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HYPOPHYSECTOMY MAY NON-SELECTIVELY ALTER PHARMACOKINETIC PARAMETERS TO ENHANCE THE ABILITY OF HALOPERIDOL TO INCREASE STRIATAL DOPAMINE RECEPTOR DENSITY IN THE RAT

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Abstract—We have investigated the effect of a range of doses of haloperidol (0.625–5.0 mg/kg/day) or saline, administered for 14 days, followed by a 3 day drug washout period, to sham operated or hypophysectomized rats. Haloperidol increased the number of specific striatal ^{3}H-spiperone binding sites (B_{max}) in sham-operated animals at doses of 2.5 and 5.0 mg/kg/day, and in hypophysectomized animals at all doses used (0.625–5.0 mg/kg/day). The inhibition of locomotor activity produced by haloperidol was greater in hypophysectomized than sham-operated animals. Plasma and striatal haloperidol levels after equivalent doses were greater in hypophysectomized than in sham-operated animals. We conclude that hypophysectomy may enhance the ability of haloperidol to induce striatal dopamine receptor supersensitivity in the rat, and that this may be due to differences in the pharmacokinetic handling of haloperidol between sham-operated and hypophysectomized animals.

Repeated administration of neuroleptic drugs to rodents for periods of weeks, followed by several days drug withdrawal, induces an increase in striatal dopamine receptor numbers, as defined by the specific binding of ^{3}H-haloperidol or ^{3}H-spiperone [1, 2]. Such animals also show an increase in the hyperactivity [3] and stereotypy [4] responses to dopamine agonists such as apomorphine. The onset of striatal dopamine receptor supersensitivity is accepted as an adaptive change to the reduction in dopaminergic activity caused by persistent neuroleptic-induced blockade of striatal dopamine receptors.

Recently, Hruska *et al.* [5] suggested that hypophysectomy prevents the elevation of B_{max} for ^{3}H-spiperone binding caused by neuroleptic treatment. Since blockade of pituitary dopamine receptors by neuroleptic treatment elevates circulating levels of prolactin [6] it appeared that this hormone might influence striatal dopamine function. Indeed, Hruska *et al.* [7] reported that administration of ovine or rat prolactin to rats could increase striatal dopamine receptor numbers. In contrast to this view, our own previous investigation suggested that repeated administration of a single high dose (5 mg/kg) of haloperidol for 17 days, followed by a 3 day washout period, did induce striatal dopamine receptor supersensitivity in hypophysectomised rats, and that there was no difference in the effect of neuroleptic drug treatment between sham-operated and hypophysectomized animals [8]. More recently, Hruska and Pitman [9] confirmed that high doses of haloperidol (4 mg/kg/day for 20 days, followed by 7 days drug withdrawal) in their hypophysectomized animals induced an increase in striatal dopamine receptor density, but suggested that hypophysectomy increased the threshold dose of neuroleptic required to induce striatal dopamine receptor supersensitivity. They reported that lower doses of haloperidol, which increased specific ^{3}H-spiperone binding in striatum of sham-operated animals, did not alter striatal ^{3}H-spiperone binding in hypophysectomized rats.

We have re-examined the effect of hypophysectomy upon the ability of a range of doses of haloperidol, administered daily for 14 days, to alter striatal dopamine receptor function. Since hypophysectomy may also alter the pharmacokinetic profile of haloperidol, we have in addition measured plasma and striatal concentrations of haloperidol in these animals. We find that low doses of haloperidol, which do not induce striatal dopamine receptor supersensitivity in sham-operated rats, do cause an increase in striatal dopamine receptor numbers in hypophysectomized animals and that this is associated with higher plasma haloperidol levels in hypophysectomized animals.

