"Strain" differences in illness-induced taste aversion*

ROBERT ADER
School of Medicine and Dentistry
University of Rochester, Rochester, N.Y. 14642

Sprague-Dawley and Long-Evans rats, obtained from Blue Spruce Farms, and Sprague-Dawley rats, obtained from ARS/Sprague-Dawley, were compared in their aversion to a distinctly flavored drinking solution (CS) paired with injection of 10 or 20 mg/kg of cyclophosphamide (UCS) or with injection of a vehicle placebo (25% ethanol). Placebo treatment did not induce any aversion to the CS, and the magnitude and duration of the conditioned avoidance response was directly related to the intensity of the UCS. At the low dose only, the SD/ARS rats displayed an aversion to the CS. At 20 mg/kg all groups showed an initial aversion to the CS. There were no differences between the two strains obtained from the same commercial supplier, but the SD/ARS animals showed a greater initial aversion and a more sustained response than the other two strains.

The single pairing of a distinctively flavored drinking solution (CS) with the injection of a toxin capable of inducing gastrointestinal disturbance (UCS) results in the subsequent avoidance of the distinctively flavored fluid. This "bait shyness" (Barnett, 1963; Rzóska, 1953) or illness-induced taste-aversion paradigm (Garcia, Ervin, & Koelling, 1966; Garcia, McGowan, Ervin, & Koelling, 1968) is sensitive to variations in the magnitude of the CS (Dragoin, 1971), the UCS (Cappell & LeBlanc, 1971; Dragoin, 1971; Elsmore & Fletcher, 1972; Garcia, Ervin, & Koelling, 1967; Revusky, 1968), and the CS-UCS interval (Kalat & Rozin, 1971; Nachman, 1970; Revusky, 1968; Smith & Roll, 1967) and, presumably, is mediated centrally rather than peripherally (Rozin & Kalat, 1971).

Rozin (1968) reported differences between the illness-induced taste-aversion behavior of half-wild and domestic rats which were consistent with the observations of Richter (1953) and Rzóska (1953) on the behavior of wild rats in response to poisoning. More recently, Dragoin (1971) compared two domesticated strains—Sprague-Dawley (albino) and Long-Evans (hooded) rats—in the taste-aversion situation. The hooded animals were found to develop the stronger and more persistent aversion to sour water associated with injections of the illness-inducing agent, cyclophosphamide. The question of strain differences remains equivocal, however, because the two populations were procured from different commercial sources (Dragoin, personal communication, 1973). In the course of preliminary experiments we, too, noticed strain differences in behavior, but our populations also were obtained from different commercial suppliers. The present study, then, was undertaken to provide a more unequivocal test of the relevance of strain differences to performance in the illness-induced taste-aversion situation.

This research was supported by USPHS Grants MH-16,741 and K5-MH-6318 from the National Institute of Mental Health. The technical assistance of Sumico Nagai is gratefully acknowledged.

METHOD

The Ss were 43 Sprague-Dawley (SD/BS) and 41 Long-Evans (LE/BS) rats, obtained from Blue Spruce Farms, Altamont, New York, and 40 Sprague-Dawley (SD/ARS) rats, obtained from ARS/Sprague-Dawley, Madison, Wisconsin. The 80-day-old males were housed individually under a 12-h light-dark schedule (light from 0500 to 1700 h) and initially provided with food and water ad lib. Over a 2-week period, the time that water was available was decreased until the total daily allotment was confined to a 10-min period beginning at 0930 h. After a week under this regimen, the animals were provided with water made sour by the addition of hydrochloric acid (.5 ml/liter). Immediately after the 10-min drinking period, randomly selected experimental animals from each strain were injected intraperitoneally with 10 or 20 mg/kg cyclophosphamide (Meade-Johnson, Evansville, Indiana). An additional sample of control animals from each strain was given placebo injections of the vehicle (25% ethanol). Injections were administered from coded solutions. During the following 2 recovery days, all animals were provided with plain tap water during their 10-min drinking period. On the third day after treatment sour water was again presented, but there was no further treatment with cyclophosphamide. Subsequent extinction sessions with sour water were each preceded by 2 days in which animals were given plain water. The daily intake of plain water was recorded to assure that animals had returned to their previously determined baseline level. The intake of sour water was subjected to a repeated-measures analysis of variance.

RESULTS AND DISCUSSION

The intake of sour water on the test day (immediately before the administration of cyclophosphamide) varied between 12.7 ± 1.0 and 14.6 ± 1.1 ml. There being no differences as a function of strain or the subsequent dose of cyclophosphamide, the intake of sour water on the three extinction trials was analyzed in terms of absolute values. These data are shown in Fig. 1.

