Use of DES-Treated Rats as an Animal Model for Assessment of Pituitary Adenoma Imaging Agents

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Prolactin (PRL) secreting pituitary adenomas are the most common type of pituitary tumors. An imaging agent which specifically localized in prolactinomas would be of considerable clinical value for both initial detection and also for monitoring the effects of dopamine agonist therapy. Tritiated spiroperidol (^{3}HSp) was selected for initial evaluation as a possible imaging agent based on: (1) demonstrated localization in the pituitary and (2) demonstrated binding to human PRL-secreting tumor tissue. DES was implanted in Fischer F344 rats and induced prolactinoma formation was evidenced by increased pituitary weight, elevated serum PRL levels and by an increase in the proportion of PRL-secreting cells in the pituitary. ^{3}HSp concentrations in pituitary and other tissues of DES-treated rats were assessed in female rats and correlation studies showed that a 5-fold increase in serum PRL was associated with a 6-fold increase in both pituitary weight and % dose/organ accumulation of ^{3}HSp. The number of pituitary D_2 receptors per mg of protein in tissue homogenates was similar in both normal and DES-treated females. A blocking study with (+)-butaclamol demonstrated a D_2 receptor-mediated component to ^{3}HSp localization. In summary, an animal model for prolactinoma was characterized. An assessment of ^{3}HSp accumulation indicates that radiolabelled spiroperidol shows excellent potential for detecting PRL-secreting tumors of the pituitary.

Introduction

Prolactin (PRL) secreting pituitary adenomas are the most common type of pituitary tumors. The high incidence of these tumors only became apparent within the past 9–10 years as a result of the development and general availability of a radioimmunoassay for measurement of PRL in serum.[1,2] These tumors are common in females who usually present with galactorrhea, amenorrhea or infertility although other local effects such as visual disturbances from compression of the optic chiasma may be evident. It is now recognized that approximately 20–25% of all women with amenorrhea have prolactinomas.[3,4]

The detection of prolactinomas currently depends on physical symptoms, elevated serum PRL levels and abnormal CT scans of the sella turcica. However, other disorders such as pituitary cysts may present with both elevated serum PRL and abnormal CT scans.[5] Not only have surgically confirmed prolactinomas been found in patients with normal CT scans and with elevated serum PRL,[6–8] but abnormal CT scans have a predictive value of only 22% for pituitary tumors in patients with no clinical history of pituitary disease.[9] CT scans do not functionally characterize tumors but merely indicate density changes which are presumed to reflect the presence of a tumor. Thus, diagnosis may be imprecise and often rests on the association of an elevated serum PRL level with a possible CT scan abnormality.

Prolactinomas have been demonstrated using [^{99m}Tc]pertechnetate.[10,11] However, [^{99m}Tc]pertechnetate does not functionally characterize tumors but reflects increased vascularization and vascular permeability associated with tumor presence. Nuclear magnetic resonance (MR) has recently been evaluated for pituitary tumor imaging[12,13] but MR also does not functionally characterize tumor type.

Thus, an imaging agent which specifically localizes

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in prolactinomas based on some functional characteristic of the tumor would be of considerable clinical value. Positive imaging of these tumors would enable a definite diagnosis of PRL-secreting adenoma to be made and this would represent an improvement over existing CT scans. Earlier detection may be possible and the effects of medical therapy (e.g. bromocriptine) on functional status and tumor size could be monitored in a serial manner.

Prolactin secretion appears to be largely under dopamine control. Dopamine, which is secreted into the hypophyseal portal blood, may inhibit PRL secretion by binding to receptors in the pituitary.[14] The anterior pituitary is thought to contain exclusively postsynaptic D_2 receptors.[15,16] Studies indicate that most human prolactinomas have intact dopamine receptor sites on the PRL-producing cells.[17–19] There are contrasting reports regarding the numbers of receptor sites in human prolactinomas. One study by Cronin et al. using spiroperidol found increased numbers of binding sites[18] while Bression and colleagues using ^{3}H-domperidone report decreased numbers.[19] Further quantification studies using a uniform receptor concentration assay are necessary to clarify this point. Regardless, the increase in PRL-secreting cells (mammotrophs) in prolactinomas coupled with the presence of dopamine receptors capable of binding ^{3}H-neuroleptics[15] raises the possibility of receptor-mediated imaging of these tumors with a radiolabelled D_2 receptor antagonist.