MATERIALS AND METHODS

Surgery. Male Wistar rats (310 ± 2 g at the time of surgery, Bantin & Kingman) were housed in groups of 6 under standard conditions of temperature (23 ± 2°) and lighting (12 hr light/dark cycle, 06.00 hr to 18.00 hr). The rats were anaesthetized using etorphine hydrochloride 10 μg/kg i.v. and methotrimeprazine 2 mg/kg i.v. (Immobilon, C-Vet Ltd.) and were hypophysectomized or sham-operated using a modification of the parapharyngeal tech-

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nique of Smith [10]. Animals were revived using diprenorphine hydrochloride 0.5 mg/kg i.v. (Revivon, C-Vet Ltd.). All animals received 50 mg/kg i.p. ampicillin trihydrate (Penbritin, Beecham Ltd.). Hypophysectomized animals were maintained with 0.9% saline and 5% glucose solution in addition to their normal drinking water.

Drug treatment. Following a 14 day post-operative recovery period the animals received either haloperidol (0.625–5.0 mg/kg/day, i.p.) or an equivalent volume of 0.9% saline (0.1 ml/100 g, i.p.).

Haloperidol (Janssen Pharmaceutica) was dissolved in a minimum volume of glacial acetic acid, and diluted to volume with distilled water. The pH of the resulting solution was adjusted to 5.6–6.0 by addition of 2 N sodium hydroxide.

Drugs were administered daily to the animals between 10.00 and 12.00 hr for 14 days. In order to account for the difference in weights between sham-operated and hypophysectomized animals, and for the weight changes of the animals, all rats were weighed daily, and the total amount of drug administered was adjusted daily for body weight. On the last day of drug treatment, some animals were killed by decapitation between 11.00 and 13.00 hr, 1 hr following haloperidol administration. Trunk blood samples were collected into heparinized tubes and the plasma separated and stored at −20° for subsequent determination of haloperidol concentrations and prolactin levels.

All the remaining animals were allowed a 3 day drug washout period following the 14 days administration of haloperidol and were then used for biochemical determination of striatal dopamine receptor function.

Spontaneous locomotor activity. Spontaneous locomotor activity was assessed on day 7 of haloperidol treatment, 1 hr following drug administration. Animals were placed in individual perspex cages (40 × 26 × 26 cm) each fitted with two lamps (20 cm apart) throwing collimated beams of light onto two photocells. Cages were housed in a darkened room at 21°. Locomotor activity was assessed automatically by a PET 4002 computer during 5 min time segments for a total of 1 hr following placement of animals in the cages, and time segment data were summed to give a cage total. Treatment group means and standard errors were then calculated from the cage totals.

Specific ^{3}H-spiperone binding to striatal preparations. For the determination of specific ^{3}H-spiperone binding to striatal preparations rats were killed by decapitation. The brains were rapidly removed onto ice and the paired corpora striata were dissected out and were stored at −20° for a maximum of 48 hr. The skulls from these animals were retained for histological examination of the pituitary fossa. Striatal preparations were prepared from thawed striatal tissue according to the technique of Leysen *et al.* [11], using a final tissue dilution of 600 vol. in 50 mM Tris–HCl (pH 7.6) containing 120 mM sodium chloride. The specific binding of ^{3}H-spiperone (21 Ci/mmol; Amersham International) was determined in triplicate using 6 concentrations between 0.03 and 1 nM. Specific binding was defined by the incorporation of (±)-sulpiride (10^{-5} M, Delagrange). Specific ^{3}H-spiperone binding was determined in membrane preparations obtained from individual animals, using 6–7 animals per treatment group.

The specific binding data from individual animals was analysed using both Scatchard and Eadie–Hofstee transformations, with linear regression techniques, in order to obtain estimates of the number of specific binding sites (B_{max}; pmol/g wet weight of tissue) and the dissociation constant (K_d; nM). These estimates, together with the original data, were then analysed by a computer fitting program applied to the original saturation isotherm, corresponding to a single site model, using calculations of the sum of squares of error as a measure of exactness of fit. The final estimates of B_{max} and K_d obtained by this analysis were used to calculate group means and standard errors.

Anatomical and histological examination. Skulls from all hypophysectomized animals were placed in a fixing decalcifying solution (formic acid 5%, formalin 5%, distilled water 90%) for 2 weeks and an area including the pituitary fossa was then isolated for histological examination. Samples were processed through wax and sections through the pituitary fossa were cut at 20 μm. Sections were stained with haematoxylin and eosin and were examined for the presence of pituitary tissue.

