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Vol. 68, No. 3
Printed in U.S.A.

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Vol. 68, No. 3
Printed in U.S.A.

Blockade of Neonatal Activation of the Pituitary-Testicular Axis: Effect on Peripubertal Luteinizing Hormone and Testosterone Secretion and on Testicular Development in Male Monkeys*

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ABSTRACT. The objective of this study was to examine the effect of blockade of neonatal activation of the pituitary-testicular axis, using a GnRH agonist, on sexual development in male rhesus monkeys. Monkeys were treated with either a GnRH agonist (10 μg/day; n = 8) or vehicle (n = 9) for 112 days using osmotic minipumps beginning at 10–13 days of age. In control monkeys serum LH and testosterone concentrations during the first 3 postnatal months were similar to those in adults; they then declined to very low levels. GnRH agonist administration caused an immediate and precipitous decline in serum LH and testosterone concentrations to very low levels, and both remained low throughout the rest of the agonist administration period. Neither group had any significant elevation in serum LH or testosterone concentrations during the next 2 yr. In the control monkeys serum LH and testosterone began to rise during the third year, with a rapid increase occurring during the fall coincident with the breeding season. This peripubertal rise of LH and testosterone secretion was associated with rapid enlargement of the testes and the appearance of sperm in ejaculates. The monkeys who had received GnRH agonist had subnormal serum LH and testosterone increases, and testicular enlargement was also attenuated compared to that in the control animals during the third year of life. Semen samples were recovered from only 50% of the GnRH agonist-treated monkeys during this period, and the sperm count per ejaculate was suppressed. The serum LH responses of the GnRH agonist-treated monkeys to an iv bolus dose of GnRH (5 μg/kg EW) during the third year were normal. These results suggest that the induction of reversible hypogonadotropin-hypogonadism in neonatal male monkeys alters subsequent testicular development and peripubertal endocrine changes. Thus, neonatal activation of the pituitary-testicular axis may be a critical developmental event in the process of sexual development in male primates. (*J Clin Endocrinol Metab* 68: 0000, 1989)

THE EARLY postnatal period of development is associated with an active period of LH and testosterone secretion in humans (1–4) and other primates (5–12). Serum LH, FSH, and testosterone concentrations are elevated for the first 3–6 months of postnatal life before falling to low basal levels where they remain until the time of puberty. The significance of the elevated gonadotropin and testosterone secretion during this period to subsequent sexual maturation of the male is unknown, and the consequences of abnormal pituitary-gonadal function at this time are uncertain. Neonatal human males with cryptorchidism have been reported to have reduced (13, 14), normal (15), or elevated (16) serum testosterone levels. Similarly, the gonadotropin responses of cryptorchid males to GnRH have been reported to be subnormal (17) or normal (18). While there may be no general agreement as to whether the hypothalamic-pituitary-testicular axis is functioning normally during the neonatal period in these patients, reduced testosterone production during this period may be responsible for the high frequency of defects in the seminiferous tubules of cryptorchid children and the high incidence of oligospermia in men treated as children for cryptorchidism (19).

Several years ago we reported that it was possible to block neonatal activation of the pituitary-testicular axis in male rhesus monkeys by continuous infusion of a GnRH agonist (20). In this study, we describe the effect of this blockade on subsequent changes in LH and testosterone secretion and on the process of testicular de-

Received August 25, 1988.

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* This work was supported by NIH Grants RR-08248 (via cofunding from the NIMH), RR-00165, and HD-23295; NSF Grant BNS 83-07295; and USAID Grant DAN-5053-G-SS-5018-00.

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velopment from the postnatal period until the onset of puberty. The objective was to determine whether the neonatal rise in testosterone was critical for normal sexual development in male primates.

Materials and Methods

Ten male rhesus monkeys (*Macaca mulatta*) that were born in 1984 to a heterosexual group of approximately 75 monkeys were studied. Six monkeys were treated continuously with 10 μg/day GnRH agonist (D-Trp[6]-*N*-α-Me-Leu[7]-des-Gly[10]-Pro[9]-NHEt-GnRH; Wyeth Laboratories, Philadelphia, PA), and 4 received vehicle (sterile water) from 10–122 days of age using osmotic minipumps (2 mL; Alza Corp., Palo Alto, CA). GnRH agonist or vehicle treatment was initiated at 10–13 days of age rather than at birth to allow a recovery period after parturition for both the mother and infant. The infants were kept with their mothers within the social group in a large outdoor compound (30 × 30 m) with attached indoor quarters during the first 3 yr of life. Then, all 10 monkeys were moved to another outdoor compound (15 × 15 m) containing 8 ovariectomized female monkeys in order to facilitate more extensive monitoring during the peripubertal period.

