

Effects of Experimentally Induced Hyperprolactinemia on the Hypothalamus, Pituitary, and Testes in the Golden Hamster

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Hyperprolactinemia was induced in adult male golden hamsters by transplantation of four homologous pituitaries under the renal capsules. The resulting elevation of plasma prolactin (PRL) levels was accompanied by a dramatic increase in the concentration of FSH in peripheral plasma. In contrast, plasma LH levels were not affected. The content and concentration of testicular LH receptors, testicular weight, and plasma testosterone levels were significantly greater in hyperprolactinemic hamsters than in the sham-operated control animals. Experimentally induced hyperprolactinemia was associated also with an increase in the hypothalamic content of LHRH and norepinephrine, while the dopamine level in the hypothalamus was not affected. Furthermore, hyperprolactinemia appeared to have increased the release of LH and FSH from the incubated hemipituitaries in the presence and in the absence of LHRH, but only release of LH under basal conditions was significantly affected. The authors conclude from these observations that experimentally induced hyperprolactinemia stimulates testicular function in the golden hamster by increasing the release of endogenous FSH and by increasing the number of LH receptors in the testes. Comparison of these findings with the results of similar experiments in rats and mice suggests that the number of testicular LH receptors can be profoundly influenced by chronic changes in plasma levels of both LH and PRL and that PRL can stimulate LH binding only when LH levels are reduced or unaltered.

Key words: hyperprolactinemia, hypothalamus, pituitary, testis, prolactin, follicle-stimulating hormone, norepinephrine, testosterone, dopamine, luteinizing hormone releasing hormone.

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Pathologic elevation of peripheral prolactin (PRL) levels (hyperprolactinemia) in men is frequently associated with hypogonadism and disturbances in sexual function ranging from reduced libido to complete impotence (Buvat et al, 1978; Thorner and Besser, 1978). In experimental animals, hyperprolactinemia can be produced by transplanting, under the kidney capsules, several pituitary glands from other animals (Chen et al, 1970; Bartke et al, 1977). Using this procedure, the authors have demonstrated that induction of hyperprolactinemia in male rats and mice significantly suppresses copulatory behavior without altering testicular weight or plasma testosterone concentrations (Svare et al, 1979; Doherty et al, 1981). Plasma LH concentrations are reduced in hyperprolactinemic rats (Bartke et al, 1977; Svare et al, 1979) and increased in hyperprolactinemic mice (Klemcke and Bartke, 1981), and maintenance of normal testosterone levels appears to be due to compensatory changes in testicular LH binding.

In contrast to these findings, transplantation of four ectopic pituitary glands in male hamsters produced a significant increase in testicular weight without affecting copulatory behavior or plasma LH levels. The present study was undertaken in an attempt to elucidate the mechanisms

responsible for these unexpected effects of hyperprolactinemia in male hamsters. The authors have examined the effects of hyperprolactinemia on plasma LH, FSH, and testosterone concentrations; on testicular LH binding and testosterone production *in vitro*; on hypothalamic norepinephrine, dopamine, and LHRH levels; and on the responsiveness of the adenohypophysis to LHRH *in vitro*.

Materials and Methods

Animals

Adult golden (Syrian) hamsters, Lak:LVG(SYR), were obtained from Charles River Lakeview and housed throughout this study in a room with controlled illumination (14 hours light:10 hours dark) and temperature (23.5 ± 1 C), with constant access to food (Wayne Breeder Blox) and water. Adult females were sacrificed, and their pituitaries were removed. Nine males were grafted with two pituitaries under each kidney capsule, for a total of four ectopic pituitaries per recipient, while nine animals were sham-operated and served as controls. Blood samples were withdrawn by cardiac puncture under light ether anesthesia two and six weeks after surgery, and plasma was saved for measurements of LH and FSH levels. Eight weeks after surgery, the animals were decapitated without the use of anesthesia. Trunk blood was collected for measurements of PRL, LH, FSH, and testosterone levels. The brain was immediately removed and frozen on dry ice for subsequent dissection of the hypothalamus and measurement of dopamine, norepinephrine, and LHRH levels. The anterior pituitary was removed, bisected, and used for studies of gonadotropin release *in vitro*. The testes were removed, weighed, and decapsulated. One testis was used for determination of hCG (LH) binding, while another was cut in half and used for determination of basal and hCG-stimulated testosterone release *in vitro*. The weight of the seminal vesicles, together with coagulating glands, and the adrenal glands was also determined.