Development of a suitable imaging agent depends not only on the synthesis of an appropriate radiopharmaceutical but on the availability of an animal tumor model with characteristics similar to human prolactinomas. A recent publication has shown that implantation of diethylstilbestrol (DES) in Fischer F344 rats resulted in the induction of PRL-secreting hyperplasia/tumor of pituitary tissue in almost all animals within 8–12 weeks after implantation.[20] Treatment with estradiol had no effect on the affinity of the dopamine receptor for spiroperidol[21] but the effect of estrogens on the number of dopamine receptors in the rat pituitary is uncertain and has been reported to remain constant[21] or to be reduced by approximately 50%.[22] The presence of functioning pituitary dopamine receptors together with elevated serum PRL levels suggests that the DES-treated F344 rat is a suitable animal model for the assessment of potential imaging agents for prolactinomas.

As we have previously reported on the uptake of ^{3}HSp in the normal pituitary of Fischer F344 rats[23] and as ^{3}HSp binding to human PRL-secreting tumor tissue has been demonstrated,[18] we evaluated ^{3}HSp in the DES-induced prolactinoma model rats. The concentration and retention of spiroperidol or its analogs in any pituitary tumor have not been determined.

Thus, we have studied (1) the time course of ^{3}HSp activity in tissues of DES-treated female F344 rats, (2) the effect of (+)-butaclamol on ^{3}HSp pituitary concentration, (3) the number of D_2 receptors in normal and DES-treated female rat pituitary, and (4) the correlations between ^{3}HSp concentration in the pituitary, serum prolactin levels and percent and number of PRL-producing cells in pituitary tissue of male and female rats treated with DES.

Materials and Methods

The following compounds or reagents were obtained from commercial sources: ^{3}H-spiroperidol (25–30 Ci/mmol) (New England Nuclear), diethylstilbestrol (Aldrich Chemical Co.) avidin–biotin peroxidase complex (Vector Laboratory), diaminobenzidine hydrochloride, pargyline (Sigma Chemical Co.) (+)-butaclamol hydrochloride (Research Biochemicals Inc.). Dow Corning Silastic tubing and silicone adhesive type A were obtained commercially, as were the scintillation fluids used in counting, Ox-triti-scint (Romac) for tissue samples and ACS (Amersham) for binding assays.

Polyclonal antiserum to rat prolactin was obtained from the NIADDK. The NIADDK Pituitary Hormone Distribution Program supplied materials and protocols for the double antibody RIA for rat prolactin.

Fischer F344 rats, male and female, were purchased (Charles River). Animals were exposed to alternating 12 h periods of light and dark and received rat chow and water ad libitum during the study.

Tumor model

Prolactin secreting adenomas were induced by implanting DES-containing Silastic tubing s.c. into 30 day old rats under ether anesthesia through a small incision in the back.[20] Control rats were implanted with empty Silastic tubing. The DES-implants were prepared as described except that 3/4 in. lengths of tubing were used and these were filled with 10 mg of DES. Both blank and DES-implants were soaked in 2% BSA solution for 24 h prior to implanting in the rats.