An additional group of 10 infants that were born in the same colony during 1983 also were studied. Five of these monkeys were given GnRH agonist for 112 days, as described above. The other 5 monkeys served as controls [only 2 of these monkeys were subjected to surgical procedures (pump implanted and removed)]. We reported previously the effect of GnRH agonist administration on serum LH and testosterone levels and on the response to GnRH during the neonatal period in this group of monkeys (20). In the 1983 birth cohort there were no detectable differences in body weight gain or crown-rump length during infancy between control monkeys subjected to the surgical protocols and those that were not or between control and agonist-treated monkeys (20). Thus, surgical procedures *per se* did not alter development during infancy. The 1983-born males were removed from the heterosexual group at 3 yr of age and kept indoors in controlled lighting (12 h of light and 12 h of dark) and temperature (22–25 C) conditions in single animal caging. Of the 5 animals treated with the agonist in 1983, only 2 animals are still alive, and only their data are included. One of the animals died of yersiniosis at approximately 1 yr of age, a second was killed at 2 yr of age because of inoperable laryngeal stenosis, and a third was killed at 3 yr of age because of repeated irreducible rectal prolapse. There was no evidence that these medical problems were related to GnRH agonist administration during infancy.

Treatment procedures

Minipumps were implanted sc under sterile conditions in ketamine-anesthetized (20–30 mg/kg) infants. The pumps were normally replaced every 4 weeks using similar sterile procedures. In certain monkeys, the pumps had to be replaced earlier because of infection or pump failure. In such monkeys we were unable to detect a significant effect on serum LH and testosterone concentrations.

Blood samples (1 mL; 1000–1400 h) were taken from unsedated monkeys before and after 4 and 10 days of GnRH agonist or vehicle administration and thereafter twice monthly for the remainder of the treatment period. After the monkeys reached 4 months of age the frequency of blood sampling was reduced to 1/month, and the volume of blood taken was increased to 3 mL/sample. Beginning at 3 yr of age, testicular volume was determined at monthly intervals, and the monkeys were subjected monthly to rectal probe electroejaculation under ketamine anesthesia, as previously described (21). When we were successful in collecting a semen sample; the sperm count and the percentages of motile and live sperm were determined. At yearly intervals beginning at 1 yr of age, each 1984-born monkey received an iv bolus dose of 5 μg/kg BW weight GnRH. Blood samples were taken before and 30 and 60 min after GnRH administration. Serum samples were stored at −20 C until assayed for LH and testosterone.

Hormonal assays were performed at intervals throughout the study. Serum LH was assayed in duplicate using the mouse interstitial cell-testosterone bioassay as originally described by Van Damme *et al.* (22) and as modified by Steiner and Bremner (8). The sensitivity of the LH assay was 0.2 mg/L, and the usable range of the assay was from 0.2–10 mg/L. The intra- and interassay coefficients of variation were 8.1% and 19.5%, respectively. The LH results are expressed in terms of the rhesus monkey pituitary gonadotropin standard, LER-1909-2, which has a potency of 0.0032 × NIH LH S1. Serum testosterone concentrations were measured in duplicate by RIA, as reported previously (23). The intra-assay and interassay coefficients of variation were 5.0% and 8.2%, respectively, and the sensitivity of the assay was 1.04 nmol/L.

Hormone levels that were undetectable were assigned values corresponding to the sensitivity limit of the assay (0.2 mg/L for LH; 1.04 nmol/L for testosterone). The hormonal data were initially analyzed using a two-way analysis (treatment × age) of variance, followed by a least significant difference test for between-group differences or a Tukey test for multiple comparisons within groups (24). The testicular volume data were first subjected to Bartlett's test for homogeneity of variance. The test indicated that the variance in the data between groups was not homogeneous. As a result, raw data were subjected to a square root transformation before two-way analysis of variance. $P < 0.05$ was considered significant.