Body weights of all animals were measured daily throughout the postoperative recovery period, and during drug administration. On sacrifice, the testes and adrenals of some animals were dissected free of surrounding tissue and were weighed. Organ weights were calculated as weight per gram of total body weight. The mean of these values obtained in hypophysectomized animals was then expressed as a percentage of the mean calculated for sham-operated animals.

Prolactin and haloperidol assays. Prolactin concentrations were estimated in 10 μl aliquots of plasma, assayed in triplicate by a homologous double antibody radioimmunoassay [12] using reagents provided by NIADDK (Baltimore, MD). Prolactin concentrations were expressed as ng/ml of prolactin standard (NIADDK-rPrl-RP-3). The sensitivity of the assay was 5 ng/ml of NIADDK-rPRL-RP-3 and the mean interassay coefficient of variation was 14% in plasma pools with low concentrations of prolactin.

Haloperidol concentrations in plasma and in striatal tissue were measured by a radioreceptor binding assay [13, 14]. Concentrations of haloperidol in 50 μl samples were estimated by determining the displacement of ^{3}H-spiperone from a rat striatal membrane preparation compared to that for known concentrations of a haloperidol solution.

Striatal membrane preparations were prepared as described for the determination of specific striatal ^{3}H-spiperone binding, and were incubated for 15 min at 37° with 0.1 nM ^{3}H-spiperone, together with standards or samples. Plasma samples were thawed immediately prior to analysis. Striatal tissue was thawed and the paired corpora striata from individual animals were homogenized in 1.0 ml of deionized water, using an Ultra-Turrax homogeniser (10 sec). Samples were centrifuged at 48,000 *g* for 10 min at 4°. The resulting supernatant was decanted and retained, and the pellet was resuspended in 1.0 ml of

deionized water and centrifuged as above. The supernatant was decanted and retained, and the two supernatant samples were pooled and used as the sample in the assay. Reference curves were obtained by incubating tissue and ligand with known amounts of haloperidol added to normal rat plasma or to homogenized normal rat striatal tissue. The potency of samples in producing inhibition of binding of ^{3}H-spiperone is expressed here as the apparent equivalent of haloperidol in ng/ml, as determined by comparison with standard curves obtained as described above. Assay results showing less than 10% or greater than 90% inhibition of ^{3}H-spiperone binding were discarded in order to avoid those regions of the standard curve which depart from linearity. Samples yielding inhibition of ligand binding above the 90% limit were retested at higher dilution, as required to bring them within range. The range of the assay, over which the standard curve was linear, was approximately 10–3000 ng/ml for haloperidol in both plasma and striatal supernatant samples. The interassay coefficient of variation for samples containing low concentrations of haloperidol was 13% for plasma samples and 16% for striatal supernatant samples.

Although the radioreceptor assay detects only "neuroleptic activity", haloperidol is mainly metabolized by oxidative *N*-dealkylation with the production of only neuropharmacologically inactive metabolites [15]. Thus for haloperidol the problem of metabolite interference in the assay is not important. Further, the assay appears to be capable of detecting the bound component of haloperidol in plasma since the recovery of haloperidol from plasma samples was about 90%. This is probably a result of the substantial dilution of the sample in the assay. However, the recovery of haloperidol from striatal tissue samples was much lower, at approximately 30%, presumably due to poor extraction of haloperidol from the tissue on homogenization.

Statistical analysis. This experiment was designed to determine the effect of haloperidol administration upon the various parameters measured. Therefore, in both sham-operated and hypophysectomized animals, each drug treatment group was compared to the saline-treated group using Dunnett's *t*-test. Also at each level of drug treatment the sham-operated and hypophysectomized groups were compared using Student's *t*-test. Data was also analysed by two factor analysis of variance.

