strengthen the idea that isoenzymic shifts underlie the mechanism of cardiac adaptation to new functional demands.

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Inhibition of tumor promotion by a lecanoric acid analogue[1]

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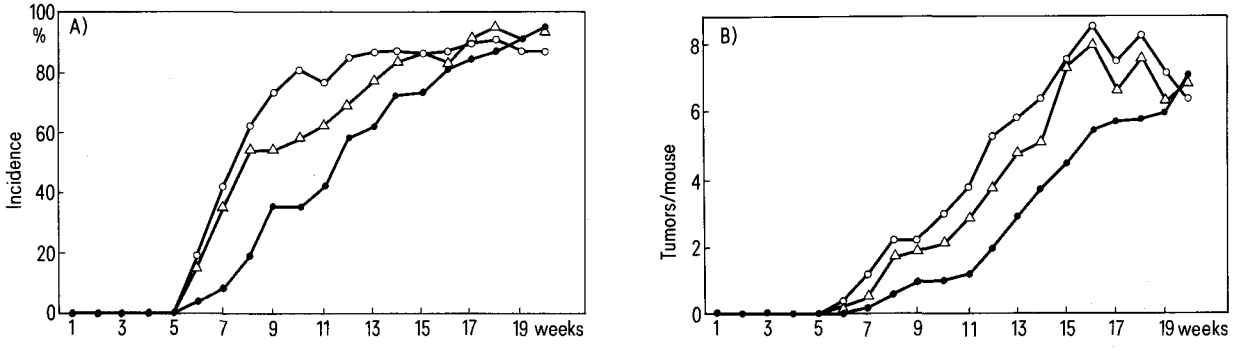
Summary. 3′,5′-Dichloro-2,4′-dihydroxybenzanilide, an inhibitor of histidine decarboxylase, inhibited skin tumor promotion induced by 12-O-tetradecanoylphorbol-13-acetate in mice.

Lecanoric acid has been isolated from culture filtrates of *Streptomyces* as an inhibitor of histidine decarboxylase[2]. Because lecanoric acid was easily metabolized in animals, a number of its analogues containing a peptide bond in place of an ester bond were synthesized, and were shown to inhibit histidine decarboxylase, arachidonic acid release and prostaglandin synthetase[3]. Since 12-O-tetradecanoylphorbol-13-acetate, a tumor promoter in mouse skin, is known to enhance these biological activities[4,5], lecanoric acid analogues were expected to inhibit tumor promotion. Therefore, we studied the inhibitory effects of lecanoric acid analogues on in vivo tumor promotion.

Materials and methods. Female CD-1 mice were purchased from Charles River Japan Inc. Lecanoric acid analogues were kindly supplied by the Central Research Laboratory of Sanraku-Ocean Co., Ltd. TPA was purchased from Consolidated Midland Corporation.

The backs of 7-week-old mice were shaved and 0.1 mg of 7,12-dimethylbenz(a)anthracene (Tokyo Kasei Co., Ltd) in 0.1 ml of acetone was applied. From 1 week later TPA (0.01 mg) and 1 mg of 3′,5′-dichloro-2,4′-dihydroxybenzanilide (Product number SD-170) or 4′-methoxy-4-methyl-2-hydroxy-benzanilide (SD-702) or TPA alone dissolved in 0.1 ml of acetone were applied twice a week for 20 weeks. Each group consisted of 26 female CD-1 mice.

Results and discussion. Data on the incidence of tumor bearing mice and the number of tumors are shown in figure A and B, respectively. Two mice, one from the control group in week 19 (keratoacanthoma) and the other from the SD-702 group in week 16 (thymic lymphoma), were lost during the experiment. Application of SD-170 decreased both the incidence and number of tumors, as shown in figure A and B. The table shows that the tumors were smaller in the SD-170 group than in the control group. SD-



Effect of lecanoric acid analogues on mouse skin tumor promotion. Mice were painted with TPA alone (○), TPA and SD-170 (●) or TPA and SD-702 (△) twice a week. *A* Incidence of tumor bearing mice. *B* Number of tumors per mouse.

702 did not inhibit tumor promotion significantly. Neither SD-170 nor SD-702 influenced the body weight of animals during the experiment.