Results

The mean serum LH concentrations in the 1984-born control monkeys were elevated for the first 4 months of postnatal life. They then declined to near the level of detection (0.2 mg/L; Fig. 1, *top*). The mean serum LH levels in the GnRH agonist-treated monkeys fell rapidly from a pretreatment value of 3.1 ± 1.5 (±SE) mg/L to less than 1.0 mg/L after 2 weeks of treatment and were lower ($P < 0.05$) than those in the control monkeys on most occasions during the first 3 months of postnatal life (Fig. 1, *top*).

The changes in serum LH concentrations were paralleled by comparable changes in serum testosterone levels (Fig. 1, *bottom*). A two-way analysis of variance indicated

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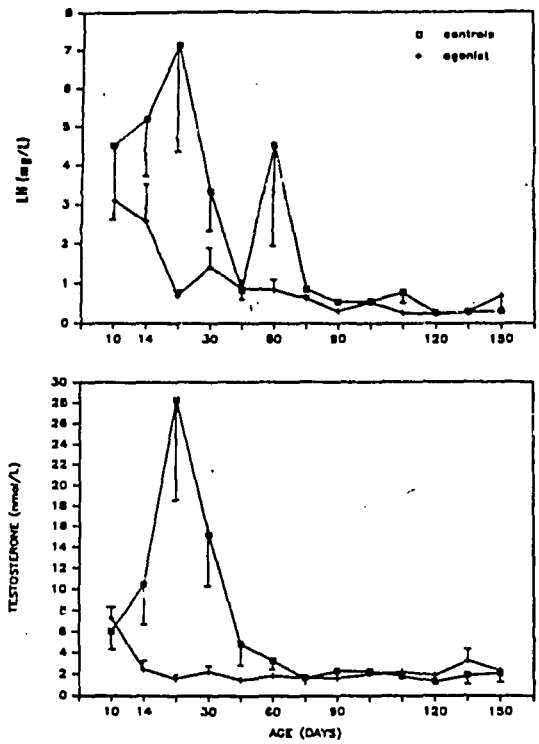

FIG. 1. Effect of GnRH agonist administration on me... (±SE) serum LH (*top*) and testosterone (*bottom*) concentrations in infant male rhesus monkeys. Control, n = 4; agonist-treated, n = 6. The animals were born in 1984. The scale of the x-axis has been expanded during the early neonatal period for clarity and to accommodate the additional blood samples taken during this period.

that there was a significant effect of GnRH agonist administration ($P < 0.025$) and age ($P < 0.01$), and a significant interaction ($P < 0.001$) between these two variables on serum testosterone levels. In the control monkeys, the mean serum testosterone concentration increased from 6.0 ± 2.0 nmol/L at 10–13 days of age to a peak of 28.4 ± 10.9 nmol/L at 3 weeks of age; it then gradually declined to less than 2 nmol/L by 75 days. GnRH agonist treatment caused an immediate decrease in mean serum testosterone values from 7.3 ± 1.5 nmol/L to undetectable values after 2 weeks, and they remained low for the remainder of treatment. Thus, GnRH agonist administration abolished the active period of LH and testosterone secretion characteristic of the neonatal period in monkeys. The changes in serum LH and testosterone concentrations as a result of neonatal GnRH agonist administration reported here for 1984-born monkeys are comparable to those reported earlier (20) for monkeys born in 1983.

GnRH agonist administration did not alter early postnatal growth in the 1984-born monkeys. There were no differences in body weight gain and crown-rump length between the control and agonist-treated monkeys during the first 20 weeks of postnatal life (Table 1).

By the time GnRH agonist administration was terminated between 122–125 days of age, the serum LH and testosterone values in the control and GnRH agonist-treated monkeys were similar (Fig. 1). Thereafter, the mean serum LH and testosterone concentrations remained near the minimum levels of detection in both groups between 0.5–2.0 yr of age (data not shown).

The mean serum LH and testosterone concentrations in the 1984-born control and GnRH agonist-treated monkeys between 2 and 4 yr of age are shown in Figs. 2 and 3 (*top panels*). There were no differences in serum LH and testosterone concentrations between the two groups from 2 until 3 yr of age. In the control monkeys serum LH concentrations began to rise just before 3 yr of age (January 1987), and from January until September of that year they averaged about 1.0 mg/L. These values were significantly above the limit of detection, but were still below adult values. Beginning in October 1987, serum LH concentrations increased rapidly, coincidous with the breeding season, to a peak level of 4.1 ± 0.2 mg/L in November, and then declined to 0.5 ± 0.05 mg/L by April of 1988. This same pattern of serum LH concentrations was found in the GnRH-treated monkeys during the third year of life; the values in these monkeys were slightly but not significantly lower than those in the control monkeys. The serum LH concentrations also were slightly lower in the two 1983-born GnRH agonist-treated monkeys compared to those in the 3-yr-old age-matched control monkeys (Fig. 2, *bottom*).

