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ANTIFERTILITY EFFECTS OF SC-20775 IN NORWAY AND POLYNESIAN RATS

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Abstract: SC-20775 (17 α -ethynyl-11 β -methylene-18 α -pregnen-20-one-3-cyclopentyl ether), a synthetic estrogen, showed promise as a chemosterilant for Norway rats (*Rattus norvegicus*) and Polynesian rats (*R. exulans*) in three preliminary laboratory studies. When females of both species were offered single feedings of 0.0012 or 0.012 percent SC-20775 in bait and then paired with males, birth of litters was 5–18 days later than for control females. When lactating female Norway rats were treated by gavage with 0.1, 1, or 10 mg/kg SC-20775, nursing young showed a significant percentage of gonadal abnormalities at 120 days; these effects, particularly testis weight in males, appeared dose-dependent. When small colonies of Polynesian rats (5 females and 2 males each) were offered SC-20775 in bait five times during a 70-day period, bait aversion reduced consumption (average SC-20775 per baiting, 0.58 mg/kg), but only 4 of 17 treated females became pregnant versus 13 of 20 control females.

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In the state of Hawaii, rats do major damage to sugarcane crops; the heaviest losses are caused by Norway and Polynesian rats, particularly the latter (Hood 1968). In a search for methods to alleviate this problem, one of the techniques this laboratory is investigating is the chemical inhibition of reproduction; we have screened a number of compounds for this purpose. One, SC-20775, a synthetic estrogen provided by G. D. Searle & Company (reference to trade names does not imply endorsement of commercial products by the U.S. Government), showed promise as a control agent for both Norway and Polynesian rats in three preliminary tests described here.

METHODS

Polynesian rats used in these studies were live-trapped at Hilo, Hawaii, and air-freighted to this laboratory; Norway rats were live-trapped locally. All rats were held at least 30 days before testing. Except in the colony breeding study, rats of the two species were maintained in separate rooms where temperature and light were controlled (72–78 F and a 14:10 hour light:dark cycle). Unless otherwise indicated, food (lab chow) and water were available

ad libitum. During baiting periods, no food source other than the bait was available. The bait used in the cage breeding and colony breeding studies was a mixture of 80 percent ground lab chow and 20 percent dried molasses. Treated bait was surface-coated with SC-20775 in ether; the solvent was removed in a rotary flash evaporator. The control bait was treated in a similar manner, but without SC-20775. In the cage breeding study, the bait mixtures (treated and untreated) were formed into 50-mg tablets in a Stokes' single punch tablet machine. All rats were necropsied and examined for gross gonadal abnormalities.

Cage Breeding Study

Adult female rats—30 Norway and 36 Polynesian—were randomly assigned to three treatment groups each. The rats were individually caged and offered untreated bait tablets for two nights. The third night, one group (controls) were again offered untreated tablets, but the second and third groups were offered tablets containing 0.0012 and 0.012 percent (by weight) SC-20775. The treated food (5 and 15 g per rat, Polynesian and Norway, respectively) was left in the cage for 16 hours. The day

Table 1. Effects on fecundity when 30 Norway and 36 Polynesian rat females were each offered SC-20775 in bait and then paired with a male.

Rat species	SC-20775 treatment		No. of females that gave birth	No. of days	
	% in feed	mg/kg eaten (mean \pm sd)		Between pairing and parturition (mean \pm sd)	Parturition delayed (from controls)
Norway	0	0	9	26.0 \pm 4.5	
	0.0012	0.21 \pm 0.18	9	30.9 \pm 4.6	4.9
	0.012	2.00 \pm 1.05	7	37.3 \pm 6.8*	11.3
Polynesian	0	0	7	27.0 \pm 3.0	
	0.0012	0.46 \pm 0.19	3	32.0 \pm 6.1	5.0
	0.012	2.16 \pm 1.68	7	45.1 \pm 7.6*	18.1

* Significantly different from control and 0.0012 percent treatment at $P < 0.05$.

After dosing, an untreated male was placed with each female, and these pairs were held until the female gave birth or until 70 days after pairing. Immediately after birth, the litters were killed and counted, and the adult females were killed and necropsied.

Study of Effect on Nursing Young

Within 48 hours after parturition, 28 separately caged lactating female Norway rats were randomly assigned to 4 groups, treated by gavage, and returned to their litters. The control group received only the carrier (corn oil); the other three groups received the carrier containing 0.1, 1.0, or 10.0 mg/kg SC-20775. Surviving young were weaned at 22 days of age and caged separately by treatment group and sex. At about 120 days of age, the young were killed and necropsied.

Colony Breeding Study

Eight colony pens (3.0 \times 3.0 \times 1.2 m) were placed in two large Butler buildings where light was controlled (14:10 hour light:dark cycle). The pen floors were covered with about 15 cm of wood chips; temperatures under this covering ranged from 64 to 87 F during the study. There were two treatment and two control pens in each building; each was provided with nesting material and 20 liter-size cans for

harborage. Five adult Polynesian rat females were placed in each pen and given lab chow for 5 days. On the sixth and seventh days, each pen received 400 g of ground bait (80 percent ground lab chow, 20 percent dried molasses, overcoated with 7 percent glycerol); the four control pens received untreated bait, and the four treatment pens received bait containing 0.005 percent SC-20775. On the eighth day, lab chow was offered again, and two adult males were added to each pen. All rats were offered the bait for 2 days at 14-day intervals (2 days bait, 12 days lab chow). Because of aversion problems, for the fourth and fifth baitings the bait was changed to a commercial cereal (oatmeal with brown and maple sugar) containing 0.0125 percent SC-20775. At 70 days, all adult rats were collected, killed, and necropsied.