Immunohistochemical staining

The anterior and posterior pituitary lobes were removed separately and the anterior pituitary fixed in 3 mL of 10% formalin for 24 h at 23°C before being embedded in paraffin. Tissue sections were cut sagittally with a microtome (5 μm) and stained with hematoxylin and eosin. Other sections were stained for PRL by immunohistochemical methods.[24] After inhibiting endogenous peroxidase with 1% methanol–H_2O_2, tissues were washed in phosphate buffered saline (PBS), then treated with normal goat serum to suppress nonspecific binding for 30 min. Rat anti-PRL serum (produced in rabbits and used at 1:1000 dilution) was applied for 1 h at 23°C. The tissues were washed with PBS treated with 1:200 dilution of rabbit biotin-IgG made in goat for 30 min,

followed by PBS washes, then incubation with avidin–biotin peroxidase complex for 30 min. Diaminobenzidine (DAB) was used as the chromogen (10 mg DAB in 50 mL PBS, pH 7.2 and 0.001% H_2O_2) for 5 min.

Controls consisted of substituting normal rabbit serum for the primary antibody and absorbing each antibody with specific antigens for 24 h before performing the assay. Additional controls consisted of omitting biotin–IgG or avidin–biotin peroxidase complex. All of these controls resulted in no staining of the tissues. The number of cells staining positively for PRL was counted by systematically sampling the entire pituitary tissue using a 4 mm² grid in the microscope ocular. A minimum of 1000 cells per slide were counted and scored as negative or positive if a brown-black reaction product was present in the cytoplasm.

Serum prolactin assay

Serum PRL was determined for all rats, male and female, control and DES-treated, using a published radioimmunoassay procedure.[25]

D_2 receptor binding assay

Female Fischer F344 rats under ether anesthesia were killed by decapitation. Normals were 8 weeks of age; DES-treated were sacrificed 4 weeks after implant. The pituitaries were rapidly removed and washed free of blood in cold saline. The anterior lobes were separated and stored at −70°C until assayed. Pituitaries from both normal and DES-treated rats were assayed simultaneously. Tissue samples were homogenized at low speed with a Tekmar homogenizer using 30 vol of cold buffer (0.25 M sucrose, 15 mM Tris, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1 mM EDTA,[32] 2 μM pargyline, 0.1% ascorbate, pH 7.4, 25°C). The homogenate was centrifuged twice as described.[21] The final pellets were resuspended in Tris buffer (as above but omitting sucrose) and incubated for 10 min at 37°C. The homogenates were then assayed for protein content[26] and diluted with buffer to a final concentration of about 0.2 mg protein/100 μL.

For binding studies, 600 μL samples were prepared in triplicate as described by Cronin and Weiner.[27] Assays contained about 0.2 mg protein. Membrane bound ³HSp was separated by rapid filtration (<5 s) under vacuum over Schleicher & Schuell No. 34 glass fiber filters and washed with 3 × 4 mL cold Tris buffer. The filters were placed in scintillation vials and 3 mL scintillation fluid added. The samples were stored until translucent, then counted. All values were corrected for background.

Specific binding was defined as the total counts of ³HSp minus the counts obtained in the presence of 1000-fold excess of (+)-butaclamol (pharmacologically active form). Scatchard analysis was performed to determine the apparent dissociation constant K_D, and the maximal number of receptor sites, B_{max}, for both normal and DES-treated pituitary.

Tissue distribution studies

DES-treated. Female Fischer F344 rats were implanted with DES as described above and sacrificed 4 weeks later. Tissue distribution studies were performed as described[23] at 5 min and at 1 and 2 h post injection.

(+)-Butaclamol treated. Female rats implanted with DES were treated with (+)-butaclamol (2 mg/kg, $n = 6$, and 5 mg/kg, $n = 6$) 45 min prior to ³HSp injection (25 μCi). Tissue distribution studies were performed as described at $t = 1$ h post ³HSp injection.

Correlation studies

Protocol. Correlation studies were similarly performed on male and female rats. Thirty day old Fischer F344 rats (12 per group for each time period of 4 and 8 weeks) were implanted with blanks or DES. After 4 weeks for female rats, and after 4 and 8 weeks for male rats, the animals were separated into two groups of six animals and treated as follows. All animals were killed by decapitation, pituitaries removed and blood collected. Serum was kept frozen until use for PRL assay. The uteri of all female rats were removed, cleaned of fat, connective tissue and excess fluid and weighed. Six were treated as described above for tissue distribution studies. Six pituitaries were fixed for determination of the percentage of PRL-producing cells by immunohistochemical staining.