The patterns of serum testosterone values during the third year of life in the 1984-born monkeys were similar to those of serum LH. Quantitatively, the differences in serum testosterone concentrations between the control and the GnRH agonist-treated monkeys were much greater (Fig. 3, *top*). In the control monkeys the mean serum testosterone levels rose from 4.9 ± 0.6 (±SE) nmol/L in September 1987 to greater than 15 nmol/L in October, November, and December 1987 before declining to 5.7 ± 0.9 nmol/L in January 88. During this same period, the mean serum testosterone levels in the GnRH agonist-treated monkeys never exceeded 5.5 nmol/L (effect of agonist treatment; $P < 0.01$). The differences in serum testosterone concentrations were comparable between the GnRH agonist-treated and control monkeys born in 1983 (Fig. 3, *bottom*).

The mean testicular volume was lower ($P < 0.05$) in the 1984-born GnRH agonist-treated monkeys compared to that in the control monkeys during the third year of life (September through May; Fig. 4, *top*). The GnRH

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TABLE 1. Body weights and crown-rump (CR) lengths in control (n = 4) and GnRH agonist-treated (n = 6) male rhesus monkeys born in 1984

	Treatment week					
	0	4	8	12	16	20
BW (kg)						
Control	0.55 ± 0.04	0.65 ± 0.06	0.85 ± 0.05	1.02 ± 0.06	1.21 ± 0.10	1.21 ± 0.04
Agonist	0.54 ± 0.03	0.72 ± 0.03	0.81 ± 0.04	0.91 ± 0.05	1.13 ± 0.05	1.25 ± 0.05
CR (cm)						
Control	21.1 ± 0.6	22.6 ± 0.8	24.1 ± 0.7	25.5 ± 0.6	26.6 ± 0.4	27.6 ± 0.3
Agonist	20.8 ± 0.5	22.7 ± 0.3	23.4 ± 0.7	24.9 ± 0.5	26.4 ± 0.4	26.9 ± 0.3

Values are the mean ± SE. GnRH agonist treatment was begun between 10 and 13 days of age and terminated between 122–125 days of age.

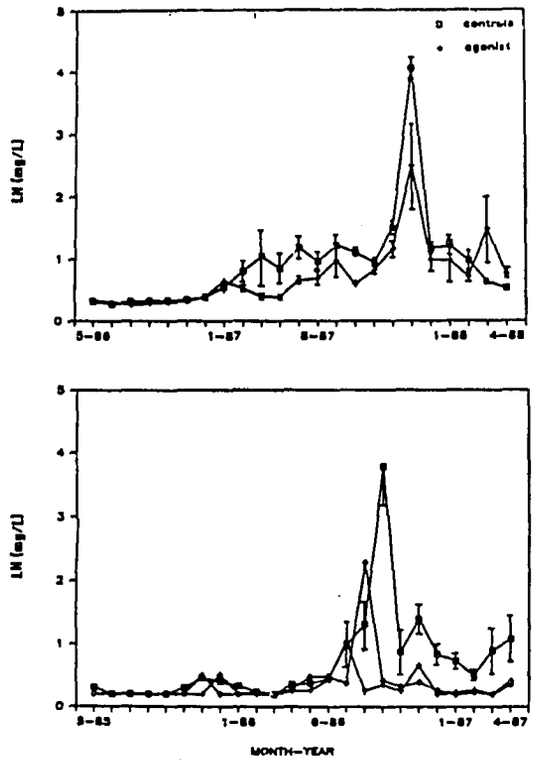

FIG. 2. Effect of neonatal GnRH agonist administration on mean (± SE) serum LH concentrations in rhesus monkeys from 2–4 yr of age. The animals in the *top graph* were born in 1984 (control, n = 4; agonist-treated, n = 6); those in the *bottom graph* were born in 1983 (control, n = 5; agonist-treated, n = 2). The individual values for the two agonist-treated monkeys born in 1983 are shown in the *bottom graph*.

