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# Does hyperprolactinemia affect hepatic regeneration independent of sex steroids?

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## Abstract

Prolactin, administered exogenously, has been shown to be trophic to the liver, causing increases in the liver weight–to–body weight ratio, in ornithine decarboxylase activity, and in thymidine kinase activity. To investigate the effect of endogenous hyperprolactinemia on hepatic regeneration, pituitary isografts were placed beneath the renal capsule in rats 2 weeks before the rats underwent a two-thirds partial hepatectomy. Prolactin levels 2 weeks after the transplant were greater in the animals with the pituitary isografts compared with levels in controls. The increase in the liver weight–to–body weight ratio after hepatectomy was similar in the rats with pituitary transplant and the controls. However, chronic hyperprolactinemia was associated with increased basal levels of ornithine decarboxylase activity and thymidine kinase activity. Both ornithine decarboxylase activity and thymidine kinase activity increased after partial hepatectomy, and the magnitude of the changes was similar for both groups of animals. The levels of estrogen receptor activity before the partial hepatectomy and the reduction in receptor activity that follows partial hepatectomy were similar in the two groups of animals. Moreover, the levels of androgen receptor activity within the liver before partial hepatectomy and the increase in receptor activity after hepatectomy were similar in the two groups of animals. Thus, chronic sustained hyperprolactinemia has no beneficial effect on the hepatic regenerative response, despite induction of both basal ornithine decarboxylase and thymidine kinase activities.

The mammalian liver responds to injury with a hepatic regenerative response that occurs rapidly and at a rate that exceeds that experienced by most embryonic and malignant tissues.[1,2] The origin and nature of the factors that initiate and terminate this regenerative response remain unknown.[3] Many studies have suggested that the liver may be the source of at least one of the factors that initiate hepatic regeneration.[4–8] Thus, extracts from the regenerating liver have been shown to stimulate liver growth, whereas extracts prepared from intact livers either inhibit or have no effect on liver growth.

Prolactin receptors are known to exist in the liver, and transiently increased levels of prolactin have been shown to increase the activity of ornithine decarboxylase, a key enzyme in the biosynthesis of polyamines present in the liver, which is considered to be the initiation site for subsequent hepatic regeneration.[9–13] An increase in the hepatic activity of thymidine kinase, the rate-limiting enzyme for DNA synthesis, has been seen also in response to a transient prolactin exposure.[12] In several studies, prolactin has been reported to act as a trophic factor, causing an increase in the liver weight–to–body weight ratio and producing a hepatic hyper-

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plastic response.[14,15] Moreover, prolactin administration to dwarf mutant mice reverses both the growth retardation and the liver atrophy present in such animals. [16]

Recent studies have indicated that the growth-promoting effects of prolactin, in organs like the pigeon crop-sac, involve both direct and indirect actions of prolactin. [17] Thus, the growth-promoting effects of prolactin on the liver also may involve both direct and indirect effects, inasmuch as extracts prepared from the regenerating liver are known to stimulate hepatic growth in the absence of prolactin.[4–8]

Prolactin levels are known to be increased in individuals with cirrhosis, particularly individuals with portal systemic encephalopathy.[18] This endogenous hyperprolactinemia is thought to occur on a central basis as a result of the accumulation of false neurotransmitters that modulate prolactin secretion. This endogenous hyperprolactinemia may actually be advantageous to individuals with cirrhosis and may enhance hepatocellular regeneration, thereby maintaining hepatic function despite advanced disease. Therefore, attempts to correct the hyperprolactinemia in such cases may be disadvantageous, particularly in cases with far-advanced disease.

All studies that have examined the effect of prolactin on the regenerative response of the liver have involved the administration of exogenous hormone to intact animals. In the present study we have investigated the effect of endogenous hyperprolactinemia, such as that which occurs in cases of advanced disease with portal systemic encephalopathy, produced by pituitary isografts, on the hepatic regenerative response that follows a 70% partial hepatectomy in female rats.

