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The effects of bromocriptine and prolactin on porphyrin biosynthesis in the *Harderian gland* of the male hamster, *Mesocritecus auratus*

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Abstract. Porphyrin biosynthesis was examined in the Harderian gland of the male golden hamster by fluorometric assays of gland porphyrin content and by measuring the activity of a rate-limiting enzyme for haem biosynthesis, 5-aminolaevulinic acid synthase. Both porphyrin content and enzyme activity are low in normal male glands but were greatly raised in males castrated for 6 weeks. However, porphyrin synthesis remained at basal levels in castrates given the dopamine agonist bromocriptine; this suppression could be reversed by simultaneous prolactin administration, and castrated males receiving prolactin alone exhibited very high enzyme activity and porphyrin content. Bromocriptine also prevents the morphological feminisation of the Harderian gland which would normally occur after castration; again, the simultaneous administration of prolactin permits feminisation to occur. The results support the hypothesis that, while androgens have an inhibitory effect on porphyrin synthesis within this model, other factors, including prolactin, are permissive.

Key words: Porphyrin – Harderian gland – Bromocriptine – Prolactin – Hamster, *Mesocritecus*

Introduction

Many human disorders of porphyrin production (the porphyrias) appear to be under hormonal control in that they are rare before puberty, are commoner in women than in men, and attacks are exacerbated by hormone changes which occur during the menstrual cycle, during pregnancy, or when taking oral contraceptives (Moore et al. 1987). Experimental laboratory models of porphyrin overproduction are often unsatisfactory in that they must be pharmacologically induced by drugs such as allylisopropyl acetamide (Marks 1983; Sweeney 1985; Moore and Disler 1988). However, the rodent Harderian gland (particularly that of the golden hamster) may provide a useful physiological model in that porphyrin production is far higher than in tissues such as liver or kidney, and there are sex differences in, and hormonal control of, porphyrin synthesis (Payne 1990; Payne et al. 1992; Spike et al. 1992). Thus, while the male hamster Harderian gland has a limited capacity for porphyrin biosynthesis under normal conditions, castration leads to greatly increased production which can be suppressed by the simultaneous administration of androgens (Hoffman 1971; Clabough and Norvell 1973; Payne et al. 1977). The female gland has an extremely high capacity for porphyrin biosynthesis which can be reduced by ovariectomy (Spike et al. 1986) and severely reduced by androgen administration (Sun and Nadakavukaren 1980; Spike et al. 1985).

Androgens thus appear to act as primary inhibitors of porphyrin synthesis within this gland. However, recent studies suggest that other factors may be involved. In particular, if castrated males are given the dopamine agonist bromocriptine which inhibits prolactin secretion, the expected rise in porphyrin content within the gland does not occur (Buzzell et al. 1989). Furthermore, procedures likely to result in hyperprolactinaemia increased the expected post-castrational rise in gland porphyrin content (Buzzell et al. 1992). These studies do not give complete insight into the phenomenon since they have been restricted to measuring gland porphyrin content (much of which is in the form of static, stored deposits) without examining the activity of the enzymes of porphyrin synthesis, and they have not established that the simultaneous administration of prolactin can counteract the effects of bromocriptine, nor whether prolactin administration can augment porphyrin synthesis when administered alone. This is important because other trophic hormones may also affect Harderian gland activity, including thyroid hormones and gonadotrophins (Buzzell and Menendez-Pelaez 1992; Rodriguez et al. 1992; Webb

Abbreviations: ALA, 5-aminolaevulinic acid; ALA-s, 5-aminolaevulinate synthase; GH, growth hormone

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et al. 1992), which could in turn be controlled by dopaminergic systems (Foord et al. 1983; Dieguez et al. 1984; Kuljis and Advis 1989). Also, no examination was made of gland histology and ultrastructure, both of which alter according to the gland's capacity to synthesise porphyrins (Payne et al. 1992; Payne 1994). The present study was undertaken to clarify these points.

