Certainly this assumption deserves further investigation and it cannot be entirely ruled out at present that increased potency may be due to a reduced enzymatic rate of degradation[9]. An interesting correlation between [1-Aib]angiotensin II and [1-N^4, N^4-diMe-Asn]-angiotensin II reveals that dimethylation of the N^4-asparaginyl carboxamide reduces the affinity of the analogue, probably because of repulsion of the side chains of essential residues like 3-Val and 4-Tyr[18,19].

1 All optically active amino acids are of the L configuration. Abbreviations used follow the recommendations of IUPAC-IUB as found in Biochemistry *14* (1975) 449 and Biochem. J. *126* (1972) 773. Other abbreviations: Aib, α-aminoisobutyric acid or α-methyl-alanine.

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An early effect of testosterone propionate upon hypothalamic function in the neonatal rat

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Summary. Rats treated neonatally with testosterone propionate exhibit a reduced uterine growth response to estradiol administration prepubertally. This androgen-induced impairment is the consequence of developmental effects on both the ovary and the hypothalamic-pituitary complex, although the latter is the more sensitive.

Neonatal treatment with estrogens or androgens is known to result in impaired reproductive function in the adult rat at hypothalamic[1], ovarian[2], and uterine[3] sites. Futhermore, the etiology of this impaired or reduced reproductive tissue function is clearly evident in the immature rat[4-6]. The impaired uterine responsivity evident in the androgenized or estrogenized prepubertal rat appears to be the consequence of decreased function of the hypothalamic-pituitary-ovarian axis[6].

The purpose of this work was to gain some insight into the relative influence of altered hypothalamic or ovarian function upon the development of the uterine response syndrome observed in the prepubertal rat injected with sex steroids during infancy. Only neonatal testosterone propionate (TP) exposure was utilized in this study since, unlike estradiol, it results in an impaired uterine response to exogenous estrogen without a concomitant reduction in cytoplasmic estrogen receptor in the immature rat uterus[5,6].

Materials and methods. Sprague-Dawley derived rats were obtained from Charles River Breeding Labs and bred in the UAH animal facility. The morning on which pups were found was designated day 1 of life. Testosterone propionate (Sigma Chemicals) was injected s.c. on day 3 in 0.1 ml peanut oil at a dose of 1250 µg. Controls received an equal volume of the oil vehicle. On day 8 ovaries were reciprocally transplanted between animals which had been previously treated with TP or peanut oil. Control transplants to the dorsal neck region were also performed on animals having received the peanut oil injection on day 3. All transplant procedures were carried out under hypothermia-induced anesthesia and involved short-term culture in ice-cold Eagles Medium (Difco).

At 21 days of age the animals in the various treatment groups were injected s.c. with either 0.1 µg or 1.0 µg estradiol-17β in physiological saline. Uteri were excised, trimmed of connective tissue, and weighed on an analytical balance 24 h after the estradiol injection. The weight of the uteri from the experimental treatment groups was expressed relative to the weight of the uteri from the control treatment groups. The presence of a functional ovarian graft in the experimental animal was also confirmed at autopsy.

Results. Neonatal exposure to TP produces an apparent impairment of hypothalamic and ovarian function as indicated by the parameter of prepubertal uterine growth response to exogenous estradiol (table). These results are in general agreement with the reduced uterine responsivity noted in intact prepubertal rats injected neonatally with TP[4-6]. However, normal rats with ovarian transplants from TP-treated individuals exhibited a less severe impairment of uterine responsiveness than those animals treated with TP and possessing normal ovarian transplants. 21-day-old

Effect of ovarian or hypothalamic exposure to testosterone propionate (TP) neonatally upon prepubertal uterotrophic responses

Treatment	24 h uterine growth response to estradiol-17β			
	Mean weight (mg) ± SEM		Relative growth	
	0.1 μg	1.0 μg	0.1 μg	1.0 μg
Control ovarian transplant	40.7 ± 1.1	42.5 ± 1.4	1.000 (12)	1.000 (11)
Normal rat + TP ovaries	38.8 ± 2.0[b]	38.0 ± 1.4[a,b]	0.953 (8)	0.894 (10)
TP rat + normal ovaries	29.4 ± 1.4[a]	34.5 ± 1.8[a]	0.722 (11)	0.812 (11)