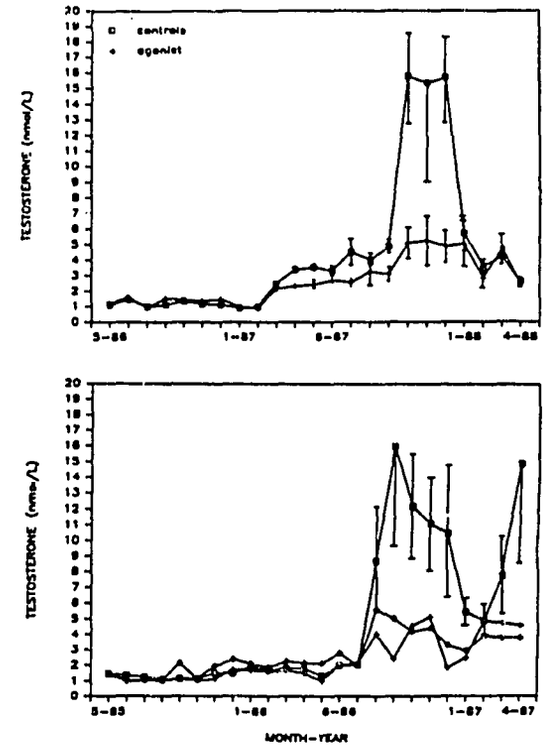

FIG. 3. Effect of neonatal GnRH agonist administration on mean (± SE) serum testosterone concentrations in rhesus monkeys from 2–4 yr of age. The animals in the *top graph* were born in 1984 (control, n = 4; agonist-treated, n = 6); those in the *bottom graph* were born in 1983 (control, n = 5; agonist-treated, n = 2). The individual values for the two agonist-treated monkeys born in 1983 are shown in the *bottom graph*.

agonist-treated monkeys born in 1983 also had smaller testes than the control monkeys during their third year (Fig. 4, *bottom*).

We were able to collect semen samples by electroejaculation from all 4 control monkeys born in 1984 [13 ejaculates/16 attempts (81%)] but from only 3 of the 6 GnRH agonist-treated animals [6 ejaculates/20 attempts (30%)] during the fall and winter of their third year. The sperm counts in 3 of the control monkeys were in the low normal to normal adult range (range, 20–2500 × 10^6/mL; mean ± SE, 532 ± 276 × 10^6/mL). We were able to collect only 2 samples from the fourth control monkey; both samples had low sperm counts (2–3 × 10^6/mL). The mean percent motile and percent live sperm/ejaculate

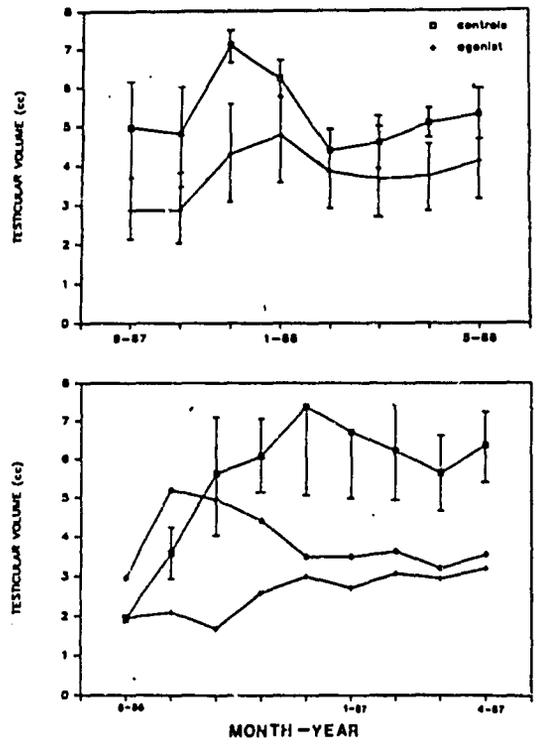

FIG. 4. Effect of neonatal GnRH agonist administration on mean (± SE) testicular volumes in rhesus monkeys during the third year of life. Animals in the *top graph* were born in 1984 (control, n = 4; agonist-treated, n = 6); those in the *bottom graph* were born in 1983 (control, n = 5; agonist-treated, n = 2). The individual values for the two agonist-treated monkeys born in 1983 are shown in the *bottom graph*.

were 65 ± 7% (±SE) and 73 ± 3%, respectively, for the 4 control monkeys. In the 3 GnRH agonist-treated monkeys who had an ejaculatory response, the sperm counts were low (1–67 × 10^6/mL; mean ± SE, 42.2 ± 27.6 × 10^6/mL), and the percent motile and percent live sperm per ejaculate values were comparable to those in the control monkeys.