## METHODS

### Animals and chemicals

Adult female inbred Wistar rats weighing 150 to 250 gm were purchased from Harlan Sprague-Dawley, Indianapolis, Ind. Carbon 14–labeled ornithine (57.6 mCi/mmol), tritiated estradiol (99 Ci/ml), R1881 (87 Ci/mmol), and unlabeled R1881 were purchased from DuPont NEN Medical Products, North Billerica, Mass. Tritiated thymidine (5 ml/mmol) and ACS scintillation fluid were obtained from Amersham Corp., Arlington Heights, III. Absolute ethanol and DEAE cellulose paper were purchased from U.S. Industrial Chemical Co., Tuscola, III., and BioRad, Richmond, Calif., respectively. Sigma Chemical Co, St. Louis, was the source for the unlabeled ornithine, pyridoxal phosphate, Tris base, diethylstilbestrol, adenosine triphosphate, sodium molybdate, nicotinamide adenine dinucleotide, calf thymus DNA, and bovine serum albumin. All other chemicals were obtained from Fisher Chemical Co., Pittsburgh, Pa.

### Surgical procedures

The rats were randomly allocated to either of two groups, the experimental group or the control group. Pituitary transplantation in the experimental rats was accomplished via a right loin incision exposing the right kidney and the insertion under the renal capsule of two pituitary glands obtained from two donor animals. The pituitary isografts were maintained in position by closing the renal capsule with 5.0 chromic catgut. The animals in the control group underwent an identical sham procedure during which the renal capsule was opened and closed with 5.0 chromic catgut without the insertion of two pituitary glands. Two weeks later both experimental and control groups of rats underwent a standard two-thirds partial hepatectomy as described previously by Higgins and Anderson.[19] All surgical procedures were performed under light ether anesthesia between 9 and 11 AM to eliminate any effect of diurnal variations on the hepatic regenerative response.

At various times up to 48 hours after partial hepatectomy, animals from both the experimental and control groups were bled for prolactin levels, anesthetized with ether, weighed, and killed. The livers were removed, weighed, and homogenized in 4 vol ice-cooled buffer consisting of 0.25 mol/L sucrose, 1.5 mmol/L EDTA, 10 mmol/L mercaptoethanol, and 10 mmol/L Tris-HCl (pH 7.4) with a Brinkmann Polytron homogenizer (Brinkmann Instruments Inc., Westbury, N.Y.). Hepatic cytosol was prepared by centrifugation at 103,000 *g* for 1 hour at 4° C. All cytosolic enzyme assays were performed immediately after preparation of the cytosol.

### Prolactin assay

The serum prolactin levels in the animals in the study were determined by radioimmunoassay with materials obtained from the National Hormone and Pituitary Program of the National Institutes of Health. All samples were assayed in a single assay to eliminate interassay variation. The sensitivity of the assay was 0.1 mg rat prolactin per tube. The intraassay and interassay coefficients of variation for this assay were 10% and 15%, respectively.

### Ornithine decarboxylase activity

Ornithine decarboxylase activity within the liver cytosol was determined by measuring the $^{14}CO_2$, released from labeled ornithine.[20] In brief, this assay consisted of the preincubation of 0.4 ml cytosol for 5 minutes at 37° C with a mixture containing 0.2 mmol/L pyridoxal phosphate, 5 mmol/L dithiothreitol, 1.5 mm L-ornithine in 10 mmol/L Tris-HCl (pH 8.0). Thereafter, 0.5 μCi L-$^{14}$C-D-L-ornithine was added to the mixture, and 250 μl ethanolamine–ethylene glycol (2: 1) was placed in the center well to act as a $CO_2$ trap. The assay flask was then sealed and incubated at 37° C for 1 hour. The reaction was terminated by the addition of 0.1 ml saturated trichloroacetic acid solution to the reaction mixture. The reaction flask was maintained at 37° C for an additional 1 hour, and the $CO_2$ trapping solution was then removed and placed into a glass scintillation vial containing 10 ml ACS scintillation fluid. The radioactivity present in the $CO_2$ trapping solution was measured in a liquid scintillation system (Tri-Carb 460 CD; Packard Instrument Co., Downers Grove, III).