Pituitary Incubations

Pituitary halves were preincubated in 1 ml of Medium-199. After 30 minutes of preincubation, the medium was removed and discarded, and 2.0 ml of fresh medium or medium containing 5×10^{-7} M LHRH (Beckman Lot #B90448) was added. The incubation tubes were placed in a Dubnoff Bath at 37 C, shaking at 60 cycles/minute, and were gassed with 95% O₂:5% CO₂. Two hours later, the incubation was terminated, at which time the pituitary halves were weighed and the media frozen for subsequent determination of hormone content.

Testicular Incubations

Testicular tissue was incubated for 4 hours in Krebs Ringer bicarbonate buffer containing glucose (1 mg/ml) in an atmosphere of 95% O₂:5% CO₂ in a Dubnoff met-

abolic shaker at a temperature of 32 ± 1 C (Dufau et al, 1971; Klemcke and Bartke, 1981). Half of each testis was incubated with 12.5 mIU hCG per ml and the other half, without hCG. Concentration of testosterone in the incubation media was measured by radioimmunoassay as described below.

Measurements of Hormones

The concentrations of LH, FSH, and PRL were measured using ovine:ovine LH radioimmunoassay and NIAMDD rat FSH and rat PRL kits, as described previously (Bex et al, 1978; Bartke et al, 1981). These procedures have been validated for measurement of gonadotropins and PRL in the golden hamster (Goldman and Porter, 1970; Bast and Greenwald, 1974; Bex et al, 1978). The results were expressed in terms of NIAMDD rat LH and FSH reference preparations RP-1 and arbitrary units of PRL, equal to the amount of PRL in 1 μ l of pooled lactating hamster serum. Testosterone levels were measured by radioimmunoassay without chromatographic separation of testosterone and dihydrotestosterone, since hamster testes produce negligible amounts of the latter steroid (Lau et al, 1978; Ewing et al, 1979).

Dissection of the Hypothalamus; Measurements of Catecholamines and LHRH

Within four hours after sacrificing the animals and freezing their brains, the tissues were partially thawed, and the hypothalamus was dissected free. The hypothalamus consisted of a tissue block 2.5 mm deep, extending from the rostral border of the optic chiasm to the rostral margin of the mammillary bodies and laterally to the hypothalamic sulci. The tissue blocks were weighed and sonicated in 0.4 N perchloric acid containing 10^{-3} M sodium bisulfite. The tissue blocks did not differ in weight between the sham-operated and grafted hamsters (28.9 ± 2.0 mg vs. 29.8 ± 1.9 mg). An internal standard, dl-alpha-methyldopamine, was added to each sample and to the assay standard to estimate procedural losses. Catecholamines were absorbed onto activated alumina and were extracted and separated by high-pressure liquid chromatography using electrochemical detection, according to the method of Keller et al (1976). Norepinephrine and dopamine standards were run with each group of samples, and catecholamine contents were calculated by comparing peak heights. Values were corrected for the percent recovery of the internal standard, which averaged $84.5 \pm 1.8\%$. The intra-assay variation was 3.1%, and the interassay variation was 3.4%.

Aliquots of the hypothalamic homogenates used for catecholamine determinations were neutralized with NaOH and further diluted in assay buffer for determination of LHRH content by radioimmunoassay, as previously described (Siler-Khodr and Khodr, 1979).

Measurements of Testicular hCG Binding

Preparation of testes for binding studies and techniques for measurement of Iodine-125 (¹²⁵I)-hCG binding to unoccupied binding sites were previously re-

ported (Bex et al, 1978; Klemcke et al, 1981). Briefly, testicular tissue was homogenized in phosphate-buffered saline (PBS), and the homogenate was centrifuged at $100 \times g$ for 5 minutes. The supernatant was then removed and recentrifuged at $1786 \times g$ for 20 minutes at 4 C. After being washed, the pellet was resuspended in PBS and served as the source of hCG-binding sites. Binding of hCG (CR-121), previously iodinated via a chloramine-T procedure and purified on a concanavalin A-Sepharose column, was measured in triplicate by addition of 100- μ l (20 mg tissue) aliquots of these testicular preparations to saturating quantities of 125 I-hCG. Nonspecific binding was measured in duplicate in the presence of 100 I.U. hCG (Ayerst). Incubations were conducted at 23 C for 20 hours. The specific activity of iodinated hCG was determined by self-displacement in a radioligand receptor assay. This hCG binding assay has been validated for hamster testes with respect to saturability, tissue and hormone specificity, and linearity with increasing tissue concentrations (Klemcke et al, 1981).