Results

Effects of DES treatment

The effects of DES on uterine and pituitary weight were determined. Uterine weight was 320 ± 60 mg for 10 mg DES implanted for 4 weeks. This is comparable to 250 mg reported for 4 weeks of treatment with 5 mg DES[20] As expected, pituitary weights also increased and are presented in Table 3. For both males and females, the 10 mg dosage of DES used resulted in higher pituitary weights than reported after 5 mg DES treatment.[20]

The induction of PRL-secreting tumor was verified by the increase in weight of the anterior pituitary, by the elevation of serum PRL levels and by an increase in the numbers of PRL-secreting cells. In both male and female rats, the increase in PRL-secreting cells was uniformly distributed in the anterior pituitary. Figures 1A and B are examples of pituitary tissue from normal and DES-treated female rats after immunohistochemical staining.

Time course in DES-treated rats

The concentration data of ³H-activity in various tissues from DES-treated rats is compiled in Table 1.

Table 1. ^{3}H-spiroperidol activity levels in DES-treated female rats[a,b]

	Time		
	5 min	1 h	2 h
Anterior pituitary	0.29' ± 0.046	0.321 ± 0.014	0.224 ± 0.035
Posterior pituitary	—[c]	0.220 ± 0.053	0.097 ± 0.029
Uterus	0.144 ± 0.017	0.123 ± 0.003	0.131 ± 0.016
Blood	0.026 ± 0.004	0.017 ± 0.002	0.021 ± 0.005

[a]$n = 3$, Fischer F344 rats sacrificed 4 weeks after 10 mg DES implant.
[b]Data as % kg dose/g, mean ± SEM.
[c]Posterior pituitary not adequately distinguishable from anterior pituitary for two of the rats.

Over a time span from 5 min to 2 h, the concentration in anterior and posterior pituitary, uterus and blood was approximately constant for both normal (data from Ref. 23) and DES-treated female rats. In DES-treated animals, anterior pituitary values were approximately 10 times that seen in other tissues.

The posterior pituitary could usually be visually distinguished from the anterior pituitary at 4 weeks after DES treatment in female rats. However, in female rats implanted with 10 mg DES and sacrificed 8 weeks later, the tumors of all rats ($n = 9$) appeared necrotic and hemorrhagic. Concentration data in such tumors is of questionable validity so further evaluation was not performed. The posterior pituitary could not be distinguished from anterior pituitary in these rats.

Butaclamol blocking study

DES-treated female rats were pretreated with two dosages of (+)-butaclamol—2 and 5 mg/kg. Results were similar for all tissues examined at both dosage levels and only percent kg dose/g values for 2 mg/kg are presented in Table 2.

D_2 receptor binding assay

Scatchard analysis of ^{3}HSp specific binding to

Table 2. ^{3}H-spiroperidol activity for (+)-butaclamol treated rats and percent reduction relative to controls[a,b]

Tissue	% kg dose/g	% Reduction[c]
Anterior pituitary	0.232 ± 0.014	28 ± 7
Posterior pituitary	0.238 ± 0.055	—
Uterus	0.079 ± 0.002	36 ± 4
Blood	0.016 ± 0.001	—

[a]$n = 6$, Fischer F344 rats implanted with 10 mg DES. Rats injected with (+)-butaclamol (2 mg/kg) 45 min prior to ^{3}HSp injection (25 µCi). Sacrifice at $t = 1$ h post ^{3}HSp injection.
[b]Data as % kg dose/g, mean ± SEM.
[c]Percent relative to % kg dose/g at $t = 1$ h for DES-treated rats (data in Table 1). Only statistical differences are listed.

anterior pituitary homogenates from normal and DES-treated female rats was performed. The apparent K_D is 0.15 ± 0.06 nM for normals and 0.19 ± 0.08 for DES-treated animals. The maximum number of D_2 receptor sites (B_{max}) was also similar for normal (71 ± 13 fmol/mg protein) and DES-treated rats (63 ± 11).