### Thymidine kinase activity

Thymidine kinase activity within the liver cytosol was determined by measuring the in vitro conversion of thymidine to thymidine phosphate.[21] The reaction mixture contained 0.1 ml cytosol, 850 μl incubation buffer consisting of 5 mmol/L adenosine triphosphate and 3.6 mmol/L $MgCl_2$, in 50 mmol/L Tris-HCl (pH 8.0), and 50 μl of a μmol/L tritiated thymidine. The reaction was maintained at 37° C for 10 minutes and terminated by the immersion of the reaction vessel into boiling water for 2 minutes. After cooling in an ice bath, the denatured protein was removed by centrifugation at 1500 *g* for 5 minutes at 4° C. A 0.1 ml aliquot of the supernatant was then spotted on a 3.8 × 3.8 cm piece of DEAE cellulose paper. The paper was washed twice with 1 mmol/L ammonium formate for 5 minutes followed by distilled water for 3 minutes. Thereafter, the paper was placed in a glass scintillation vial, and the radioactivity was eluted into solution by the addition of 1 ml of a 0.1 mol/L HCl and 0.2 mol/L KCl mixture. After 15 minutes 10 ml ACS scintillation fluid was added to the vial, and the amount of radioactivity in the scintillation fluid was determined as described above for ornithine decarboxylase.

### Estrogen and androgen receptor assays

The activity of the cytosolic estrogen receptors in the liver was determined by measuring the specific binding of a saturating concentration of tritiated estradiol.[22] To stabilize the estrogen receptor, the hepatic cytosol was diluted 1: 1 with buffer consisting of 40 mmol/L sodium molybdate, 1.5 mmol/L EDTA, and 10 mmol/L Tris-HCl (pH 7.4). Total tritiated estradiol binding was measured by mixing 200 μl of the diluted cytosol with 25 μl of 30 nmol/L

radioactive steroid and 25 μl ethanol. Nonspecific binding was measured in a parallel assay in which the ethanol was replaced with 25 μl (3 μmol) unlabeled diethylstilbestrol dissolved in ethanol. All assays for estrogen receptor contained 1 μmol/L 2-methoxyestriol to block any contribution of a male-specific estrogen binder to total estrogen binding. The mixture was incubated for 2 hours at 4° C, and the reaction was terminated by the addition of 0.4 ml of 1% dextran-coated charcoal to remove any unbound steroid.[22] The mixture was then centrifuged for 5 minutes at 1500 *g* at 4° C, and the supernatant was transferred carefully to a scintillation vial containing 8 ml ACS scintillation fluid. The radioactivity present in the mixture was counted as described above.

The assay for cytosolic androgen receptor activity in the hepatic cytosol was similar in design to that described above for the cytosolic estrogen receptor assay, with the following differences.[23] Tritiated R1881, a synthetic androgen, was used as the radioactive ligand, and unlabeled R1881 was used in the assays for nonspecific binding. The binding of R1881 to glucocorticoid receptors was blocked by the addition of 5 μm triamcinolone acetonide to the androgen receptor assay mixture. The mixture was allowed to incubate overnight at 4° C, after which any excess steroid was removed with dextran-coated charcoal. After centrifugation at 1500 *g* for 5 minutes at 4° C, the resultant supernatant was decanted into a scintillation vial with 8 ml ACS scintillation fluid, and the radioactivity result in the supernatant was counted as previously described for the estrogen receptor assay.

### Miscellaneous methods

The method of Lowry et al.[24] was used to determine the cytosolic protein concentration, with bovine serum albumin being used as the standard.

### Statistical methods

All results are presented as mean values ± SEM. Statistical analysis of the data was performed by using Student's *t* test. A *p* value of less than 0.05 was used to identify a significant difference.

## RESULTS

The serum prolactin levels in the two groups of animals in the study are shown in Fig. 1. An approximately fourfold increase in prolactin levels above that of the controls was seen in the animals with pituitary grafts 2 weeks after pituitary transplantation. Prolactin levels increased further in the experimental group after partial hepatectomy but remained unchanged after partial hepatectomy in the sham-operated controls.

The rate of hepatic regrowth after a 70% partial hepatectomy is presented in Fig. 2. The liver weight–to–body weight ratio increased approximately twofold between 6 and 48 hours after partial hepatectomy in both groups. No statistical difference in the rate of hepatic growth between the two groups of rats was seen at any time point.