The six monkeys born in 1984 who received GnRH agonist clearly fell into two separate groups, based both on their serum testosterone levels and whether we were able to collect semen samples from them during their third year of life (Fig. 5). A comparison of the serum testosterone data between the GnRH agonist-treated monkeys from which we were either able or unable to collect sperm revealed a significant interaction ($P < 0.025$) of the two variables (semen sample *vs.* no semen sample × time). Three monkeys had a subnormal but significant peripubertal rise in semen testosterone concentrations, and it was from the same monkeys that we

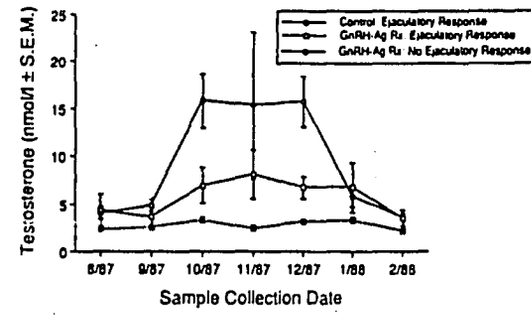

FIG. 5. Mean (±SE) serum testosterone concentrations in control and agonist-treated monkeys during the fall months of the third year of life. The animals were born in 1984. The agonist-treated monkeys were separated into two groups of three monkeys each according to whether we were able to collect semen samples from them.

were able to collect semen samples. The other three monkeys had neither a significant rise in serum testosterone concentrations nor an ejaculatory response during this period. The reduced serum testosterone levels in these three monkeys was probably a result of lower ($P < 0.025$) serum LH concentrations (data not shown).

The responses of 1984-born monkeys to an iv bolus dose of GnRH at 1, 2, and 3 yr of age are shown in Fig. 6. There were no differences in the serum LH responses to GnRH between the control and GnRH agonist-treated animals at any age, and the LH responses to GnRH increased with age in both groups (Fig. 6, *top*). The serum testosterone values both before and after GnRH treatments were reduced ($P < 0.05$) in the GnRH agonist-treated monkeys compared to those in the control monkeys at 3 yr of age (Fig. 6, *bottom*), but the incremental responses were similar. The serum testosterone responses to GnRH also were very similar in the GnRH agonist-treated and control monkeys at 1 or 2 yr. In both groups of monkeys the serum testosterone responses to GnRH increased with increasing age.

Neonatal GnRH agonist administration did not significantly affect body weight in monkeys between 10 days and 4 yr of age, although the tendency was for body weight to be reduced in the GnRH-agonist-treated monkeys between 2 and 4 yr of age (Table 2).

Discussion

These results suggest that the early postnatal period is a critical period in the maturation of the hypothalamic-pituitary-gonadal axis in male primates. During the first 3–5 months of life, there is activation of the hypothalamic-pituitary-testicular axis (1–12). We found that reversible inactivation of the pituitary and testes by GnRH agonist administration during the first 4 months of postnatal life in male monkeys retarded peripubertal testic-

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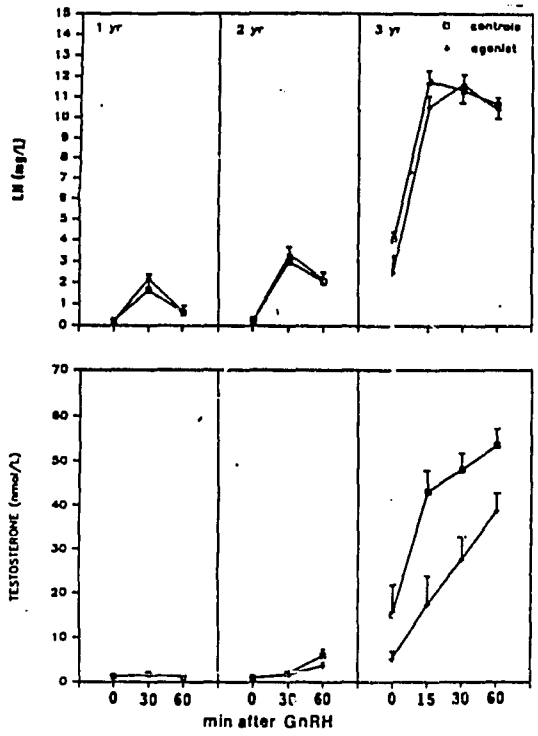