Materials and methods

The animals used were 31 adult male golden hamsters (*Mesocritecus auratus*, Waterhouse) of closed colony laboratory stock established in the Anatomy Department of Glasgow University in 1968. The following groups were examined: 1) Untreated (control) males ($n=8$); 2) Males bilaterally castrated for 6 weeks ($n=8$); 3) Males bilaterally castrated for 6 weeks and receiving bromocriptine ($n=6$); 4) Males bilaterally castrated for 6 weeks and receiving bromocriptine + prolactin ($n=5$); 5) Males bilaterally castrated for 6 weeks and receiving prolactin ($n=4$).

In the case of animals receiving bromocriptine (group 3), this was administered continuously by osmotic mini-pumps (Alzet Model 2002) implanted under the skin of the back. Each was filled with 0.2 ml propylene glycol containing 14 mg 2-bromo-α-ergocriptine methanesulphonate (Sigma), resulting in a daily dose of 1 mg; pumps were replaced every 2 weeks. Where bromocriptine-treated castrates also received prolactin ($n=5$), the latter was also administered by osmotic mini-pump containing 0.2 ml saline containing 2.8 mg of sheep pituitary gland prolactin (Sigma); this resulted in each animal receiving some 0.2 mg per day (6 IU).

At the end of the treatment period, each animal was killed with an overdose of pentobarbitone sodium and exsanguinated by transcardiac perfusion for 1 min with mammalian Ringer plus lignocaine. One Harderian gland was removed and divided into two portions. One portion was used for assaying the porphyrin content of the gland, the other for determining the activity of the rate-limiting enzyme for porphyrin biosynthesis, ALA-s. ALA-s activity was measured by a modification of the method of Fitzsimmons et al. (1986) adapted to tissue homogenates. Whole Harderian glands were homogenised in incubator buffer and the uptake of ^{14}C from succinate to ALA after HPLC separation was measured radiochemically. Protein content of the homogenate was determined colourimetrically by BioRad Protein assay (Bio-Rad, Richmond, Calif., USA) and the results expressed as nmol ALA synthesised per hour per gram of protein. Tissue porphyrin content was measured on gland homogenates by the method of Spike et al. (1986b).

The empty orbit was pressure packed with tissue paper and plasticene and the animal subsequently perfused with 500 ml 3% buffered glutaraldehyde. Following this, the second Harderian gland was removed and divided into two portions, one which was processed for light microscopy, and a portion which was processed for transmission electron microscopy. Light microscopic measurements were made to determine (1) the percentage of tubule profiles containing at least one Type II cell, (2) the percentage of epithelial cells which were Type II cells using a grid intersection method, and (3) the number of mast cells per mm^2 of section. Electron microscopic measurements were made on photomontages of three complete tubule profiles per animal to determine (4) the number of polytubular complexes per μm^2.

Type II cells and polytubular complexes are typical of the male gland which has a low rate of porphyrin synthesis; the highly productive female gland does not possess Type II cells or polytubular complexes, but possesses some 40 times more mast cells than the male gland (Payne et al. 1982).

The porphyrin content, ALA-s activity, frequency of Type II cells and polytubular complexes in the Harderian glands of the control and treatment groups were compared by one-way analysis of variance (F). Where these proved significant, individual intergroup comparisons were made using confidence intervals (Statgraphics; Statistical Graphics Corporation).

Results

Porphyrin biosynthesis within the Harderian glands

Intact (control) males possessed very little porphyrin within the Harderian gland and had low ALA-s activity. Conversely, males castrated for 6 weeks had considerably elevated synthesis. However, if castrated males received bromocriptine they showed no such rise. The simultaneous administration of prolactin to the bromocriptine-treated castrates resulted in significantly higher porphyrin levels and enzyme activity. Finally, castrated males treated with prolactin alone showed the highest rise in porphyrin levels, and animals so treated had porphyrin levels significantly higher than any other group (Table 1).

Morphological changes

Type II cells typical of the male gland are reduced after castration to negligible numbers. This decrease is not only prevented by bromocriptine, but castrates treated with this dopamine agonist possessed significantly more Type II cells than normal males. The expected fall in Type II cell numbers does occur if bromocriptine-treated castrates are simultaneously treated with prolactin, and occurs in animals treated with prolactin alone. Similar changes also occur in polytubular complexes which decrease in castrates, are preserved with bromocriptine treatment, but decrease in castrated males given both bromocriptine and prolactin, and in mast cells which increase in number in castrates, do not increase in bromocriptine-treated castrates, but increase in bromocriptine-treated castrates which also receive prolactin (Table 2 and Fig. 1a–d).