The chronic hyperprolactinemia present in the experimental group compared with the sham-operated control group was associated with an increased basal level of ornithine decarboxylase activity within the liver before partial hepatectomy, as shown in Fig. 3. After the 70% partial hepatectomy, a twofold to threefold increase in the activity of this enzymatic activity present in the hepatic cytosol was observed in both groups of animals. The peak activity after partial hepatectomy was observed at 6 hours in the control animals and at 24 hours in the animals with transplants. The ornithine decarboxylase activity at 24 hours after partial hepatectomy was similar in both groups of animals in the study.

The activity of thymidine kinase in the hepatic cytosol of the two groups of animals in the study is shown in Fig. 4. As was the case with the ornithine decarboxylase activity, the basal activity

present in the liver before the 70% partial hepatectomy was greater in the animals with the pituitary grafts than in the sham-operated controls ($p < 0.05$). After partial hepatectomy, a significant increase in thymidine kinase activity was seen within the liver in both groups of animals. Moreover, the magnitude of the induced change in thymidine kinase activity was similar for both groups of animals.

As presented in Fig. 5, the hepatic cytosolic estrogen receptor activity before the 70% partial hepatectomy was similar in the two groups of animals in the study, despite a fourfold increase in the basal prolactin level in the animals with the pituitary isografts. Partial hepatectomy was followed by a marked reduction in the cytosolic activity of the estrogen receptor in both groups, and as was the case with thymidine kinase, the magnitude of the response was similar for both groups of animals at each of the time points observed.

The level of androgen receptor activity was similar in the two groups of animals in the study before the partial hepatectomy (Fig. 6). A slight decrease in androgen receptor activity was observed initially at 6 hours, but by 24 hours a minimal increase in androgen receptor activity was seen in both groups of animals. At 48 hours after partial hepatectomy, the hepatic androgen receptor levels were no different from those observed before the hepatic resection.

## DISCUSSION

The results of the present study reveal that chronic sustained endogenous hyperprolactinemia induced by ectopic pituitary isografts does not influence the regenerative response observed in rats after partial hepatectomy, as has been reported to occur with the administration of exogenous prolactin, which produces only a transient hyperprolactinemia. Chronic sustained endogenous hyperprolactinemia did not modify the activity of hepatic estrogen and androgen cytosolic receptors seen either before or after a 70% partial hepatectomy.

Previous studies have suggested that the administration of exogenous prolactin enhances the hepatic regenerative response and may even be involved in the regulation of this unique hepatic response to injury. Specifically, the administration of exogenous prolactin has been shown to increase the liver weight–to–body weight ratio at various time points after partial hepatectomy and to produce hepatocyte hyperplasia in intact rats.[14] The administration of prolactin to animals has been shown also to significantly increase hepatic RNA synthesis[16] and to reverse the growth retardation and hepatic atrophy present in congenital dwarf mice.[15] Furthermore, the administration of exogenous prolactin has been coupled to the induction of activity of hepatic ornithine decarboxylase, an enzyme thought to initiate and regulate the regenerative response to injury.[11–13] With this background in mind, and recognizing that chronic sustained hyperprolactinemia occurs often in individuals with cirrhosis, particularly those with advanced disease with portal systemic encephalopathy, it appeared appropriate to investigate the effects of chronic sustained hyperprolactinemia on the regenerative response after partial hepatectomy.

Pituitary isografts, placed remote from the hypothalamus, are well known to be free of hypothalamic inhibitory factors that regulate prolactin secretion and to produce an excessive sustained secretion of endogenous prolactin.[25–28] In the present study, pituitary grafts, placed under the renal capsule, were used to produce a fourfold increase in basal prolactin levels. The regenerative response of the liver in response to a 70% partial hepatectomy was examined in animals with and without chronic sustained hyperprolactinemia.

Ornithine decarboxylase, the rate-limiting enzyme in polyamine synthesis (which is thought to play an essential role in proliferating tissues), and thymidine kinase (the enzyme that phosphorylates thymidine before it is incorporated into DNA during DNA synthesis) were used as biochemical indices of hepatic regeneration.