Correlation studies

The relationship between serum PRL levels and the percent of PRL-secreting cells present in control and DES-implanted male and female rats is presented in Table 3. The increase in serum PRL levels to

Table 3. Correlation between serum prolactin levels, anterior pituitary weights, percent prolactin secreting cells and ^{3}H-spiroperidol concentration at $t = 1$ h post injection[a]

		Male		Female	
		Control	DES	Control	DES
Serum prolactin	4 wk	93 ± 10	1170 ± 110	506 ± 139	2500 ± 199
(ng/mL)	8 wk	180 ± 27	3600 ± 340		
Anterior pituitary	4 wk	5.18 ± 0.37	21.1 ± 3.0	5.41 ± 0.75	33.81 ± 2.80
(mg)	8 wk	5.26 ± 0.3[b]	107 ± 17		
Percent prolactin	4 wk	14.4 ± 1.4	35.7 ± 2.2	32.3 ± 1.4	79.7 ± 1.0
secreting cells[c]	8 wk	15.2 ± 0.8[d]	46.4 ± 1.8[d]		
% kg dose/g					
Anterior pituitary	4 wk	0.219 ± 0.013	0.317 ± 0.008	0.363 ± 0.022	0.311 ± 0.140
Posterior pituitary	4 wk	0.081 ± 0.030[d]	0.182 ± 0.012	0.254 ± 0.038	0.220 ± 0.053
Anterior pituitary	8 wk	0.482 ± 0.084[b]	0.278 ± 0.014		
Posterior pituitary	8 wk	0.292 ± 0.095[b]			
% dose/organ					
Anterior pituitary	4 wk	0.008 ± 0.001	0.062 ± 0.008	0.016 ± 0.002	0.093 ± 0.010
Posterior pituitary	4 wk	0.002 ± 0.000	0.003 ± 0.006	0.002 ± 0.000	0.003 ± 0.000
Anterior pituitary	8 wk	0.011 ± 0.001[b]	0.218 ± 0.032		
Posterior pituitary	8 wk	0.002 ± 0.000			

