Effect of Antihistamine on Reproductive Organ and Body Growth and Attainment of Puberty in Female Rats[1] (34587)

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Antihistamines are widely used for symptomatic relief of common cold, Parkinsonism, and especially of exudate allergy such as pollinosis and uticaria (1–3). Beta-dimethylamino-ethyl-benzhydryl ether hydrochloride (Benadryl)[2] is also recommended for the management of emotionally disturbed children (4). Considerable information is available concerning the various side effects of these agents. However, less attention has been given to the effect of prolonged administration of antihistamines on the reproductive system in the immature animals. The present report describes the effect of Benadryl on body and reproductive organ growth and the attainment of puberty in immature female rats.

Materials and Methods. Weanling female rats of the Sprague-Dawley strain[3] were divided randomly into control and test groups. They were maintained under the same environmental conditions, fed with Purina chow, *ad libitum,* and supplied with tap water. The initial body weight was measured on day 22. Beginning on day 23, rats in the test group received, regardless of body weight, daily subcutaneous injections of 50 μg of Benadryl in 0.1 ml solution for 14 days. Controls were treated similarly with distilled water. Twenty-four hr after the last injections, rats were killed by chloroform inhalation. The final body weight was measured and the opening of the vaginal orifice was examined immediately; the ovaries, uteri, and adrenal glands were removed and weighed on a torsion balance. Meanwhile, the presence of corpus luteum and ripening graafian follicles on the ovaries also was observed. The body growth and the growth of the reproductive organs were judged, respectively, by the body weight gain or final body weight and the final weights of the ovaries and uteri. The attainment of puberty was judged by the opening of the vagina and the presence of corpus luteum in the ovaries. The relative weights of ovaries, uteri, and adrenal glands (organ weight in mg/100 g of body wt) were calculated. The mean parameters of final body weight, body weight gain, absolute and relative organ weights of Benadryl-treated rats were compared by Student's t test with those of the appropriate controls. The differences were considered statistically significant when the levels of confidence were 95 % or higher.

Results. As shown in Table I, the mean final body weight, body weight gain, as well as the absolute and relative weights of the ovaries and uteri of Bendaryl-treated rats decreased significantly in comparison with those of the appropriate controls. This decrease in weight indicated that the body growth and the growth of reproductive organs were retarded. However, in treated rats, the mean absolute adrenal gland weight (38.5 $\pm$ 1.5 mg) was essentially the same as the controls (39.5 $\pm$ 1.3 mg). In fact, the mean relative adrenal weight (37.7 $\pm$ 2.0 mg) of treated rats was significantly higher than the controls (30.1 $\pm$ 0.9). None of the Benadryl-treated rats showed signs of opening of the vagina, whereas five out of eight rats (or 62.5 %) in the control group had the vagina opened at

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[2] Parke-Davis and Company, Detroit, Michigan.

[3] Holtzman Company, Madison, Wisconsin.

TABLE I. Effect of Antihistamine on Body and Reproductive Organ Weights and Vaginal Opening in Female Rats.

Treatment[a]	Body wt (g)		Ovarian wt		Uterine wt		Rats with vagina opened (%)
	Final	Gain	(mg)	(mg/100 g of body wt)	(mg)	(mg/100 g of body wt)	
Vehicle (8 rats)	131.5 ± 2.2[b]	82.0 ± 1.6	63.4 ± 2.4	48.1 ± 1.3	149.9 ± 9.1	114.0 ± 6.6	62
Benadryl, 50 μg/rat (7 rats)	102.7 ± 3.2[c]	52.9 ± 3.1[c]	31.3 ± 1.0[c]	30.9 ± 1.3[c]	57.2 ± 4.3[c]	55.5 ± 3.4[c]	0

[a] Daily subcutaneous injections for 14 days.
[b] Mean ± SE.
[c] $p < 0.001$ compared to appropriate controls.

the time of autopsy when the animals were 37 days of age. Gross examination of the ovaries revealed that none of the ovaries of treated rats had corpus luteum or mature ovarian follicles, whereas the ovaries of rats with vaginal opening in the control group had fresh corpora lutea. The ovaries of the other rats in the control group showed mature ovarian follicles.