The results of these studies clearly demonstrate that chronic sustained hyperprolactinemia does not influence the hepatic regenerative response seen after partial hepatectomy in the rat. This finding was unexpected, because prolactin is known to induce ornithine decarboxylase,[11–13] and the level of this enzyme within the liver of the animals in the study that had hyperprolactinemia was higher ($p < 0.05$) (Fig. 3) than it was in the control rats that did not have hyperprolactinemia. These results wre unexpected also, because the thymidine kinase activity present in the liver of the animals with the pituitary isografts before partial hepatectomy was greater ($p < 0.05$) (Fig. 4) than that seen in the control animals without pituitary isografts. These results are important in that they suggest that treatment of chronic portal systemic encephalopathy directed at correcting the endogenous hyperprolactinemia seen in this condition probably does not have an untoward effect on the hepatocellular regenerative response, which may be crucial for the maintenance of adequate hepatic function.

Prolactin receptors are well known to be induced by estrogen administration.[29] Moreover, estradiol levels increase after major hepatic resection in humans and animals.[23] In addition, hyperprolactinemia has been shown to induce adrenal androgen production, and both estrogens and androgens have been reported to act as either inducers or modifiers of the hepatic regenerative response to a variety of stimuli.[23] However, despite these findings, chronic sustained hyperprolactinemia, as produced in these studies, did not affect the hepatic regenerative response.

The liver of the male rat loses many of its male-specific characteristics during the regeneration that occurs after partial hepatectomy.[23] An increase in serum estradiol levels and total hepatic estrogen receptor activity and a reduction in serum testosterone levels and hepatic androgen receptor activity are known to occur after partial hepatectomy both in male rats and in humans, and these may be linked somehow to the observed hepatic regenerative response.[23] Although the total hepatic estrogen receptor level increases after a partial hepatectomy, the cytosolic estrogen receptor activity is reduced as the estradiol receptor shifts from a cytosolic location to the nucleus. It is this transfer of the cytosolic estrogen receptor to the hepatic nucleus that is thought to play an initiating role in the regulation of liver regeneration.[23]

It was anticipated that sustained hyperprolactinemia might alter the androgen-estrogen balance of the animals, both in terms of the two major sex hormones and their levels in serum and in terms of their receptor activities in sex steroid–responsive tissues, particularly the liver, and thereby might affect the rate of hepatic growth occurring after a 70% hepatectomy in a positive direction. However, the chronic sustained hyperprolactinemia produced in these studies had no effect on the activity of hepatic estrogen and androgen receptors, either before or after the partial hepatectomy stimulus. As a result, the changes in hepatic estrogen and androgen receptor activity observed after partial hepatectomy were comparable to those described previously in normal animals.[23]

In the absence of a change in the activity of hepatic cytosolic sex steroid receptors, chronic sustained hyperprolactinemia has no beneficial effect on the hepatic regenerative response, despite basal inductions of both ornithine decarboxylase and thymidine kinase activities within the liver, which would have been expected to have primed the liver to undergo a regenerative response. These data further suggest an important regulatory role for sex steroids, and particularly for their receptor activities and variation within the hepatocyte, on the hepatic regenerative response that follows hepatic injury.

## Acknowledgments

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## Abbreviations

| | |
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| **ACS** | aqueous counting solution |
| **DEAE** | diethylaminoethyl |
| **EDTA** | ethylene-diaminetetraacetic acid |
| **Tris** | *tris*-(hydroxymethyl)-aminomethane |

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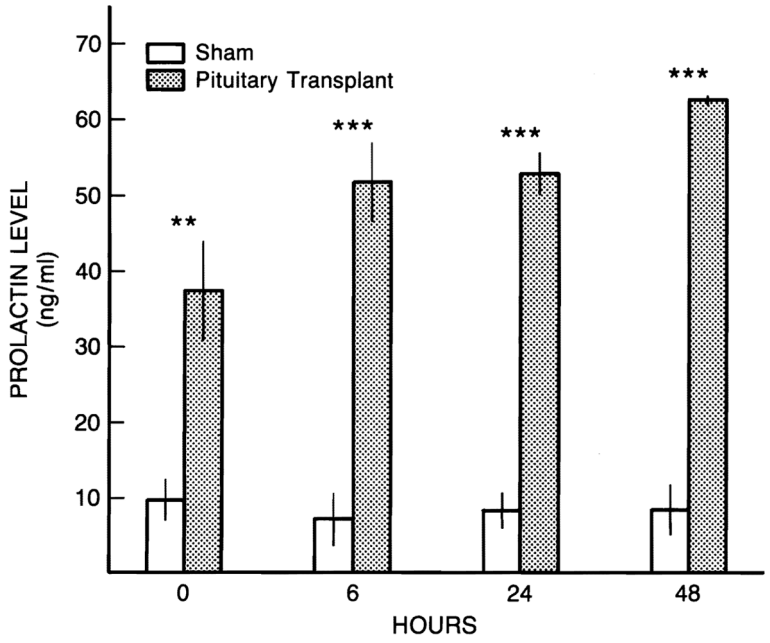


