

Dopamine Blockade Reverses the Inhibition of Prolactin Which Results from Intrahypothalamic Pituitary Grafts (42054)

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Abstract. When mated with fertile bucks, rats with anterior pituitary (AP) tissue grafted into the hypothalamus did not exhibit prolongation of the diestrous cycle. Treatment of these rats with α -methyl-*p*-tyrosine, reserpine, or haloperidol for 1 or 2 days after mating increased the interestrous interval by a few days in all rats and to more than 8 days (leading to pseudopregnancy or pregnancy) in 20% of the cases. The same treatment in unmated normals resulted in 80% becoming pseudopregnant. To get more than 70% of rats with hypothalamic AP grafts pregnant or pseudopregnant required dopamine-blocking drugs for 3 or 4 consecutive days. Pregnancy was prolonged in 50% and lactation was impaired in 78% of the grafted rats which littered. Both impairments, like the original failure of the luteotrophic response, are attributed to the effects of PRL autofeedback from the hypothalamic AP grafts. These experiments provide further evidence that the mechanism whereby PRL in the hypothalamus inhibits PRL secretion involves elevation of dopamine. © 1985 Society for Experimental Biology and Medicine.

Anterior pituitary (AP) tissue grafted into the hypothalamus of the rat was found to be antiluteotrophic, fertile matings failing to interrupt regular 4- to 5-day diestrous cycles (1, 2). It was subsequently found that these rats with AP grafts in the hypothalamus failed to exhibit the usual prolactin (PRL) surge on the afternoon of proestrus, and that no PRL surges occurred after mating (3, 4). Because the only AP cell type uniformly present in these grafts was the lactotrophs (1, 2, 5) and because pregnancy and pseudopregnancy were terminated by prolactin implants made in the hypothalamus (6, 7), the absence of pseudopregnancy and pregnancy in grafted rats was attributed to PRL autofeedback. Evidence is accumulating that one mechanism whereby PRL can inhibit its own secretion is via enhancement of dopamine (DA) production by the tuberoinfundibular dopaminergic (TIDA) neurons (8, 9). This study sought to determine whether inhibition of DA synthesis or action after mating in rats with intrahypothalamic AP grafts could restore luteotrophic PRL secretion. Reestablishment of luteotrophic function by DA blockade would lend support to the hypothesis that PRL autoregulation is brought about by elevated DA secretion.

Material and Methods. Female Wistar rats (180-220 g) were selected for grafting after showing two normal 4-day cycles. A quarter

to a half AP from 6- to 30-day neonates, close relatives from the same inbred strain, was introduced into the hypothalamus under ether anesthesia and stereotaxic control. On the stereotaxic instrument used, the ear bars and palate bar are in the same horizontal plane and the coordinates (6.4 mm anterior to interaural line, 0-0.5 mm lateral to mid-sagittal plane, 1.5-1.7 mm above the sphenoid bone) located the grafts in or near the paraventricular nucleus.

Rats were housed at $23 \pm 1^\circ\text{C}$, fed a pelleted ration *ad lib* and illuminated daily between 0700 and 1900 hr. Vaginal smears were taken daily postoperatively and, after two to four normal cycles, males of proven fertility were joined one per four females.

The presence of spermatozoa confirmed individual mating dates, and rats with successful AP grafts in the hypothalamus uniformly returned to estrus (usually with evidence of another mating) 4 or 5 days later. Rats which became pregnant after fertile mating, were not used again in this study and were later found to have no AP tissue in serial sections of their hypothalami.

Treatments. Three drugs were used in these studies, the effects of which were likely to constitute a blockade of DA synthesis or receptors (10). One or other of the following drugs was injected daily for 1-4 days as shown under Results.

α -Methyl-*p*-tyrosine (AMT), which depresses DA synthesis by inhibiting tyrosine hydroxylase, was suspended in 0.9% NaCl solution and injected ip at 200 mg/kg.

Reserpine (RES) (Sigma), which depletes catecholamine stores, was injected sc at 1.0 mg/kg in 1% ascorbic acid.

Haloperidol (HAL) ("Serenace," Searle), a DA-receptor blocker, was injected ip at 0.5 mg/kg.