Discussion

The results confirm those previously reported (Woolley and Worley 1954; Hoffman 1971; Spike et al. 1990; Payne

Table 1. The porphyrin content (nmol · g tissue^{-1}) and the activity of the rate-limiting enzyme for porphyrin synthesis 5-amino-laevulinate synthase (ALA-s) (nmol ALA formed · h^{-1} · g protein^{-1}) in the Harderian glands of untreated male hamsters (control), in males castrated for six weeks (cast), and in males castrates for six weeks and treated with bromocriptine (cast + bro), bromocriptine plus prolactin (cast + bro + pro) or prolactin alone (cast + pro).

	n	content	Porphyrin	activity	ALA-s
control	8	78 ± 11	*	337 ± 69	*
cast + bro	6	104 ± 10	*	405 ± 83	*
cast + bro + pro	5	408 ± 55	*	2108 ± 861	*
cast	8	728 ± 73	*	2059 ± 22	*
cast + pro	4	1355 ± 255	*	2510 ± 4	*
F		$P<0.001$		$P<0.001$	

See text for details

All figures are means ± SEM. Groups are significant different ($P<0.05$) if their asterisks are not in vertical alignment

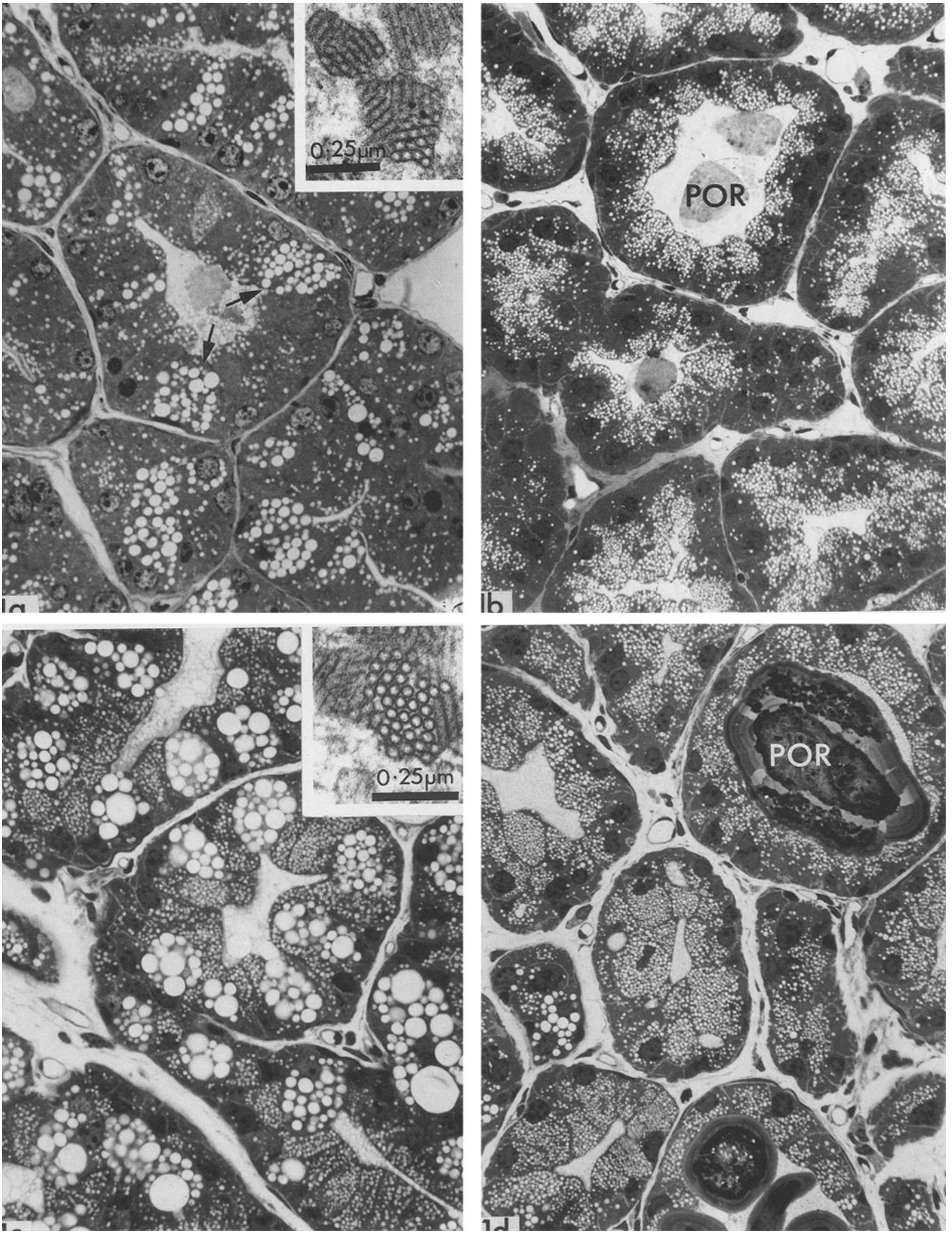
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Table 2. The frequency of tubules containing Type II cells, the frequency of Type II cells, the frequency of polytubular complexes (*ptc*) per unit area and the frequency of mast cells per unit area in intact control male hamsters (con), in males castrated for six weeks (cast), in males castrated for 6 weeks and receiving the dopamine agonist bromocriptine (+bro), in castrated males receiving both bromocriptine and prolactin (+bro+pro) and in castrated males receiving prolactin alone (+pro)