Statistical Analysis

For measurements of LHRH, adenohipophyseal hormones, and testosterone, all samples were processed in the same assay. The significance of differences between the means was determined by t test.

Results

Transplantation of four pituitaries produced the expected increase in plasma PRL concentrations (Table 1). This induced hyperprolactinemia was associated with significant increases in weights of testes and seminal vesicles (weighed together with their secretions) and significant reductions in body weight and adrenal weight. The weight of the *in situ* pituitary was not affected. There was a fivefold increase in plasma FSH levels two weeks

after pituitary transplantation. Six and eight weeks after surgery, the concentration of FSH in the plasma of hyperprolactinemic animals remained elevated, but the difference between the groups was less pronounced due to a gradual increase in FSH levels in sham-operated controls. The apparent slight suppression of plasma LH levels in pituitary-grafted hamsters was not significant.

Eight weeks after surgery, concentration and total content of testicular hCG (LH) receptors were significantly increased in hyperprolactinemic hamsters (Table 2). Plasma testosterone levels were also increased in pituitary-grafted males. However, the apparent difference between control and hyperprolactinemic animals in the amount of testosterone produced *in vitro* under basal conditions was not significant. In the presence of hCG, the testes of control and hyperprolactinemic animals produced identical amounts of testosterone.

Hyperprolactinemia was associated with a significant increase in the concentrations of LHRH and norepinephrine in the hypothalamus, while dopamine concentrations were comparable in the two groups (Table 3). Addition of LHRH to incubations of pituitaries from control and pituitary-grafted hamsters caused significant stimulation of the release of LH ($P < 0.05$ by paired t test), but not of FSH. Under both basal and LHRH-stimulated conditions, pituitaries of hyperprolactinemic hamsters appeared to have released considerably more LH and FSH than did the pituitaries of control males, but only the difference in basal LH release was statistically significant.

TABLE 1. Effects of Four Ecotopic Pituitary Homografts on the Weight of the Testes, Seminal Vesicles, and Adrenals and on Plasma Concentrations of PRL, LH, and FSH in Adult Male Golden Hamsters*

	Sham	Grafts	P
Body weight (g)	140 \pm 6.3	118 \pm 4.1	.025
Testes weight (mg)	2836 \pm 126	3317 \pm 87	.01
Seminal vesicle weight (full) (mg)	1887 \pm 61	2212 \pm 97	.025
Seminal vesicle weight (empty) (mg)	278 \pm 24	321 \pm 18	N.S.
Adrenal weight (mg)	28.2 \pm 1.5	24.3 \pm 0.9	.05
Pituitary weight (mg)	2.01 \pm 0.15	2.26 \pm 0.10	N.S.
PRL (after 8 weeks) (units/ml)	50 \pm 18	751 \pm 112	.001
LH (after 2 weeks) (ng/ml)	51 \pm 7.5	35 \pm 8.9	N.S.
LH (after 6 weeks) (ng/ml)	44 \pm 8.1	39 \pm 6.2	N.S.
LH (after 8 weeks) (ng/ml)	41 \pm 5.8	35 \pm 6.6	N.S.
FSH (after 2 weeks) (ng/ml)	62 \pm 5.5	294 \pm 28.9	.001
FSH (after 6 weeks) (ng/ml)	84 \pm 12.2	255 \pm 22.7	.001
FSH (after 8 weeks) (ng/ml)	130 \pm 15.8	325 \pm 32.5	.001

* Means \pm SE.