Criteria. Selection of grafted rats for treatment was on the basis of failure of mating to prolong the diestrous cycle on two or more occasions. The effectiveness of the treatments was assessed from the changes in vaginal smear patterns, positive responses indicated by prolongation of the interval between consecutive estrous smears, the interestrous interval. Because the grafted rats ovulate normally (1) and had been mated with fertile males, pregnancy was possible if the treatment resulted in fully functional corpora lutea. The time and date of parturition were recorded for all pregnant rats, and the progress of lactation was followed from daily weighings of the pups. Foster pups (up to six) were provided as necessary to ensure the maintenance of an adequate suckling stimulus.

Following treatment all rats were tested by mating at subsequent cycles to confirm that

mating alone was incapable of prolonging cycles. At the conclusion of the study the brains of all grafted rats were examined in serial section, by methods previously described (1), to confirm the presence of grafted AP tissue. Only data from rats with confirmed grafts were included below. All grafts contained acidophils but not all contained stainable basophils.

Results. *Experiment I.* Two weeks after receiving neonatal AP tissue in the hypothalamus, 16 female rats were joined with fertile males. Two rats became pregnant and were later found to have no visible graft in sections of their brains. The remaining 14 rats failed to become pregnant, nor did they exhibit pseudopregnancy prolongation of their cycles despite matings on a total of 40 occasions. Injections of AMT for 1 day or more following the next mating led to a significant increase in the mean interestrous interval from 4.5 to 7.3 days, i.e., 4- to 5-day cycles were replaced by 6- to 9-day cycles. These data are shown in Table I and it should be noted that subsequent cycles, where no AMT was given, reverted to the normal duration, i.e., 4 or 5 days, so that AMT affected only the cycle in which it was injected.

In Table II the effects of the duration of AMT treatment on the duration of the interestrous interval in mated rats with AP grafts

TABLE I. EFFECT OF AMT^a IN PROLONGING THE INTERESTROUS INTERVALS AFTER MATING IN RATS WITH ANTERIOR PITUITARY TISSUE GRAFTED IN THE HYPOTHALAMUS

Interestrous interval (days)	Number of cycles				
	Pretreatment		With AMT mated	Post-treatment	
	Unmated	Mated		Unmated	Mated
3	2	—	—	—	2
4	23	26	—	10	16
5	11	10	—	4	10
6	2	4	7	1	—
7-9	—	—	9	—	—
10-12	—	—	2	—	—
23 ± 1 ^b	—	—	4	—	—
All cycles (No.)	38	40	18 ^c	15	28
Mean duration ^d	4.3	4.5	7.3	4.4	4.3
± SEM	±0.1	±0.1	±0.4	±0.2	±0.1

^a AMT = α -methyl-*p*-tyrosine at 200 mg/kg ip for 1 or >1 day.

^b Pregnancy.

^c Excludes four pregnant rats.

^d Analysis of variance showed that mean cycle length was significantly prolonged only by AMT treatment.

TABLE II. EFFECT OF DURATION OF AMT TREATMENT ON THE INTERESTROUS INTERVALS OF UNMATED NORMAL RATS AND MATED RATS WITH INTRAHYPOTHALAMIC AP GRAFTS

AMT ^a treatment	Individual interestrous interval (days)	
	Normal unmated	Grafted mated
D1 × 1 ^b	6, 12, 12, 13, 15, 15	6, 6, 6, 6, P ^c
D1 × 2	6, 11, 13, 13, 14, 14	6, 6
E + D1	6, 13, 13	6, 7, 7, 7, 8
E + D1 + D2	—	7, 7, 8, 9, 10, P
E + D1 + D2 + D3	—	9, 11, P, P

^a AMT = α -methyl-*p*-tyrosine at 200 mg/kg ip daily, all 0900 hr, or ×2 at 0900 and 1700 hr.

^b E = day of estrus (sperm in smear), D1 = diestrus Day 1, D2 = diestrus Day 2, D3 = diestrus Day 3.

^c P = rat became pregnant and littered.

in the hypothalamus are compared with the results of similar treatments in unmated normal controls. In 12 out of 15 normal rats AMT on 1 or 2 days lengthened the interestrous interval to 11–15 days. This contrasts with only 1 of 12 mated grafted rats in which the same dose of AMT for 1–2 days extended the interestrous interval beyond 8 days. The interestrous interval was extended beyond 8 days in rats with hypothalamic AP grafts when AMT injections were given on 3 or 4 days consecutively.

Experiment II. A second experiment was undertaken using a different DA-blocking

drug, RES, and a further 16 rats with AP tissue in their hypothalami.