FIG. 6. Mean (±SE) serum LH (*top*) and testosterone (*bottom*) responses to an iv bolus dose of GnRH (5 μg/kg BW) in control and agonist-treated monkeys. The animals were given GnRH at 1, 2, and 3 yr of age. These animals were born in 1984. Control, n = 4; neonatal GnRH agonist-treated, n = 6.

ular development.

As we reported previously (20), GnRH agonist administration to neonatal male rhesus monkeys beginning soon after birth reduces serum LH and testosterone levels to very low levels, whereas serum LH and testosterone levels in control monkeys rise to adult values during the first 3 postnatal months. When GnRH agonist administration was terminated at 122–125 days of age, there was no rebound in either serum LH or testosterone. Thus, neonatal activation of the pituitary-testicular axis was not simply delayed, but was permanently prevented.

The decline in serum LH and testosterone levels during GnRH agonist administration in neonates was most likely due to a reduction of the pituitary response to GnRH. While we did not test pituitary responses to GnRH in the agonist-treated monkeys in this study, we reported previously (20) that male neonatal monkeys treated with a GnRH agonist did not have serum LH and testosterone responses to GnRH. Presumably, GnRH receptors in the neonatal pituitary, like those in the adult pituitary, are down-regulated by chronic GnRH agonist administration (25).

We found no differences in serum LH and testosterone levels between the control and GnRH agonist-treated monkeys from 6 months of age until early in the third year of life. During this period, serum LH and testosterone levels were low, characteristic of the juvenile phase of development (26), and the serum LH and testosterone responses to GnRH were minimal in both groups. Serum LH and testosterone levels began to rise during the third year in the control monkeys. The increase was small initially, but later accelerated with the approach of the breeding season in this species (27). In contrast, the serum testosterone rise increased considerably less during the third year in monkeys treated neonatally with the GnRH agonist. Although there was a tendency for serum LH levels to be lower in agonist-treated animals during the same period, these differences were not significant. The testicular volumes of these monkeys during the third year were smaller than those in the control monkeys. These results indicate that treatment with the neonatal GnRH agonist administration resulted in mild persistent hypogonadotropic hypogonadism.

Because blood samples were collected from the monkeys on a monthly basis, it is possible that differences in episodic LH and testosterone secretion between the control and the GnRH agonist-treated monkeys may have gone undetected. Since we were concerned that repeated experimental manipulation of the large social group (such as would be required for studying pulsatile LH and testosterone secretion) might confound or compromise our results, experiments of this type were not attempted.

The responses to GnRH during the third year provide further information concerning the retarded gonadal development in the GnRH agonist-treated monkeys. The serum LH responses in the GnRH agonist-treated and control monkeys were similar, as were the testosterone responses. These results suggest that neonatal GnRH

TABLE 2. Body weight in control and GnRH agonist-treated monkeys between 10 days and 4 yr of age

	Age						
	10 days	0.5 yr	1.0 yr	2.0 yr	3.0 yr	3.5 yr	4.0 yr
Control	0.55 ± 0.04	1.5 ± 0.1	2.7 ± 0.1	4.3 ± 0.1	6.3 ± 0.1	6.8 ± 0.3	7.4 ± 0.5
GnRH agonist	0.54 ± 0.03	1.3 ± 0.1	2.7 ± 0.1	4.0 ± 0.1	5.7 ± 0.3	6.2 ± 0.4	7.1 ± 0.6

Values are the mean ± SE.

agonist administration or the decreased LH and testosterone secretion that occurred in response to it altered development of the central nervous system centers governing episodic GnRH secretion, resulting in a delay in the onset of peripubertal episodic GnRH secretion and, consequently, in LH secretion and testicular development. Alternatively, LH secretion in response to endogenous GnRH was impaired, even though LH secretion in response to a pharmacological GnRH dose was not. A third possibility, that the GnRH agonist somehow altered testicular function directly, is not likely, since that might be expected to increase serum LH concentrations in the treated monkeys.