RESULTS AND DISCUSSION

Cage Breeding Study

The results of this study are summarized in Table 1. Breeding was relatively poor in both treated and control animals, particularly among Polynesian rats. At necropsy, the reproductive tracts of males and females that had not produced litters appeared normal. The treatment had no apparent effect on the reproductive tracts of

Table 2. Effects on gonads of nursing young when 28 lactating female Norway rats (seven per group) were given a single oral dose of SC-20775.

Dose SC-20775 (mg/kg)	No. females with surviving litters	Female offspring		Male offspring		
		No. examined	% showing abnormalities	No. examined	% showing abnormalities	Mean testis weight (g/100 g body weight)
0.0	7	31	0.0 ^a	18	0.0 ^b	0.5558 ^b
0.1	7	34	73.5	12	0.0	0.5853
1.0	6	17	100.0	20	20.0	0.4788
10.0	5	18	100.0	14	78.6	0.4042

^a Means not connected by the same vertical line are significantly different at $P < 0.01$.

^b Means not connected by the same vertical line are significantly different at $P < 0.05$.

adult females or the number of young in their litters. For both species, however, the group receiving 0.012 percent SC-20775 gave birth significantly later ($P < 0.05$) than the other two groups; the delay (from the time control females gave birth) averaged 11.3 days in Norway rats and 18.1 days in Polynesian rats. In preliminary trials, 10 Norway and 12 Polynesian female rats were treated by gavage with SC-20775 at 0.5 mg/kg; the mean time between introduction of a male and parturition was 37.6 ± 3.6 days for Norway rats and 38.7 ± 7.7 days for Polynesian rats (mean \pm standard deviation). The results of the cage breeding study, as well as the preliminary trials, clearly indicated that SC-20775 can inhibit pregnancy in both rat species. Although poor breeding reduced the reliability of the results somewhat (only three Polynesian rats in the 0.0012 percent group gave birth), the length of delay in conception appeared to be dose-dependent.

Study of Effect on Nursing Young

Various steroid hormones administered to neonate rodents can cause gonadal changes. For example, when Rudel and Kincl (1966) treated by gavage lactating female laboratory rats with 100 μ g of mestranol for 5 days following parturition, the nursing females in the litter had not ovulated at 45 days and the males had significantly reduced seminal vesicles and atrophied testes.

However, Mischler et al. (1971) did not find any significant alteration in the fertility of the litter when lactating females were treated by gavage with W3566 (17 α -ethanylestradiol-3-cyclopentyl ether) or mestranol, even with a large single dose of 1.0 mg within 4 hours after parturition.

The results of the present study are summarized in Table 2. SC-20775 had clearly affected the reproductive organs of nursing young. Females showed distended uteri and inactive ovaries; males showed lesions on the caput epididymidis, a lack of sperm in the cauda epididymidis, necrotic tubules, and atrophied testes. The percentage of young showing these changes was related to dose. In females, the difference between treated and untreated animals was highly significant ($P < 0.01$). Males were not as sensitive, and only those in the highest treatment group showed a significantly larger percentage of abnormalities than the controls ($P < 0.05$). The dose-dependent effect was evident in testes weights, however; the intermediate and high treatment groups differed significantly ($P < 0.05$) from the low treatment group and controls, and also from each other.

Colony Breeding Study

The results of this study are summarized in Table 3. Consumption of SC-20775 treated bait dropped off somewhat during the second baiting and considerably during

Table 3. Effects on fecundity of Polynesian rats in eight small colonies (five females and two males each) when SC-20775 was offered in bait five times during a 70-day period.

Group	Mean amount SC-20775 (mg/kg) eaten each baiting period					Adult females		
	1st ^a	2nd	3rd	4th	5th	Total	No. pregnant ^b	Total no. fetuses ^b
Control	0.00	0.00	0.00	0.00	0.00	20	13	39
Treated	0.80	0.58	0.18	1.02	0.20	17 ^c	4 ^d	10 ^d

- ^a Males not present during first baiting.
^b Includes as fetuses two litters newly born at end of test.
^c Three females not recovered.
^d Significantly different from control at $P < 0.05$.

the third, while control bait consumption remained normal. Changing the bait brought consumption up again during the fourth baiting, but it again dropped to unacceptable levels in the fifth baiting. Overall, consumption of SC-20775 averaged only 0.56 mg/kg per baiting period, with a range of 0.20 to 1.02 mg/kg, during the 70-day study. Nevertheless, the number of pregnancies in treated females was significantly less ($P < 0.05$) than in controls, indicating the chemical affected fertility. Two males, one treated and one control, died during the study. No gonadal abnormalities were evident at necropsy in any adult test animals, male or female.

CONCLUSIONS

These three studies indicated that SC-20775 had significant antifertility effects in both Norway and Polynesian rats. In adult females, relatively low doses (1-3 mg/kg)

inhibited pregnancy and caused gonadal abnormalities in nursing young of both sexes. Although the common problem of aversion after one or two exposures must be overcome before SC-20775 can be utilized effectively in baiting programs, the compound shows potential as an antifertility compound.

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