In preliminary trials RES was given at 1 mg/kg to 22 normal rats. Seven received RES on the day of estrus, 7 on diestrus Day 1, and 8 were injected on both days. Pseudopregnancies of 12–15 days followed in 0 out of 7 treated on estrus, and in 5 out of 7 and 7 out of 8 treated on diestrus Day 1 and on both days respectively.

The results of RES treatments in the rats with AP grafts in the hypothalamus are shown in Table III. There were 76 matings following which there was no treatment, and 73 of these were followed by cycles of normal length, 4.3 ± 0.6 days. Eleven further matings in these rats were followed by RES given on diestrus Day 1 only and 20 by RES both on the day of estrus and on diestrus Day 1. Only 12 of these 31 treatments were followed by prolonged cycles, i.e., 39%. This contrasts with the 25/34, i.e., 73%, which had prolonged cycles when injected on 3 or 4 consecutive days and the 80% of normals which responded with pseudopregnancies after only one or two injections. A χ^2 test revealed that treatment with RES for 3 or 4 days resulted in a highly significantly greater proportion of rats exhibiting pseudopregnancy or pregnancy prolongation of the cycles than did RES treatment for only 1 or 2 days ($\chi^2 = 9.36$ (1, 0.01) > $P > 0.001$).

TABLE III. EFFECT OF DURATION OF RESERPINE TREATMENT IN PROLONGING THE INTERESTROUS INTERVAL IN MATED RATS WITH HYPOTHALAMIC AP GRAFTS

Treatment duration ^a (days)	Matings (No.)	Interestrous interval			
		4–6 Days (No.)	7–12 Days (No.)	23 ± 1 Days (pregnant)	
				No.	(%)
0	76	73	3	—	(0)
1 ^b	11	10	—	1	(9)
2 ^c	20	9	5	6	(30)
3 ^d	23	9	3	11	(48)
4 ^d	11	—	2	9	(82)
Total	65	28	10	27	

^a Treatment = reserpine 1.0 mg/kg/day sc.

^b On diestrus Day 1 (five/seven normals became pseudopregnant).

^c On estrus and diestrus Day 1 (seven/eight normals became pseudopregnant).

^d Beginning on estrus.

It should be noted that on RES all rats lost weight (anorexia and diarrhea), 10 and 14.3% of body weight by 48 and 72 hr, respectively.

Experiment III. AMT acts to inhibit DA synthesis and RES acts to deplete DA stores. They also caused anorexia (weight losses) and diarrhea. In this experiment HAL was used because it blocks DA receptors without these side effects. Experiment III was conducted on 22 rats in which 52 matings with fertile males resulted in no prolongation of the cycle, the mean duration of which was 4.4 ± 0.1 days. HAL was injected on diestrus Day 1, or for 3 or 4 days beginning on the day on which spermatozoa were found in the vaginal smear. Table IV shows that a single injection of HAL prolonged only 50% of cycles, whereas if given for 3–4 days 85.7% of cycles were prolonged. When the same rats were subsequently mated without treatment none out of 28 matings were followed by prolonged cycles demonstrating that it was the DA blockade which had caused the lengthening of the interestrus interval.

Induced pregnancies. Without treatment (Tables I, III, and IV above) 225 matings with fertile males in 32 rats with AP grafts in their hypothalami failed to prolong the interestrus interval. Introduction of DA blockade with AMT, RES, or HAL resulted in prolongation of the interestrus interval to 7–15 days (pseudopregnancy) after 34 or 30% of 114 matings and in pregnancy (21–24 days) after 41 (36%) of the 114 matings. The outcome of these pregnancies is shown in Table V.

Two does died pregnant, 50% littered 22 days after mating (the normal time in our colony) while 18/41 had prolonged gestations (23–25 days). The mean litter size for 20 does with 22-day gestations was 8.5 live and 1.25 dead, while the mean litter size for 12 does with 23-day gestations was 6.3 live and 1.8 dead.

Of the 39 pregnancies, the young were either eaten or deserted on six occasions; 12 litters were regularly suckled but the mothers yielded no milk to their own or to foster pups provided for 4 days. Twelve others had poor lactations which began only after 3–5 days of suckling (and pup replacement) and were of low yield between Days 6 and 11 (<5 g/day for litters of six). Only 9 out of 33 lactations (27%) were classed as normal with pups gaining weight at rates similar to untreated controls in the same colony.