		Type II cells		*ptc*	Mast cells
		(% tubs)	(% cells)		
con	8	86.2 ± 5.8	35.8 ±2.6	0.96 ± 0.22	0.35 ±0.09
cast	8	1.0* ± 0.5	0.3* ±0.2	0.18* ± 0.13	3.27* ±0.77
cast+bro	6	100	62.2* ±2.5	1.07 ±0.11	1.10 ±0.31
cast+bro+pro	5	63.2 ±22.5	10.6* ±4.5	0.02* ±0.01	2.95* ±0.68
cast+pro	4	0*	0*	0.01* ±0.01	2.59* ±0.60
F		<0.001	<0.001	<0.001	<0.001

For details of regimens, see text
All figures are means ± SEM
* Differs from control, $P<0.05$

et al. 1992) that castration of the male golden hamster leads to a substantial rise in both porphyrin content and the activity of ALA-s within the Harderian gland. Furthermore, feminisation of gland structure occurs, with a loss of Type II cells and polytubular complexes, and an increase in mast cell numbers. Previous studies have shown that both the post-castrational rise in porphyrin biosynthesis and gland feminisation are prevented by androgens; furthermore, androgen administration to females reduces porphyrin biosynthesis and masculinises gland histology and ultrastructure. Androgens have therefore been proposed as a primary inhibitory control factor for porphyrin biosynthesis in this model (Payne et al. 1977, 1992; Spike et al. 1985).

However, it is clear from both the present study and previous work (Buzzell et al. 1989, 1992) that the dopamine agonist bromocriptine can suppress the expected rise in porphyrin content in castrates. The porphyrin content of the Harderian gland consists not only of newly-synthesised intracellular material, but also of stored intraluminal porphyrin which may represent synthesis over a period of time (Payne et al. 1992); therefore, low porphyrin values are difficult to interpret since they could be due to a failure of the storage mechanism. However, the finding in the present study that ALA-s activity is also suppressed in bromocriptine-treated castrates confirms the potent effect of this dopamine agonist on porphyrin synthesis. The present study also demonstrates for the first time that post-castrational gland feminisation is also prevented by bromocriptine.