SD-170 strongly inhibits histidine decarboxylase (ID_{50}, 0.007 μg/ml) and slightly inhibits TPA-induced arachidonic acid release (40% inhibition at 20 μg/ml), while SD-702 slightly inhibits histidine decarboxylase (ID_{50}, 2.5 μg/ml) and strongly inhibits arachidonic acid release (ID_{50}, 0.35 μg/ml)[3]. Both SD-170 and SD-702 inhibit prostaglandin synthetase about 60% at 10 μg/ml[3]. Thus our results suggest that induction of histidine decarboxylase may be more important for tumor promotion than arachidonic acid release. The action of SD-170 was almost certainly biological, because neither SD-170 nor SD-702 influenced the stability of TPA when incubated with it in acetone for 3 h at 37 °C.

Retinoids[6], anti-inflammatory steroids[7] and dibromoacetophenone[8], a phospholipase A_2 inhibitor, are known to inhibit tumor promotion in mouse skin. SD-170 has very low toxicity, its LD_{50} being 3500 mg/kg in mice and 2000 mg/kg in rats on i.p. injection[9]. Thus this lecanoric acid analogue is a new inhibitor of tumor promotion with low toxicity.

Effect of lecanoric acid analogues on mouse skin tumor promotion

Week	Treatment	No. of tumors Size of tumors (mm diameter) 10	9	8	7	6	5	4	3	2	Total
13	Control (26)*	1	1	2	1	2	3	9	24	109	152
	SD-170 (26)	–**	–	–	–	–	1	2	9	64	76
	SD-702 (26)	3	–	3	–	9	1	2	18	90	126
18	Control (26)	–	1	–	1	2	8	11	37	157	217
	SD-170 (26)	–	–	–	–	1	–	4	13	133	151
	SD-702 (25)	1	–	–	2	2	4	12	29	140	190

*Number of mice; **none

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Prenatal stress and postnatal androgen: Effects on reproduction in female rats

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Summary. Heat-restraint stress applied to pregnant rats during the last trimester disrupts oestrus cycles in female offspring and alters adrenal, ovarian and uterine weights at autopsy. Sexual receptivity is left intact. Prenatal stress may operate by increasing exposure of fetal females to androgens in utero.

Stress during gestation impairs reproductive capabilities of offspring in adulthood. Prenatally stressed males exhibit a syndrome marked by diminished copulatory performance and increased lordotic potential[1-8]. Female offspring reportedly experience oestrous cycle disorders, reduced fertility, spontaneous abortions, vaginal hemorrhaging, stillbirths, neonatal mortality and low birthweight young[9-11]. Although the mechanism of prenatal stress is not clear, the abnormal actions may involve alterations in exposure to androgen. It has long been known that under normal conditions the expression of adult patterns of sexual behavior and gonadotropin secretion depend upon perinatal androgen[12-14]. Removal of androgen by perinatal castration produced genetic males who exhibit cyclic gonadotropin release and lordosis behavior characteristics of females. Conversely, early administration of androgen to genetic females produces anovulation, sterility and a reduction of sexual receptivity. Recently prenatally stressed fetal males have been shown to undergo a premature surge in plasma testosterone compared to nonstressed controls[15], and isolated plasma samples from prenatally stressed fetal females taken at about the same time as the males contain extraordinarily high levels of testosterone[16]. The question arises whether androgen may be implicated in prenatal stress by other means. If androgen plays a role in the prenatal stress syndrome, then environmental stress effects on reproduction should mimic to some extent those of exogenously-administered hormone. The present experiment compares and contrasts the effects of prenatal stress and early androgen on some reproductive functions in females.

Materials and methods. 24 Sprague-Dawley rats weighing 200-250 g were time-mated at Zivic-Miller (Allison Park, Pennsylvania) and sent to our laboratory. Upon arrival, females were housed individually in 24 × 32 × 16 cm fiberglas observation cages with San-i-cel bedding under a standard 12 h light/dark cycle beginning at 10.00 h, maintained on Purina chow and water ad libitum. On days 14-22 of gestation, 12 randomly selected females were subjected to stress of restraint, heat and bright light. Stress was applied by placing each female in an 18 × 8 cm semicircular Plexiglas restraining cage under 4 incandescent lights providing a surface illumination of 4280 lm/m^2