The analysis of variance revealed a significant difference between the three strains ($F = 3.91$, $df = 2/115$, $p < .05$) as well as an interaction of Strain by Dose by Extinction Session ($F = 10.74$, $df = 12/345$, $p < .01$). Placebo injections did not result in any decrement in the intake of sour water and there were no differences among the groups treated with the placebo solution. The Sprague-Dawley and Long-Evans animals that came from the same commercial supplier did not differ at either dose of cyclophosphamide or at any point in time. Depending upon the dose and time of sampling, however, the SD/ARS animals differed from one or both of the other strains in the direction of a

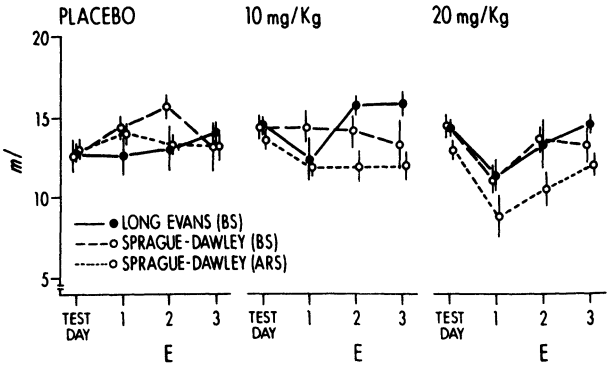

Fig. 1. Mean (± SE) intake of sour water during a 10-min drinking period on the test day (immediately before the administration of 10 or 20 mg/kg cyclophosphamide or placebo treatment) and during three subsequent extinction trials (E) for the three strains of domesticated rats.

greater initial decrease in the intake of sour water and a more sustained response.

At the relatively low dose of 10 mg/kg cyclophosphamide, neither the SD/BS nor the LE/BS animals displayed any significant decrease in their sour-water intake relative to their intake on the test day, whereas there was a significant aversion in the SD/ARS group ($t = 2.28$, $p < .05$).

At 20 mg/kg the decrease in the intake of sour water varied between 20.8% and 32.3%, which falls midway between the values of approximately 20% and 50% noted by Dragoin (1971) in response to cyclophosphamide doses of 16 and 33 mg/kg, respectively. The greater and more prolonged aversion observed by Dragoin may be due to the use of two acquisition or conditioning trials, in contrast to the single trial used here. At 20 mg/kg there was a significant initial aversion to sour water in each of the groups; the SD/ARS rats, however, displayed a more sustained response.

The present data confirm previous observations that the magnitude of a conditioned taste aversion is directly related to the intensity of the illness-inducing UCS. These results also indicated that the 25% ethanol used as the vehicle in which cyclophosphamide was administered is not, in the volume injected, capable of inducing an aversion to the distinctively flavored CS with which it was paired.

Differences between "strains" were noted. Sprague-Dawley and Long-Evans animals obtained from a single commercial supplier did not differ, but Sprague-Dawley animals obtained from a different supplier did differ from the other groups. These results are entirely consistent with differences in active avoidance behavior between animals of a single strain obtained from different vendors (Nakamura & Anderson, 1962). Differences between original breeding stock, breeding programs, as well as conditions of husbandry that prevail among commercial suppliers of laboratory animals evidently contribute to differences in behavior. Whether or not there are differences in illness-induced taste aversion as a function of genotypic differences between domesticated strains of rats, then, remains unanswered.

REFERENCES

Barnett, S. A. *The rat: A study in behavior.* Chicago: Aldine, 1963.

Cappell, H., & LeBlanc, A. E. Conditioned aversion to saccharin by single administrations of mescaline and d-amphetamine. Psychopharmacologia, 1971, 22, 352-356.

Dragoin, W. B. Conditioning and extinction of taste aversions with variations in intensity of the CS and UCS in two strains of rats. Psychonomic Science, 1971, 22, 303-305.

Elsmore, T. F., & Fletcher, G. V. Δ^9-Tetrahydrocannabinol: Aversive effects in rat at high doses. Science, 1972, 175, 911-912.

Garcia, J., Ervin, F. R., & Koelling, R. A. Learning with prolonged delay of reinforcement. Psychonomic Science, 1966, 5, 121-122.

Garcia, J., Ervin, F. R., & Koelling, R. A. Bait shyness: A test for toxicity with N = 2. Psychonomic Science, 1967, 7, 245-246.

Garcia, J., McGowan, B. K., Ervin, F. R., & Koelling, R. A. Cues: Their relative effectiveness as a function of the reinforcer. Science, 1968, 160, 794-795.

Kalat, J. W., & Rozin, P. Role of interference in taste aversion learning. Journal of Comparative & Physiological Psychology, 1971, 77, 53-58.

Nachman, M. Learned taste and temperature aversions due to lithium chloride sickness after temporal delays. Journal of Comparative & Physiological Psychology, 1970, 73, 22-30.

Nakamura, C. Y., & Anderson, N. H. Avoidance behavior differences within and between strains of rats. Journal of Comparative & Physiological Psychology, 1962, 55, 740-747.

Revusky, S. H. Aversion to sucrose produced by contingent X-irradiation. Journal of Comparative & Physiological Psychology, 1968, 65, 17-22.

Richter, C. P. Experimentally produced behavior reactions to food poisoning in wild and domesticated rats. Annals of the New York Academy of Sciences, 1953, 56, 225-239.

Rozin, P. Specific aversions and neophobia resulting from vitamin deficiency or poisoning in half-wild and domestic rats. Journal of Comparative & Physiological Psychology, 1968, 66, 82-88.

Rozin, P., & Kalat, J. W. Specific hungers and poison avoidance as adaptive specializations of learning. Psychological Review, 1971, 78, 459-486.

Rzóska, P. Bait shyness: A study in rat behaviour. British Journal of Animal Behaviour, 1953, 1, 128-135.

Smith, J. C., & Roll, D. L. Trace conditioning with X-rays as an aversive stimulus. Psychonomic Science, 1967, 9, 11-12.

(Received for publication January 26, 1973.)