RESULTS

Assessment of hypophysectomy

Hypophysectomized rats lost body weight continually over the period of the experiment, while sham-operated animals resumed their normal growth pattern, after an initial postoperative weight loss. The final body weight of the hypophysectomized animals was approximately 70% of the weight of sham-operated animals (hypophysectomized 233 ± 6 g, sham-operated 349 ± 12 g, $P < 0.05$, Student's *t*-test). The normalized weights of the adrenals and testes were about 50% of the corresponding values in sham-operated animals. Adrenal weights: sham-operated, 0.0115 ± 0.0007; hypophysectomized 0.0056 ± 0.0004 g/g body weight, $P < 0.05$, Student's *t*-test. Testicular weights: sham-operated, 0.813 ± 0.037, hypophysectomized 0.416 ± 0.40 g/g body weight, $P < 0.05$, Student's *t*-test. Hypophysectomy did not alter striatal wet weights (Sham operated 65 ± 4 mg, hypophysectomized 67 ± 6 mg).

Histological examination of the hypophysectomized animals showed that in most cases the pituitary fossa was empty, although in some animals small fragments of pituitary tissue remained around the pituitary stalk. In these animals prolactin concentrations were reduced to the same extent as in completely hypophysectomized animals and therefore these animals were not discarded from the analysis of results. In sham-operated animals the pituitary was intact.

In hypophysectomized animals plasma prolactin concentrations were reduced to undetectable levels, both in saline treated and haloperidol treated groups (<5 ng/ml). In sham-operated animals haloperidol treatment caused an elevation in prolactin concentrations (saline treated 12 ± 2; 0.625 mg/kg/day, 72 ± 10; 1.25 mg/kg/day, 70 ± 17; 2.5 mg/kg/day, 134 ± 55; 5.0 mg/kg/day, 173 ± 40 ng/ml). This effect was significant at doses of 2.5 and 5.0 mg/kg/day ($P < 0.05$, Dunnett's *t*-test).

Spontaneous locomotor activity

The spontaneous locomotor activity of both sham-operated and hypophysectomized animals measured on day 7 of haloperidol treatment, 1 hr after drug administration, was markedly reduced as compared to saline treated controls ($P < 0.05$, Dunnett's *t*-test, Fig. 1). Hypophysectomy itself did not alter spontaneous locomotor activity in saline-treated animals ($P > 0.05$, Student's *t*-test). In haloperidol treated animals, although spontaneous locomotor activity was lower in hypophysectomized animals than in sham-operated animals at all dose levels of

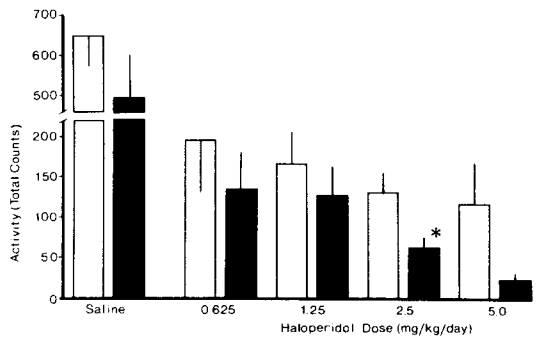

Fig. 1. Effect of hypophysectomy and neuroleptic treatment on spontaneous locomotor activity, measured on the 7th day of treatment, 1 hr following drug administration. Results are the means (± SEM) of data obtained from 7–9 animals and are expressed as total activity counts accumulated over a period of 1 hr following placement in automated activity cages: open columns, sham-operated; closed columns, hypophysectomized. Haloperidol treatment produced a significant reduction in locomotor activity at all doses used, in both hypophysectomized and sham-operated animals ($P < 0.05$, compared to corresponding saline treated animals, Dunnett's *t*-test). *$P < 0.05$ compared to sham-operated controls, Student's *t*-test.

