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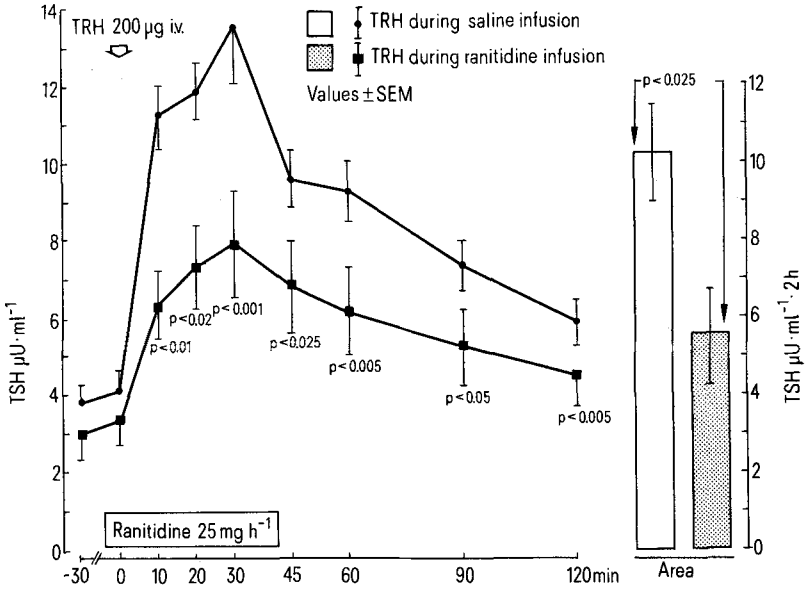
Summary. Ranitidine, given by i.v. infusion, decreased TSH response to TRH in 7 subjects. This effect, completely different from that obtained with cimetidine, suggests that the action of ranitidine is likely to be independent of H_2-receptor blockade and rather may be related to the cholinergic-like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



Left side: TSH response to TRH during saline (●——●) or ranitidine (■——■) infusion in 7 healthy volunteers. Right side: TSH secretory area. Vertical bars are standard errors of the mean.

was used for drug administration, the other one for repeated blood withdrawal. Following the collection of 2 blood samples (−30 and 0 min), ranitidine was infused from 0 to 60 min at the dose of 25 mg · h^{-1}. At zero time TRH was given as a bolus injection and further blood samples were collected over a 2-h period (fig.).

TSH in plasma was assayed by a double antibody radioimmunoassay using Biodata reagents. Ranitidine was added to the tubes containing the solutions for the standard curve in concentrations up to 1 µg · ml^{-1}. No interference in RIA procedure could be demonstrated.

Quantitative evaluation of hormone secretion was made by an integration of area under the plasma immunoreactivity, after subtraction of basal values. Calculations were performed by using a computer program and data expressed in µU · ml^{-1} · 2 h. All data presented are mean ± SEM. Student's t-test for paired data was used to determine statistical significance.

Results. Results obtained are depicted in the figure. The TSH response to TRH was significantly decreased - by about 45% at peak time - during ranitidine infusion, in comparison with control (saline) values. Also, the TSH areas under-the-curve were significantly different.

Discussion. Our experiments showed that ranitidine, given by i.v. infusion, is able to decrease significantly the TSH response to TRH. In addition, in preliminary experiments performed in 6 patients whose TSH levels were abnormally high as a consequence of primary hypothyroidism, ranitidine was again capable of inducing a consistent decrease of circulating TSH. Our data differ from those obtained by Pasquali et al.[5] who found that chronic ranitidine administration did not change the TSH response to TRH. These authors, however, performed the experiment 12 h after the last oral administration of ranitidine, with a consequent very low plasma levels of the H_2-antagonist[7]. On the contrary in our experimental conditions higher and constant plasma levels of ranitidine were guaranteed by i.v. infusion. Two hypotheses may be suggested to explain this peculiar effect of ranitidine:

1. The decrease of TSH is a direct consequence of the H_2-receptor blockade.

2. The decrease of TSH is a non-specific property of the molecule of the H_2-antagonist.

Experiments performed with cimetidine, another H_2-antagonist and betazole, an H_2-agonist, gave contradictory results[8,9]; therefore the use of modern selective H_2-agonists like impromidine[10] are necessary to investigate the 1st hypothesis.

As for the 2nd hypothesis, recent data in the literature tend to emphasize the occurrence of side-effects independent of the H_2-receptor blockade for all the available H_2-antagonists, including ranitidine[2].

Ranitidine was found to be devoid of some of the endocrine effects peculiar to cimetidine[2]; on the other hand it is not active on dopamine[11] and on adrenergic receptors[12]. Conversely it has a remarkable effect on cholinergic receptors although not in all tissues and species[13]. In the rabbit, acetylcholine was found to inhibit TSH release[14], and the occurrence of muscarinic receptors in the sheep pituitary has been demonstrated[15]; therefore one may tentatively speculated that this endocrine effect of ranitidine could be related to an interference with the cholinergic system.

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