[a]$n = 6$, Fischer F344 rats implanted at 30 days with 0.0 mg DES (control) and 10.0 mg DES, mean ± SEM.
[b]$n = 3$.
[c]Percent per minimum of 1000 cells counted.
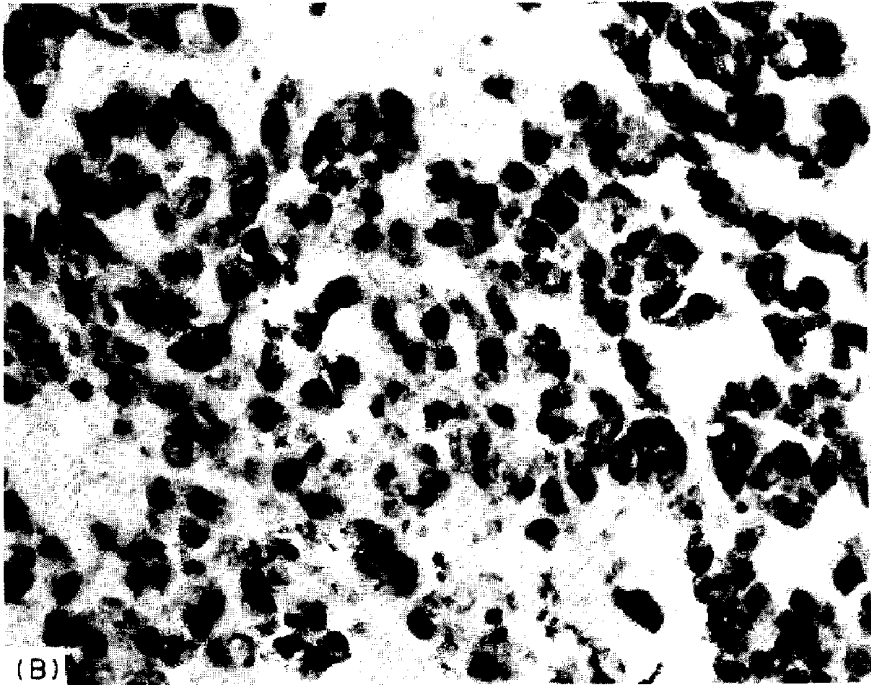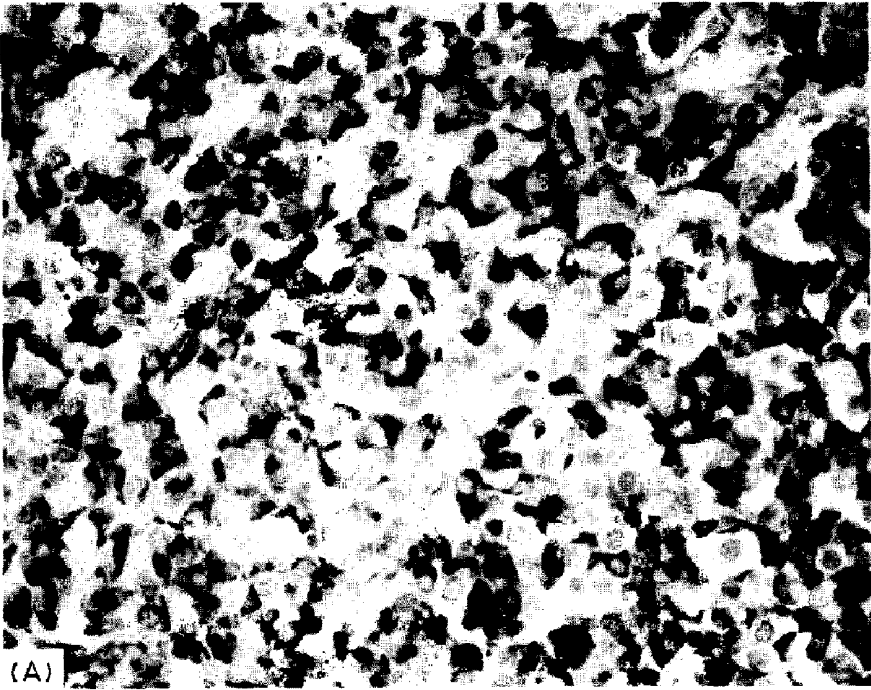[d]$n = 5$.

Fig. 1. (A) Normal anterior pituitary gland from a female rat stained for PRL by immunohistochemistry. A black reaction product is present in the cytoplasm of PRL-producing cells. (Immunoperoxidase × 330.) (B) Pituitary gland from DES-treated female rat stained for PRL by immunohistochemistry. Most of the tumor cells contain immunoreactive PRL. (Immunoperoxidase × 330.)

1170 ± 110 ng/mL for males and to 2500 ± 199 for females was associated with a 2.5 fold increase in the percent of PRL-secreting cells in the anterior pituitary of both male and female rats at 4 weeks. When placed in conjunction with increasing pituitary weight, this increase in percent of PRL-secreting cells corresponds to a 10 fold increase in the total number of PRL-secreting cells for males and a 15 fold increase for females. Male rats were also evaluated at 8 weeks as the pituitary tumors, in contrast to females at 8 weeks, were smaller, less vascularized and did not appear hemorrhagic (see *Time course in DES-treated rats* above).