Table 1. The effect of hypophysectomy and neuroleptic treatment for 14 days plus 3 days drug withdrawal on the number of binding sites (B_{max}) and the dissociation constant (K_d) for specific ^{3}H spiperone binding to rat striatal preparations

	Sham-operated		Hypophysectiomized	
	B_{max} (pmol/g wet weight tissue)	K_d (nM)	B_{max} (pmol/g wet weight tissue)	K_d (nM)
Saline	16.7 ± 0.8	0.074 ± 0.009	14.2 ± 0.9	0.079 ± 0.02
Haloperidol (mg/kg/day)				
0.625	16.2 ± 2.0	0.061 ± 0.019	19.7 ± 0.4*÷	0.069 ± 0.019
1.25	18.9 ± 1.7	0.073 ± 0.014	19.5 ± 1.1*÷	0.072 ± 0.005
2.5	21.6 ± 2.0÷	0.078 ± 0.014	22.5 ± 1.4*÷	0.094 ± 0.016
5.0	21.0 ± 1.6÷	0.077 ± 0.011	20.0 ± 1.4*÷	0.052 ± 0.009

Each value is the mean (±SEM) obtained by computer fitting the saturation isotherm for ^{3}H-spiperone (0.03–1.0 nM) binding to tissue samples obtained from 5–7 individual animals. Each ligand concentration employed was examined in triplicate.

* $P < 0.05$ as comapred to saline treated controls, Dunnett's t test.

÷ $P < 0.05$ as compared to saline treated controls, Student's t-test.

haloperidol, this was significant only at the 2.5 mg/kg/day dose ($P < 0.05$, Student's t-test, Fig. 1) due to the low level of activity observed in all drug treated groups. Over the dose range of haloperidol employed the inhibition of locomotor activity produced by haloperidol was greater in hypophysectomized than in sham-operated animals. Two way analysis of variance showed that haloperidol inhibited locomotor activity ($F 4,73 = 30.15$, $P < 0.01$, ANOVA) and that hypophysectomy enhanced the effect of haloperidol ($F 1,73 = 6.19$, $P < 0.05$, ANOVA).

Specific ^{3}H-spiperone binding to striatal preparations

The specific binding of ^{3}H-spiperone to striatal preparations was saturable in all groups. Data transformed by Eadie–Hofstee analysis corresponded to a linear relationship, suggesting involvement of a single site. Calculated values of the product–moment correlation coefficient, r, for transformed data were all greater than 0.90 ($P < 0.05$). The coefficient of variation of error, SD (Erad) [16] for data fitted to the saturation isotherm by non-linear analysis was approximately 5% in all individuals.

The number of specific binding sites (B_{max} for ^{3}H-spiperone (0.03–1.0 nM; defined using 10^{-5} M (±)-sulpiride) in striatal tissue preparations from saline treated hypophysectomized rats was slightly lower than that found in striatal preparations from saline-treated sham-operated animals. However, this difference was not statistically significant ($P > 0.05$, Student's t-test, Table 1). In a further experiment, hypophysectomy did not alter the density (B_{max}) or affinity (K_d) of specific striatal ^{3}H-spiperone binding in rats when measured 28 days post-operatively (B_{max}; sham operated 21.6 ± 1.2, hypophysectomized 22.0 ± 2 pmoles/g tissue, K_d; sham operated 0.15 ± 0.01, hypophysectomized 0.12 ± 0.01 nM).

Repeated administration of haloperidol for 14 days, followed by 3 days drug withdrawal, caused an increase in the density of specific striatal ^{3}H-spiperone binding in both sham-operated and hypophysectomized animals. The effect of haloperidol was greater in hypophysectomized than in sham-operated animals. In sham-operated animals a comparison of groups by Dunnett's t-test found that none of the increases in the density of binding were significant ($P > 0.05$, Table 1) whilst a comparison

Table 2. Haloperidol concentrations in haloperidol-treated hypophysectomized and sham-operated rats

Dose (mg/kg/day)	Sham-operated	Hypophysectomized
Plasma haloperidol (ng/ml)		
0.625	147 ± 44	224 ± 41
1.25	156 ± 33	313 ± 65*
2.5	222 ± 53	581 ± 68*
5.0	487 ± 61	814 ± 119*
Striatal haloperidol (ng/g)		
0.625	N.D.	N.D.
1.25	N.D.	N.D.
2.5	1180 ± 100	1700 ± 280
5.0	2920 ± 380	3700 ± 620

Haloperidol concentrations were measured by radioreceptor assay 1 hr following haloperidol administration. Results are the mean (±SEM) obtained from 6–10 individual animals.