Fig. 1. a A section through the Harderian gland of an intact male hamster. The tubules have both Type I cells (with numerous small lipid vacuoles) and Type II cells (with very large lipid vacuoles, *arrowed*). All cells possess numerous polytubular complexes within the cytoplasm (*inset*), ×400 (inset ×52000 *bar*=0.25 μm). **b** Section through the Harderian gland of a castrated male hamster. Type II cells and polytubular complexes are both lacking. Porphyrin accretions (*POR*) are present in the lumen, ×400. **c** Section through the Harderian gland of a castrated male hamster receiving the dopamine agonist bromocriptine, Type II cells are supra-abundant and polytubular complexes (*inset*) occur within the cytoplasm. ×400 (inset ×64000; *bar*=0.25 μm). **d** Section through the Harderian gland of a castrated male hamster receiving both the dopamine agonist bromocriptine and prolactin, Type II cells are few and polytubular complexes are lacking, Porphyrin accretions (*POR*) are present. ×400

It is conceivable that bromocriptine has a direct effect upon the Harderian gland. For example, bromocriptine could reduce free calcium (Elsholtz et al. 1991) necessary for exocytosis, or the availability of acetylcholine (Cummings 1991) necessary for myoepithelial cell contraction, both of which could interfere with porphyrin secretion mechanisms. Alternatively, stimulation of D2 receptors by bromocriptine could alter cAMP levels and thus affect a variety of enzymatic and synthetic activities (Swennen and Denef 1982; Schettini et al. 1983; Arunakaren et al. 1990; Elsholtz et al. 1991). Whether the Harderian gland possesses D1/D2 receptors is not known.

It is perhaps more reasonable to consider that bromocriptine might act by interfering with the hypothalamo-pituitary axis, where dopaminergic neurons control several neuroendocrine systems (Andersson and Eneroth 1987). These include the release of growth hormone (Cronin et al. 1984; Lindstrom and Ohlsson 1987), ACTH (Gudelsky et al. 1989), thyroid-stimulating hormone (Andersson and Eneroth 1987; Foord et al. 1983; Dieguez et al. 1984), α-melanocyte-stimulating hormone (Goudreau et al. 1992) or even luteinising hormone (Kuljis and Advis 1989). Some of these mechanisms could readily affect the structure and activity of the Harderian gland by altering thyroid hormones (Hoffman et al. 1989, 1990; Buzzell and Menendez-Pelaez 1992; Rodriguez et al. 1992) or gonadotrophins (Menendez-Pelaez et al. 1992). Similarly, bromocriptine could affect a mediator such as somatostatin which has been found in the Harderian gland (Aguilera and Catt 1984; Puig-Domingo et al. 1988).

Dopamine is a well established inhibitor of prolactin release (Swennen and Denef 1982; Foord et al. 1983; Ben-Jonathan 1985; Lambert and McLeod 1990). In the present study, prolactin administration was clearly shown to reverse the suppressive effects of bromocriptine and can increase porphyrin biosynthesis in castrated males when administered alone. These effects can be demonstrated on both porphyrin content and the activity of the rate-limiting enzyme ALA-s. The fact that bromocriptine and prolactin administration also have profound but opposite effects on gland morphology is of considerable interest. It has been postulated (Payne et al. 1992) that there is a morphological gland type which cannot synthesise porphyrins except at a low rate (viz. a gland possessing Type II cells and polytubular complexes) and a type which can synthesise them at a high rate

(viz. a gland lacking Type II cells and polytubular complexes and possessing mast cells). It remains unclear whether the biochemical characteristics depend upon cell ultrastructure, or vice versa.

The effect of prolactin on the Harderian gland in other species is uncertain. In the rat, while hypophysectomy altered acid phosphatase, α-mannosidase and β-glucuronidase activities, neither bromocriptine nor prolactin treatment had effects on lysosomal enzymes and it was suggested that GH might be a more important control (Vaughan et al. 1988).

It is clear from the present study that prolactin can increase porphyrin biosynthesis in castrated males when administered alone and will counteract the suppressive effects of bromocriptine. These effects can be demonstrated on both porphyrin content and the activity of the rate-limiting enzyme ALA-s. This suggests that the effects of bromocriptine reported by Buzzell et al. (1989) are probably manifested through prolactin inhibition and, if so, that prolactin may be as important an excitatory influence on gland biosynthesis as androgens are an inhibitory one. It remains to be demonstrated whether the Harderian gland possesses prolactin receptors.

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