**Fig. 1.**

Plasma prolactin levels after partial hepatectomy in rats with pituitary isografts (pituitary transplant plus partial hepatectomy) and in control animals (sham transplant plus partial hepatectomy), mean ± SEM. ** $p < 0.01$. *** $p < 0.001$.

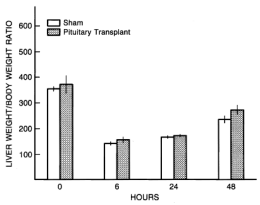


**Fig. 2.**

Changes in liver weight–to–body ratio after partial hepatectomy in animals with pituitary transplant (pituitary transplant plus partial hepatectomy) and control animals (sham transplant plus partial hepatectomy), mean ± SEM.

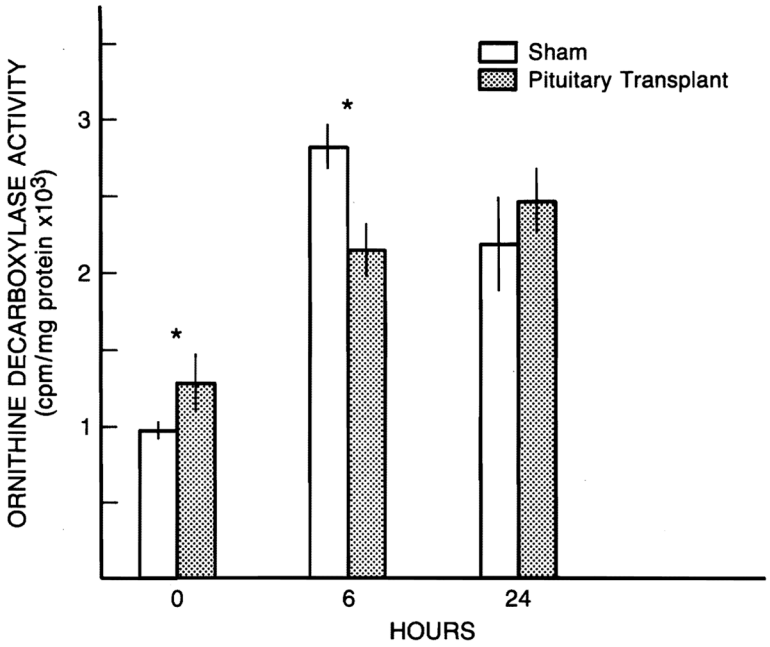


**Fig. 3.**

Ornithine decarboxylase activity (counts per minute per milligram of protein) after partial hepatectomy in animals with pituitary transplant (pituitary transplant plus partial hepatectomy) and control animals (sham transplant plus partial hepatectomy), mean ± SEM. * $p < 0.05$.

