatment with cortisol (10).

Summary. Treatment of adult female rats with medroxyprogesterone acetate caused a marked reduction in size of prolactin cells. Growth hormone cells were enlarged and increased in relative number. Gonadotropic cells responded variably: in some rats certain of them were enlarged and more intensely stained. Corticotropic cells were not affected significantly.

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