Discussion. It is well known that AP tissue grafted away from the hypothalamus is luteotrophic (11, 12). Completely the opposite is true, however, for AP grafts within the hypothalamus. Such grafts not only fail to sustain pseudopregnancy or pregnancy (1, 2, 5) but they also inhibit the proestrous and postcoital PRL surges from the *in situ* pituitary (3, 4). In this regard it is of interest that PRL released in the hypothalamus (3, 4, 5), like PRL infused into the third ventricle (13) or growth hormone secreted in the cerebral ventricles (14), does not enter the general circulation so that graft PRL is not available to the ovaries. These findings were confirmed above when over 200 fertile matings failed to prolong the diestrus cycles in rats with

TABLE IV. EFFECT OF HALOPERIDOL IN PROLONGING THE INTERESTRUS INTERVAL IN MATED RATS WITH AP TISSUE IN THE HYPOTHALAMUS

Treatment	Matings	Interestrus interval			
		4–6 Days (No.)	7–15 Days (No.)	22 ± 1 Days (pregnant)	
				No.	(%)
Nil before HAL	52	52	—	—	—
HAL × 1 ^a	10	5	3	2	(20)
HAL × 3	13	2	7	4	(31)
HAL × 4	8	1	3	4	(50)
Nil after HAL	28	28	—	—	—

^a HAL = haloperidol, 0.5 mg/kg, ip daily, for 1, 3, or 4 days.

TABLE V. RESULT OF PREGNANCIES INDUCED BY DOPAMINE BLOCKADE IN RATS WITH INTRAHYPOTHALAMIC AP GRAFTS

Pregnancy outcome	Rat (No.)	Lactation outcome			
		Not suckled (No.)	Suckled, no lactation (No.)	Suckled ^a , low yield (No.)	Yield, normal ^b
Died pregnant	2	—	—	—	—
Littered 21 days	1	—	1	—	—
Littered 22 days	20	—	6	6	8
Littered 23 days	14	5	5	2	1
Littered 24 days	3	1	—	2	—
Littered 25 days	1	—	—	1	—
Total	41	6	12	12	9

^a No weight gain by litter for 3–5 days then <5 g/day/litter of 6, Days 6–11.

^b Weight gained by litter from birth with mean increment >8 g/day/litter of 6–8, Days 6–11.

intrahypothalamic AP grafts. When PRL is abolished by CB 154 (15) or depressed by intrahypothalamic PRL implants (16), progesterone secretion is not initiated and pseudopregnancy or pregnancy is prevented.

The PRL content and secretion of *in situ* pituitaries are reduced in the presence of hyperprolactinemia resulting from ectopic AP grafts, grafts of PRL secreting tumors, and injection of heterologous PRL, while the termination of PRL surges in pregnancy may be due to the action of placental lactogen (see reviews (12, 17)). The consequential elevation of PRL within the hypothalamus increases the turnover of DA in the median eminence (18) causing a fivefold increase in DA in the hypophysial stalk blood (19). The elevated DA is believed to lower basal plasma PRL and to prevent or depress the proestrous surge, and also the TRH-induced, stress-induced, coitus-induced, and suckling-induced elevations of plasma PRL (see (20–23) and others).

DA blockade was used in the present study in an attempt to reverse the antiluteotrophic effects of intrahypothalamic AP tissue. Such a reversal might suggest graft-induced enhancement of DA to be a likely reason for the absence of the PRL surges (3, 4). Because each inhibition of DA could result in a consequent elevation of PRL (12) a crucial part of the test was comparison of the effectiveness of short term DA blockade (one injection) in normal versus grafted rats. Either

the extent of the prolongation of the interestrous interval or the proportion of rats in which pseudopregnancy was induced could be affected, or both.

In rats with intrahypothalamic AP grafts, DA-blocking drugs given once delayed the next estrus by only 1–2 days and less than 20% of rats became pseudopregnant. AMT given on 2 consecutive days prolonged the interestrous interval by only 2 or 3 days. By contrast, AMT or RES given on 1 or on 2 days induced pseudopregnancy (8–15 days) in 80% of normal rats in the present study or in 100% of normal rats in other studies (24, 25). Daily treatment for 3 or 4 days with any of the three drugs, AMT, RES, or HAL, was required in grafted rats to match the response in normals. It resulted in 8- to 15-day pseudopregnancies or 21- to 24-day pregnancies in 51 of the 65 rats with grafts. Thus the grafts clearly rendered the rats less responsive to DA blockade. Normally PRL surges over at least 48–60 hr are needed to initiate progesterone secretion (12, 17), and while DA blockade on 1 day did not provide an adequate stimulus in most graft-bearing rats, clearly blockade for 3–4 days did. Raising the AMT or RES dose level might have increased their effectiveness. One-tenth of the RES dose used here was found ineffective (2) while three times the dose used above induced pseudopregnancy in 100% of the rats (25). This higher dose was not used because of weight losses encountered and because the

80% incidence of pseudopregnancy in normal controls in the present study gave an adequate measure of control.