* $P < 0.05$ as compared to sham-operated animals, Student's t-test.

N.D., not detectable.

by Student's *t*-test found that doses of haloperidol of 2.5 and 5.0 mg/kg/3 day induced significant increases ($P < 0.05$, Table 1). In hypophysectomized animals the increases produced by haloperidol were significant at all doses used, whether analysed by Dunnett's or Student's *t*-test ($P < 0.05$, Table 1).

The dissociation constant (K_d) was not altered by hypophysectomy or by drug treatment (Table 1).

Plasma and striatal haloperidol concentrations

After 14 days administration of haloperidol (0.625–5.0 mg/kg/day i.p.) the drug was detectable both in plasma and in the supernatant obtained by homogenization and centrifugation of striatal tissue. Comparisons of haloperidol in plasma at individual dose levels by Student's *t*-test showed that after doses of 1.25, 2.5 and 5.0 mg/kg/day, i.p., haloperidol concentrations were greater in hypophysectomized than in sham-operated animals ($P < 0.05$, Table 2). Analysis of variance of plasma haloperidol concentrations in hypophysectomized and sham-operated animals showed that plasma haloperidol concentrations increased with increasing doses of haloperidol ($F\ 3,53 = 15.88$, $P < 0.01$) and that plasma haloperidol concentrations were greater in hypophysectomized than in sham-operated animals ($F\ 1,53 = 24.88$, $P < 0.01$).

Haloperidol concentrations in striatal tissue were below the detection limit of the assay after doses of 0.625 and 1.25 mg/kg/day. However, at the higher doses of 2.5 and 5.0 mg/kg/day haloperidol was found in striatal tissue in detectable amounts. Striatal haloperidol concentrations were greater in hypophysectomized than in sham-operated animals, although this difference was not significant (Table 2).

DISCUSSION

The results of the present study would support our previous conclusion [8] that hypophysectomy does not prevent the increase in striatal dopamine receptor density induced by repeated administration of a range of doses of haloperidol. Indeed, the ability of haloperidol to increase the number of specific ^{3}H-spiperone binding sites in striatal preparations appears to be enhanced by prior hypophysectomy. Hypophysectomy may alter the pharmacokinetic profile of haloperidol. Hypophysectomy can induce hypogonadism, hypothyroidism and hypoadrenalism any or all of which may indirectly alter the absorption and/or metabolism of haloperidol. These results do not support the contention of Hruska and Pitman [9] that hypophysectomy acts to increase the threshold dose of haloperidol required to induce changes in striatal dopamine receptor numbers.

Lower doses of haloperidol appear to increase ^{3}H-spiperone binding in hypophysectomized than in sham-operated rats. It may be that this is an artefact resulting from the slightly lower level of binding reported in the saline-treated hypophysectomized animals than in the sham-operated animals. However, the 0.625 mg/kg/day dose in hypophysectomized animals induced a 39% increase in the density of binding whilst in sham-operated animals no such increase was seen (4% reduction). The effect of haloperidol in the hypophysectomized animals appeared maximal at the lowest dose used. This may be because the dose response curve for haloperidol was shifted to the left but lower doses of haloperidol should be used to confirm this. It is unlikely that this profound difference is due simply to a chance difference in the control level of ^{3}H-spiperone binding. Indeed, in a second experiment hypophysectomy did not alter the density or affinity of binding measured at the same time following the operation.

It could be argued that the time period for haloperidol administration was too short for low doses of haloperidol to induce an increase in striatal dopamine receptor density. However, haloperidol administration for periods of 2 weeks or less was previously shown to be effective in inducing an increase of the specific striatal binding of ^{3}H-haloperidol [2], ^{3}H-pimozide [17], ^{3}H-ADTN [18] and ^{3}H-dopamine [19]. Also, the effects of hyperprolactinaemia in inducing an increase in the density of striatal ^{3}H-spiperone binding were reported to occur within 2 weeks or less [7, 20]. Thus, if the increase in striatal dopamine receptor numbers induced by repeated neuroleptic treatment is in part due to neuroleptic-induced hyperprolactinaemia then this effect should be apparent within the time course of the present experiment.