It is conceivable, but unlikely, that GnRH agonists have a direct effect on the central nervous system of neonates. In adult male and female monkeys, the inhibitory effects of GnRH agonists on gonadotropin secretion appear to be mediated entirely via down-regulation of pituitary GnRH receptors and postreceptor modification of LH secretion (28–30), and there is no evidence available to suggest that GnRH agonists alter GnRH secretion by the hypothalamus. Moreover, there is little evidence that GnRH analogs have a direct effect on the primate testis. The vast majority of studies, including several from our laboratory, indicate that in adult primates GnRH analogs do not alter testicular function directly (28, 31, 32). Thus, we believe it unlikely that the GnRH agonist had a direct effect on the development of either the central nervous system or testes. We, therefore, believe that its effect was on the pituitary, and the consequence was a poor pubertal increase in LH secretion.

It appears that the GnRH pulse generator is functional in the primate fetus (26). After birth, GnRH secretion and, therefore, LH secretion are episodic and circadian in primate males, and serum LH and testosterone levels reach adult levels (8, 10, 20). Moreover, bilateral orchidectomy of rhesus infants at 1 week of age causes a rise in LH and FSH secretion equal to that after castration in the adult, and LH secretion is pulsatile with a pulse frequency of one pulse per h in such animals (10, 26, 33). These data suggest that the hypothalamic-pituitary-testicular axis is fully mature at birth in male primates (26). However, this conclusion is primarily based upon data from male monkeys orchidectomized shortly after birth. Therefore, it is impossible to determine whether these monkeys would have a normal onset of puberty or normal peripubertal changes. The data from this study, using a GnRH agonist to induce reversible neonatal castration, suggest that the enhanced activity of the testis of neonatal primates may be a critical event in the developmental process that ultimately leads to sexual maturation in male primates.

It is also possible that neonatal testosterone secretion may influence not the central nervous system centers involved in the regulation of pituitary function, but, instead, those involved in the development of social and sexual behavior. The monkeys in this study were reared in a large social group for the first 3 years of life. Rose and collaborators (27) found that the peripubertal rise in serum testosterone levels in 3-yr-old adolescent male monkeys was inversely proportional to the number of adult males in the social group in which they were reared. This result may reflect the effect of the adult males on the rank of the adolescents in the social group (27). In this regard, the suppression of neonatal testosterone secretion that occurred in the GnRH agonist-treated monkeys may have influenced the interaction of these males with other members of the group, resulting in a suppression of testosterone secretion during the third year.

There appear to be parallels between neonatal GnRH agonist-treated male rhesus monkeys and human infants suffering from cryptorchidism as a result of early transient deficiency of testosterone secretion (19). This cryptorchid condition is caused by a primary deficiency of LH secretion which persists through childhood and early puberty and then disappears at midpuberty (19). It has been hypothesized that early postnatal deficiency in gonadotropin secretion and Leydig cell function contributes to impaired testicular descent and maturation (19). Adult men treated in childhood for cryptorchidism also have a high frequency of oligospermia (19). It is noteworthy that the three GnRH agonist-treated monkeys who had an ejaculatory response during the breeding season of their third year of life also had lower than expected sperm counts, although this conclusion is based on only six semen samples.

In summary, the induction of hypogonadotropic hypogonadism in neonatal male rhesus monkeys alters normal testicular development and peripubertal endocrine events. We do not yet know whether this early postnatal gonadotropin and testosterone deficiency has a permanent or only a temporary effect on pituitary-testicular function. Although these results are based on a limited number of monkeys and should not be overinterpreted, the consistency of the results across the two birth cohorts suggests that the early neonatal period may represent another period, in addition to the early prenatal period, when androgens exert an organizational influence (34) on the developing central nervous system of primates (35).

Acknowledgments

We thank Wyeth Laboratories for providing the GnRH agonist used in this study, the NIDDK for providing the rhesus monkey pituitary reference preparation (LER-1909-2) used in the LH bioassay, and Dr. Gordon Niswender for providing the antiserum for the testosterone

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RIA. We also thank Mr. Thomas Buckner, Ms. Toni Duffey, Ms. Robin King, and Ms. Janice Tittle for their expert technical assistance. The Yerkes Regional Primate Research Center is fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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