The tissue concentrations of ³H-spiroperidol are also presented in Table 3. Concentration values are presented as % kg dose/g, the normalized tissue concentration, and as % dose/organ which reflects the fraction of the dose administered which localized in the anterior pituitary. In male rats a 10 fold increase in serum PRL level is associated with an 8 fold increase in the % dose/organ and a 4 fold increase in anterior pituitary weight. In female rats a 5 fold increase in serum PRL is associated with a 6 fold increase in % dose/organ and a 6 fold increase in anterior pituitary weight. Figure 2 shows the correlation between % dose/organ and serum PRL levels in male and female rats in graphic form.

The correlation between percent PRL cells with % dose/organ and % kg dose/g is also contained in Table 3. Percent dose/organ values in the posterior pituitary are minimally affected by treatment with DES (less than 2 fold increase) and are the same for male and female rats at all time intervals. Anterior pituitary values increased dramatically, as stated above. In sharp contrast to % dose/organ increases, the % kg dose/g values relative to control values remained approximately constant for males and females at 4 weeks and showed a 50% decrease in males at 8 weeks. It is interesting that the 6 fold increase in % dose/organ for females and the 8 fold increase for males correlate with a 2.5 fold increase in the percent of PRL-producing cells for both female and male rats.

Discussion

Time course in DES-treated rats

The dissociation constants of ³HSp from human anterior pituitary and from human PRL-secreting pituitary adenomas are similar [$K_D = 2.2 \pm 0.7$ and 3.1 ± 1.4 nM, respectively (mean ± SEM[18]]. The similarity in K_D suggests that the time course for ³HSp uptake by tumor tissue may be the same as in normal tissue. Comparison of data in Table 1 with data from normal rats (See Table 1 in Ref. 23) shows that ³HSp uptake appears to be constant from 5 min to 2 h in both normal and tumor pituitary tissue. Percent kg dose/g in anterior pituitary is a normalized value and reflects concentration of injected radioactivity/g tissue. The data suggest that although the pituitary weight has increased 6 fold due to tumor, the concentration/g tissue has remained approximately constant. Because of the similarity in data between normal and DES-tumor induced rats, further time intervals were not evaluated.

Butaclamol blocking study

As with the time course results, the data obtained from rats pretreated with butaclamol are experimentally equivalent for both control[23] and DES-induced tumor bearing rats. That is, the 28 ± 7% reduction observed in anterior pituitary is lower than that reported for cortex and striatum. The reduction
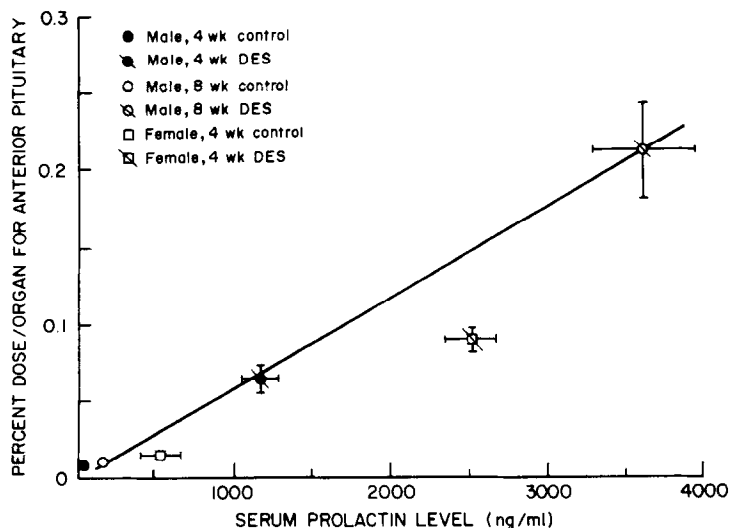

Fig. 2. Percent dose/organ vs serum prolactin level in male and female rats after treatment with DES and in controls. Sacrifice was at 1 h post injection. (Correlation factor $r = 0.9987$.)

in ^{3}HSp uptake is supportive that some concentration of ^{3}HSp is due to D_2 receptor specific binding.