TABLE 2. Effects of Four Ectopic Pituitary Homografts on Plasma Testosterone, Testicular hCG (LH) Binding, and Responsiveness to hCG *in vitro* in Adult Male Golden Hamsters*

	Sham	Grafts	P
Plasma Testosterone (ng/ml)	4.73 ± 0.55	8.81 ± 1.59	.025
Fmoles hCG bound/mg protein	4.36 ± 0.77	17.24 ± 1.93	.001
Fmoles hCG bound/2 testes	158 ± 30	688 ± 71	.001
Basal testosterone production <i>in vitro</i> (ng/g testis)	28 ± 5	39 ± 10	N.S.
hCG-stimulated testosterone production <i>in vitro</i> (ng/g testis)	74 ± 16	74 ± 6	N.S.

* Means ± SE.

Discussion

The present results provide evidence that testicular function of adult gonadally active hamsters can be significantly stimulated by transplantation of four pituitaries under the renal capsules. The authors have already reported that a single pituitary transplant can increase both testicular weight and plasma testosterone levels in this species and that four transplants increase testicular weight (Bartke et al, 1980). Effects of ectopic pituitaries on plasma hormone levels in hypophysectomized hamsters (Bartke et al, 1980), in hamsters with short photoperiod-induced testicular regression (Bex et al, 1978), and in hamsters with anterolateral hypothalamic deafferentation (Bartke and Carillo, 1981) indicate that transplanted pituitary tissue secretes copious amounts of PRL, but little, if any, LH, FSH, or GH. Thus, all effects of pituitary transplants are almost certainly due to the induction of hyperprolactinemia.

The mechanisms responsible for the changes in gonadotropin release in hyperprolactinemic hamsters are difficult to identify from the present results. The significant increase in the concentration of LHRH in the hypothalamus of hyperprolactinemic hamsters could reflect either an increase in

LHRH synthesis or an inhibition of LHRH release. Hodson et al (1980) interpreted an increase in hypothalamic content of LHRH in hyperprolactinemic rats as evidence for reduced LHRH release. However, in hyperprolactinemic rats, peripheral LH and FSH levels are either unaffected or significantly reduced (Bartke et al, 1977; Sharpe and McNeilly, 1979; Hodson et al, 1980), while in hyperprolactinemic hamsters, plasma LH levels were unaltered, and plasma FSH levels were substantially increased. Moreover, the basal rate of release of LH from incubated pituitaries was significantly increased in hyperprolactinemic hamsters. The differential effects of pituitary grafts on the release of LH and FSH *in vivo* and some of the differences between the release of gonadotropins *in vivo* and *in vitro* could be related to the ability of PRL to suppress pulses of LH release (McNeilly, 1980) or to the ability of androgens to increase the ratio of FSH to LH released by the pituitary (Denef et al, 1980). However, pituitary grafts have been shown to increase plasma FSH without altering plasma LH in castrated male hamsters (Bartke et al, 1981). The latter observation argues against the possibility that the increase in plasma FSH levels in hyperprolactinemic hamsters

TABLE 3. Effects of Four Ectopic Pituitary Homografts on Hypothalamic LHRH, Dopamine (DA), and Norepinephrine (NE) Levels and on the Release of LH and FSH During 2-Hour Incubation of Adenohypophyseal Tissue*

	Sham	Grafts	P
Hypothalamic LHRH (pg/hypothalamus)	827 ± 73	1067 ± 44	.02
Hypothalamic DA (ng/g)	435 ± 42	490 ± 22	N.S.
Hypothalamic NE (ng/g)	1528 ± 75	1812 ± 47	.01
LH release <i>in vitro</i> basal (ng/mg)	4310 ± 557	6945 ± 929	.025
after LHRH (ng/mg)	6323 ± 1260	9142 ± 1135	N.S.
FSH release <i>in vitro</i> basal (ng/mg)	83 ± 16	207 ± 54	N.S. (0.053)
after LHRH (ng/mg)	139 ± 45	237 ± 44	N.S.