Discussion. The data of this experiment indicate that Benadryl administered for a relatively long duration to immature female rats caused a retardation of body growth, of growth of reproductive organs, and of attainment of puberty. According to body weight, the daily dose of Benadryl was much lower than that used clinically. Although information obtained from experimental animals cannot be transferred directly to humans, it offers preliminary evidence for the need of clinical observations in the emotionally disturbed girls receiving prolonged Benadryl treatment. Benadryl treatment appeared to be more detrimental to ovarian and uterine growth than to body growth. This was evidenced by smaller relative weights of ovaries and uteri in treated animals than in the controls. The significant increase in relative weight of adrenal glands in the treated rats was due to the significant decrease in body weight indicating that the adrenal gland growth was less affected than the body and reproductive organ growth. It was also possible that the administered Benadryl exerted a stress effect and caused an increase in pituitary ACTH secretion which stimulated the adrenal glands.

The action mechanisms of the retardation of body and reproductive organ growth in Benadryl-treated immature female rats are not known. It has been reported that acute starvation caused a decrease in the synthesis and release of somatotropin releasing factor (SRF) by rat hypothalamus which in turn resulted in a decreased production and release of somatotropic hormone (STH) by the anterior pituitary (5–8). Restricted food intake or malnutrition also has been reported to cause a decrease in rat pituitary gonadotropin content (9), although contradictory

results have been reported (10). Under the present experimental conditions, the synthesis and release of pituitary STH and gonadotropin(s) may have decreased because of chronic malnutrition resulting from prolonged Benadryl treatment which might have interfered with the digestion through decreased secretion of all exocrine (except gastric) glands (11). Such distrubed digestion also would interfere with the availability of protein supply which has an important influence on ovarian maturation (12) and general body growth. It was also possible that Benadryl treatment caused an increase in ACTH and adrenocorticoid secretion which caused an inhibition of the action (13) and secretion (14) of pituitary STH as well as a retardation of ovarian growth and maturation (15). Since Benadryl exerts a sedative effect which might have interfered directly or indirectly with the synthesis and release of hypothalamic releasing factors, STH and possibly gonadotropins. Benadryl treatment might have caused a decrease in ovarian responsiveness to pituitary gonadotropins (16). These hypotheses are supported by the retardation of body growth and of growth and development of the ovaries with a concurrent increase in relative adrenal weight in the Benadryl-treated rats. Analysis of pituitary hormone releasing factors of the hypothalamus, pituitary STH and gonadotropin(s) content, plasma STH concentration, as well as adrenocortical and thyroid functions of Benadryl-treated immature rats may offer more valuable information.

The retardation of uterine growth in Banadryl-treated rats was mainly due to the interference with the growth and development of ovarian follicles. This would have delayed the initiation of the secretion of estrogen which is the primary hormone in stimulating uterine growth and opening of the vagina. In rat uterine tissues, it has been reported that estrogens caused a release of histamine which induced vasodilation to facilitate uterine growth and that Benadryl inhibited estrogen activity (16). In the present experiment, the administered Benadryl blocked the effect of histamine (possibly induced by a small amount of endogenous estrogen) which would interfere with the uterine growth. Furthermore, it has been reported that in the absence of estrogen the pituitary STH could cause a prepubertal subnormal uterine growth in the rat (17). Thus, the possible interference with pituitary STH secretion in Benadryl-treated rats also would interfere directly with the uterine growth. Since antihistamines competitively inhibit histamines, it might be of interest to study whether or not administration of large doses of estrogen, STH, and/or gonadotropins would prevent the retardation of the growth of reproductive organs in Benadryl-treated immature female rats.

Summary. Weanling Sprague-Dawley strain female rats were divided randomly into test and control groups. Beginning on day 23, rats in the test group received, regardless of body weight, daily subcutaneous injections of 50 μg of Benadryl for 14 days, controls received distilled water. Benadryl treatment resulted in a retardation of body growth, growth of reproductive organs, and attainment of puberty.

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