D_2 receptor binding assay

The K_D value observed for normal rats is similar to that reported using F344 male anterior pituitary, 0.10 ± 0.04 nM[28] and other rat anterior pituitary tissue.[29-32] Likewise the apparent K_d for DES-treated pituitary is comparable to values reported for estradiol treated adult male F344 rats: 0.12 ± 0.02 and 0.15 ± 0.03 nM for 15 and 90 days of estradiol treatment, respectively.[28]

The B_{max} values reported here are similar to those reported for male F344 rats.[28] These data suggest that DES treatment did not significantly alter the observed B_{max} which is in agreement with data obtained using estrogen treated adult male F344 rats[28] and adult female Sprague–Dawley rats,[21,32] and contrasts with data obtained from female Wistar rats.[29] B_{max} determination is in terms of mg pituitary protein and does not include any correction for the percent of PRL-secreting cells (see following discussion).

Correlation study

When % dose/mg pituitary is calculated by dividing % dose/organ by anterior pituitary weight (data in Table 3), the value is 0.0024 ± 0.0005% dose/mg and is independent of sex or length of DES treatment. This similarity suggests that, although pituitary weight increased, the relative uptake/mg tissue has remained constant. If one assumes that ^{3}HSp localization in the pituitary is dependent on at least an initial complex formation with the D_2 receptor, then one might expect that the concentration of D_2 receptors/mg tissue has also remained constant. Data presented earlier in D_2 receptor assay show that the concentration of D_2 receptors in DES induced rat prolactinoma is approximately the same as in controls. Consideration of the D_2 receptor concentration in connection with the (for females) 15 fold increase in the number of PRL-secreting cells suggests that the number of D_2 receptors per PRL-secreting cell has been reduced. The relationship between increases in % dose/organ and increases in the number of PRL-secreting cells may also be interpreted as support for reduction of number of D_2 receptors per cell. For males, the number of PRL cells increase about 1.3 times faster than % dose/organ; for females, this rate of increase is about 2.7. Although the relationship differs for males and females, apparently uptake as % dose/organ is not directly correlated with increasing number of PRL cells.

In general terms, for both male and female rats at 4 weeks, increasing serum PRL levels were accompanied by increases in the percent and number of PRL-secreting cells and by increases in pituitary size. These increases correlate with increasing % dose/organ values. For males and females, there appear to be different rates of increase of % dose/organ (8 fold for males, 6 fold for females),

serum PRL (12 fold for males, 5 fold for females), and number of PRL-secreting cells (10 fold vs 15 fold).

Prolactinoma imaging assessment

The goal of the present work was to develop an animal model that could be used to screen radiotracers for their potential as mammotroph (prolactinoma) imaging agents. Based on the observed uptake in rats in DES induced prolactinomas and in normal tissue, radiolabelled spiroperidol shows excellent potential for detecting both PRL-secreting pituitary tumors and normal pituitary. Since the size of the pituitary in humans is at the resolution limit of various brain imaging instruments, early presence of a prolactinoma would need to be inferred from an uptake measurement which could best be performed using single photon tomography. In the DES-stimulated pituitary, both pituitary mass and density of PRL-secreting cells increased with the net effect of increasing the uptake per organ by a factor ranging from a low of 5.8 for female rats at 4 weeks to a high of 19.8 for males at 8 weeks. It is highly likely that increases of this magnitude will lie well outside the normal variation for humans and could be detected even at count rates ranging from 12 to 70 cpm predicted in a worst case analysis of a hypothetical normal pituitary.[23] Since the pituitary is below the brain and since it is surrounded by bone, imaging the pituitary will be similar to imaging a point source in background. One can therefore expect good results in uptake measurements.

Future efforts will use this model and a series of other radiolabelled D_2 agonists and antagonists. In other studies, attempts will be made to induce pituitary adenomas in larger animals to permit direct scintigraphy evaluations.

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