* Means ± SE.

was due to suppression of inhibin production by the testis. However, it should be emphasized that results obtained in the rat and in the human indicate that hyperprolactinemia suppresses, rather than stimulates, LHRH release. The significant increase in plasma FSH levels in hyperprolactinemic hamsters in the present study provides further evidence for the ability of PRL to cause stimulation of FSH synthesis and release in this species (Bartke et al, 1981). The ability of PRL to affect the concentration of FSH, but not of LH, in the plasma of male hamsters could be interpreted also in terms of the possible existence of separate hypothalamic releasing factors for LH and for FSH and of differential effects of PRL on their synthesis or release. The authors have no explanation for the gradual increase in plasma FSH levels throughout this study. However, it is unlikely to be related to the stress of bleeding, since repeated collection of blood samples by cardiac puncture does not affect the normal pattern of changes in plasma FSH during testicular regression and spontaneous recrudescence in short photoperiod (Bartke and Siler-Khodr, unpublished observations). The effects of experimentally induced hyperprolactinemia on hypothalamic catecholamine levels observed in the present study were also unexpected. In the rat and mouse, PRL can elevate dopamine; in the mouse, it suppresses norepinephrine levels in the hypothalamus (Gudelsky et al, 1976; Morgan and Bartke, 1981). In the hamster, dopamine levels or turnover were not affected, and norepinephrine levels were increased. It is conceivable that elevation of peripheral testosterone levels may have counteracted the stimulatory effect of PRL on hypothalamic dopaminergic neurons (Kalra et al, 1981).

Maintenance of normal peripheral LH levels and a dramatic increase in testicular hCG (LH) binding in hyperprolactinemic hamsters in the present study can probably account for the significant in-

creases in plasma testosterone levels. However, the responsiveness of the testes to one dose of hCG *in vitro* was not affected. Alternately, the increase in peripheral testosterone levels *in vivo* may have been due to the increase in testicular mass. The significant increase in testes weight and in seminal vesicle weight is fully consistent with increased levels of testosterone, FSH, and PRL in the peripheral circulation.

Changes in body weight and in adrenal weight in hyperprolactinemic animals deserve a brief comment. The authors have previously reported that suppression of PRL release in adult male hamsters by bromocriptine or by exposure to a short photoperiod is often associated with an increase in body weight and that these changes can be prevented by a single pituitary graft. The present findings in animals with four transplants indicate that body weight of adult gonadally active male hamsters can be reduced by either an increase in plasma PRL levels or by PRL-induced stimulation of testicular function. The significant reduction in the absolute weight of the adrenals in pituitary-engrafted hamsters was unexpected, since hyperprolactinemia causes a very marked stimulation of adrenal weight in both rats and mice. Relative adrenal weight was nearly identical in hyperprolactinemic and sham-operated control hamsters.

Endocrine findings in hyperprolactinemic male hamsters are substantially different from those previously reported for rats and mice given identical treatment (Bartke et al, 1977; Svare et al, 1979; Klemcke and Bartke, 1981). The authors believe that the comparison of results obtained in these three species of rodents (Table 4) may offer some insight into the regulation of testicular LH binding *in vivo*. Although PRL has been shown to increase the concentration of testicular LH receptors in the rat (Aragona et al, 1977), the mouse (Bohnet and Friesen, 1976), and the hamster (Bex and Bartke, 1977; Bex et al, 1978), chronic hyperprolactinemia increases LH binding in rats and hamsters but reduces it in mice. Since plasma LH levels are increased by hyperprolactinemia only in the latter species, it is believed that increased LH release can counteract the effects of PRL on testicular LH binding. This conclusion is strengthened by the observation that the number of LH binding sites is not depleted by four pituitary grafts in hypophysectomized mice (Klemcke and Bartke, unpublished observations) and that, in mildly hypop-

TABLE 4. Endocrine Responses of Rats, Mice, and Hamsters to Hyperprolactinemia Induced by Transplantation of Four Pituitaries*

	Rats†	Mice‡	Hamsters
Plasma FSH	Reduced	Increased	Increased
Plasma LH	Reduced	Increased	Unchanged
LH receptors	Increased	Reduced	Increased
Plasma testosterone	Unchanged	Unchanged	Increased
Testicular weight	Unchanged	Unchanged	Increased

* All effects listed in this table are statistically significant.

† Data from Bartke et al, 1977, and Sharpe and McNeilly, 1979.

‡ Data from Klemcke and Bartke, 1981.

drogenic C57BL/10J mice, plasma LH levels are reduced and testicular LH binding is increased (Amador and Bartke, unpublished observations). It appears that chronic changes in plasma LH levels can cause reciprocal changes in testicular LH binding and that PRL can increase the number of LH receptors in the testis only if peripheral LH levels are suppressed or unchanged.

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