When pseudopregnancy is established by a single injection of progesterone on the day of estrus (26) the treatment is followed by establishment of a sequence of diurnal and nocturnal surges of PRL (27, 28). It is not known whether induction of pseudopregnancy by DA-blocking drugs (24, 25) is similarly accompanied by establishment of sequential PRL surges though this would seem highly likely. It may depend upon how quickly progesterone levels become elevated, as progesterone seems able to reinforce the luteotrophic secretion of PRL (12, 17, 26). It was obviously more difficult to establish the luteotrophic surges in rats with intrahypothalamic AP grafts, their need for DA blockade on 3–4 days implying the necessity to overcome a persisting DA inhibition. It also resembles the need for PRL injections on several consecutive days to establish pseudopregnancy (29) and pregnancy (2). Of interest in this regard is the fact that for optimal responses progesterone is given on the day of estrus (26) while RES is given on diestrus Day 1 (24) with the same end result of pseudopregnancy. Both may act by lowering the threshold of neurons linking the preoptic area and suprachiasmatic nuclei but why best on consecutive days is not clear.

The reversal above of the antiluteotrophic effects of hypothalamic AP grafts by DA antagonists, i.e., the lengthening of the inter-estrous interval to permit pseudopregnancy or pregnancy, means that the inhibition of the *in situ* pituitary PRL secretion observed in these rats (3, 4) was most probably due to elevated DA in the portal blood caused by graft PRL released into the hypothalamus. Earlier studies (2) had shown that replacement with either PRL or progesterone would prolong cycles also indicating the nature of the deficiency. Both synthesis (30) and release (22) of PRL are believed to have been inhibited by the elevation of DA as a consequence of hyperprolactinemia, and this mechanism was suggested by several other studies (8, 9, 20–23) to account for PRL short-loop feedback.

The partial and total failure of lactation despite continuous suckling in most of the rats was an unexpected finding here as was the increased incidence of prolonged gestations. Exposure of rats to DA-blocking drugs for the first 1–4 days of pregnancy seems most unlikely to be able to affect the course of parturition 3 weeks later. Whether AP grafts increase DA secretion to the extent that its concentration in peripheral blood is increased, and thus affects uterine contractility is a possibility worth exploration. Earlier it was reported (2, 3) that, although lactations were reduced in rats with AP grafts placed in the hypothalamus during pregnancy, they were still more than adequate for rearing of young. Furthermore, PRL rose normally after suckling 7 days postpartum (3, 4) and, though blunted in the presence of PRL excess, PRL responses usually occur after suckling (20, 23, 31). Recent studies show a decrease in the basal activity of the TIDA neurons in lactation which appears to result from a lack of responsiveness to PRL (32) so that short-loop feedback inhibition by the DA mechanism might not be expected with suckling.

In seeking a cause for the impaired lactations in rats with hypothalamic AP grafts it should be noted that impairment was not related either to the location or to the age of the grafts. Thus some rats with impaired lactation had grafts which lay dorsal to the paraventricular nuclei, or even dorsal to and posterior to the anterior commissure. Other grafts lay between the paraventricular and suprachiasmatic nuclei, or posterior to them in the anterior hypothalamic area. Lactation failure occurred in rats with grafts of only 38 days in age and those with grafts implanted more than 100 days previously. However, for rats which did not lactate in each category of graft placement or age there were others which lactated reasonably well. The grafts had been deliberately placed to avoid the supraptico-hypophysial tracts and the hypophysial portal vessels which were always spared. The occurrence of normal parturition in most rats and the presence of milk in the stomachs of 21 of 33 litters confirms that oxytocin was present. The observation that lactations tended to begin 3–5 days late in poor lactaters is also significant. The hypoth-

esis presently under investigation is whether the antepartum rise in PRL (12, 33), which occurs between the fall of placental lactogen (34) and parturition, is inhibited by the action of the hypothalamic AP grafts just as is the PRL surge at proestrus (3, 4). As a consequence lactogenesis is delayed.

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