Other recent studies also have failed to find an effect of hypophysectomy on the alteration in striatal dopamine receptor function produced by haloperidol. Thus the increase in apomorphine-induced stereotypy and striatal ^{3}H-spiperone binding [21] and the increased effect of pergolide in enhancing acetylcholine levels and reducing DOPAC levels in striatum [22] produced by repeated haloperidol treatment were all shown to be unaffected by prior hypophysectomy. From this we conclude that the intact pituitary is not essential for the regulation of striatal dopamine receptor function.

Hruska and Pitman [9] have attributed the reported reduction in the effect of low doses of haloperidol on striatal dopamine receptor density to a lack of some pituitary factor which could alter striatal dopamine receptor function directly or indirectly, either alone or in conjunction with haloperidol. They suggested that the factor might be prolactin, since administration of prolactin itself induced striatal dopamine receptor supersensitivity in intact or hypophysectomized rats [7]. Indeed, two weeks following implantation of anterior pituitary tissue the density of striatal ^{3}H-spiperone binding was increased [19]. However, in contrast, Gordon and Diamond [21] reported that prolactin administration did not alter striatal dopamine receptor function, and prolonged hyperprolactinaemia for periods of 6 months to 2 years caused by pituitary implants failed to alter the density or affinity of striatal ^{3}H-spiperone binding sites [23, 24]. Similarly, prolonged hyperprolactinaemia induced by administration of domperidone, which does not easily cross the blood–brain barrier, had no effect on ^{3}H-spiperone binding in male rats [25] or mice [26].

Further evidence against the role of prolactin, or indeed pituitary factors in general, in the control of striatal dopamine receptor function comes from our failure to find any change in the binding parameters of ^{3}H-spiperone in hypophysectomized rats as com-

pared to sham-operated animals. This is in agreement with our previous finding [8] and with those of Hruska and colleagues [5, 9] suggesting that pituitary function does not influence the density or affinity of striatal dopamine receptors in normal male rats. Recently, Gordon and Diamond [21] reported that hypophysectomy would itself induce an increase in striatal dopamine receptor density in male rats. However, in this case, where a wide range of ^{3}H-spiperone concentrations was employed the analysis of ^{3}H-spiperone binding data used a two site model, which revealed an increase in the density of the high affinity (K_d = 0.01–0.03 nM) site only. Our own data, in contrast, was fitted best by a single straight line on linear regression analysis and by a one site model. One site analysis as used by both ourselves and Hruska and colleagues showed no change in density or affinity following hypophysectomy.

Although hypophysectomy does not appear to directly influence striatal dopamine receptor function it may alter drug distribution, metabolism or excretion by a number of possible mechanisms. Hypophysectomy results in a massive alteration in endocrine state, with a reduction or arrest of the production of many hormones. The gonadal regression produced by hypophysectomy may result in a reduction in the capacity for hepatic metabolism or haloperidol via the microsomal monooxygenase system [15]. The physical damage produced by the operation may also enhance drug penetration into the brain. Our finding of greater plasma and striatal haloperidol concentrations in hypophysectomized than in sham-operated animals is in agreement with the report of Lloyd *et al.* [27] that brain haloperidol levels were greater in hypophysectomized animals at 0.5, 1 and 2 hr after a single i.p. injection, whilst the peak brain level was unchanged by hypophysectomy, occurring between 0.5–1.0 hr after administration. That the increased plasma concentrations of haloperidol are functionally significant is suggested by the enhanced inhibition of locomotor activity by haloperidol observed here following hypophysectomy. Lloyd *et al.* [26] also reported an enhanced efficacy and duration of action of haloperidol, following acute administration, in inducing catalepsy in hypophysectomized rats. The enhanced effect of low doses of haloperidol seen here in hypophysectomized animals might be explained by higher systemic concentrations of haloperidol.

In conclusion, hypophysectomy does not appear to reduce the ability of haloperidol to alter striatal dopamine receptor function in male rats. Rather, it would appear that hypophysectomy enhances the increase in striatal dopamine receptor numbers due to alterations in the pharmacokinetic profile of haloperidol.

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