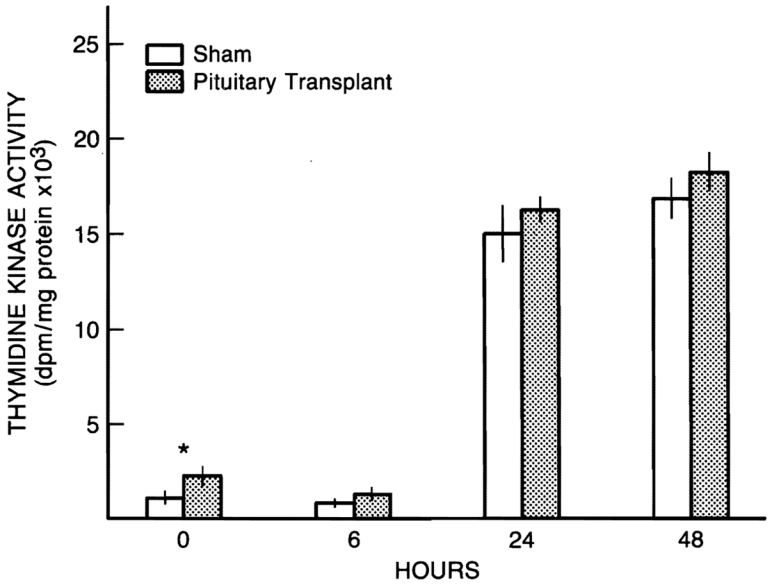


**Fig. 4.**

Thymidine kinase activity (disintegrations per minute per milligram of protein) after partial hepatectomy in animals with pituitary transplant (pituitary transplant plus partial hepatectomy) and control animals (sham transplant plus partial hepatectomy), mean ± SEM. * $p$ value < 0.05.

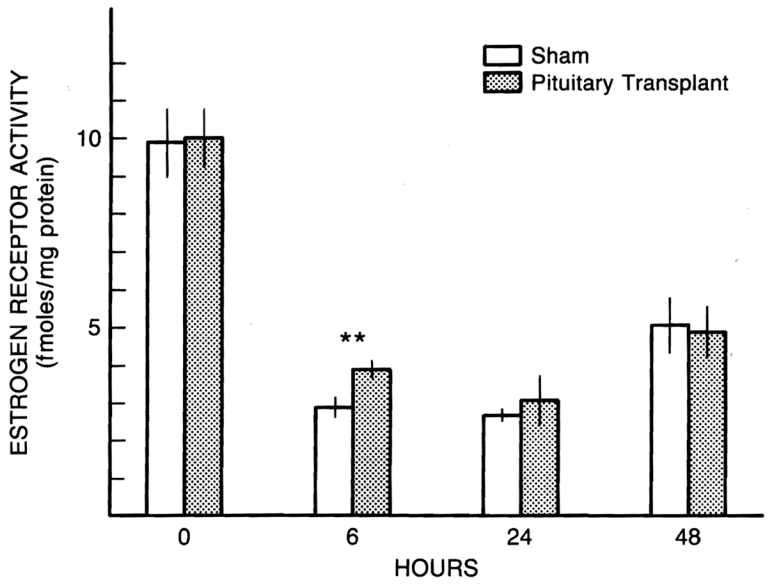


**Fig. 5.**

Changes in hepatic estrogen receptor level after partial hepatectomy in animals with pituitary transplant (pituitary transplant plus partial hepatectomy) and control animals (sham transplant plus partial hepatectomy), mean ± SEM. ** $p < 0.01$.

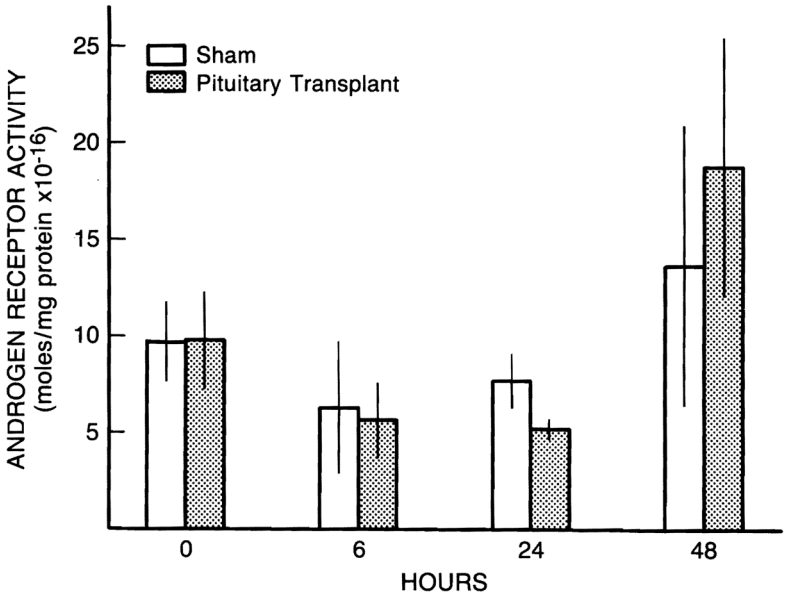


**Fig. 6.**

Changes in hepatic androgen receptor level after partial hepatectomy in animals with pituitary transplant (pituitary transplant plus partial hepatectomy) and control animals (sham transplant plus partial hepatectomy), mean ± SEM.