Female rats were injected s.c. on day 3 of life with 1250 μg testosterone propionate in peanut oil. Control rats received 0.1 ml of the oil vehicle. Ovaries were transplanted to a surgically-created dorsal s.c. pocket in the neck on day 8. Either 0.1 or 1.0 μg of estradiol-17β was injected s.c. on day 21 and uteri obtained 24 h later for growth determination. The mean uterine weight response for the control ovarian transplant group was set equal to 1000 for each estradiol dose and the mean response of the other treatment groups expressed in relation to the control response at the respective hormone concentration. The number of determinations for each experiment are given in parentheses. [a] Indicates significant differences ($p < 0.001$) between the mean uterine weight response in the experimental group and the respective control response. [b] Indicates a significantly different mean uterine weight response between animals in which only the ovaries were neonatally exposed to TP and those in which only the hypothalamus was exposed. This difference is $p < 0.001$ and $p < 0.01$ for the 0.1 and 1.0 μg estradiol injection, respectively.

rats in the former treatment group injected with 0.1 μg estradiol-17β, e.g., had a 24-h uterine weight of 38.8 ± 2.0 mg which was not significantly different than the uterine weight of 40.7 ± 1.1 mg observed in the estradiol-injected transplant control group. The uterine growth of 29.4 ± 1.6 mg measured in TP-treated rats with normal ovaries was significantly ($p < 0.001$) lower than the uterine response of the transplant control group. These weight data compare to uterine weights of 27.9 ± 1.0 mg in intact 21-day-old rats injected with physiological saline solution. At the higher estradiol dosage on day 21, both TP-treated rats with normal ovaries and normal rats with TP ovaries had uterine growth responses that were significantly ($p < 0.001$) lower than that measured in the transplant control group. However, the animals receiving the TP-exposed ovary transplants produced a significantly greater uterine growth response to both the 0.1 μg ($p < 0.001$) and the 1.0 μg ($p < 0.01$) injection of estradiol-17β on day 21 than the TP-treated rats with normal ovaries.

Discussion. In a previous report, the degree of reduced uterine responsivity at 21 days of age directly corresponded to the degree of reduction in the weight of the ovaries after neonatal steroid treatment[6]. It was suggested that endogenous estrogen secretion during infancy could be important in end organ conditioning in the development of a functionally competent uterus since neonatal ovariectomy produced a uterine response syndrome characteristic of one observed in sex hormone-treated neonatal rats having the most severe reduction in ovarian size.

This study reinforces the concept of neonatal sex steroid treatment drastically impairing the functional development of the uterine response to exogenous estradiol at weaning. However, these data suggest that the consequence of hypothalamic exposure to TP neonatally plays a much greater role in the etiology of the reduced uterine response syndrome than that resulting from any androgenic effects upon ovarian development.

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Impaired TSH response to TRH after intravenous ranitidine in man

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Summary. Ranitidine, given by i.v. infusion, decreased TSH response to TRH in 7 subjects. This effect, completely different from that obtained with cimetidine, suggests that the action of ranitidine is likely to be independent of H_2-receptor blockade and rather may be related to the cholinergic-like effect of this drug.

The problem of the interaction between H_2-receptors and pituitary hormone secretion has been raised by several reports concerning the most widely employed H_2-receptor antagonist cimitidine[1]. Recently a new H_2-receptor blocker, namely ranitidine, became available for experimental and clinical use and was found to be effective and safe in the treatment of duodenal ulcer disease[2].

A few reports[3-5] indicated that this compound, given at therapeutic oral doses, is devoid of any endocrine effect. Most of the above reports pointed out the lack of interference of this compound with basal and TRH-stimulated prolactin secretion. A release of prolactin by ranitidine was found though by Delitala et al.[6], but only following i.v. exceedingly high doses of the compound (up to 6 times the therapeutic dose). In the light of the above findings, we decided to investigate more thoroughly the possible interference of ranitidine with the pituitary TSH response to TRH in healthy volunteers.

Subjects and methods. 7 healthy male volunteers (aged from 24 to 61 years), without any endocrine or metabolic disease were studied. Informed consent was obtained from all the subjects. On different days and in random order, a test stimulus with TRH (200 μg, i.v.) was performed in each subjects during saline (control studies) or ranitidine infusion. At least 3 days were allowed to elapse between tests. After an overnight fast, indwelling needles were inserted bilaterally into antecubital veins which were kept patent with a slow infusion of physiological saline: one of them