Sensitivity to Experimental Hypertension and Aggressive Reactions in Rats (34389)

D. Ben-Ishay[1] and A. Welner[2]
(Introduced by L. K. Dahl)

Department of Medicine A, Hadassah Hebrew University Hospital and Medical School, Jerusalem, Israel

It was previously reported that two inbred strains of rats that differed in their constitutional predisposition to experimental hypertension as a result of salt ingestion and other experimental procedures (1–4) also differed in certain behavior patterns. The strain in which hypertension could be easily induced (the sensitive or "S" strain) manifested a relative aversion to drinking saline (5) and was less "explorative" than its counterpart (the resistant or "R" strain) when facing a change in its environment (6).

In the present study we compared aggressive behavior induced in members of the two strains by thirst or pain. The experiments presented below confirm a previous impression of a more submissive behavior in animals prone to hypertension.

Materials and Methods. The animals participating in this study were female rats belonging to two strains developed at Brookhaven National Laboratory (1). They had been fed a special low salt chow (0.38% NaCl) up to the age of 8 weeks and regular laboratory food (1% NaCl) thereafter, both *ad libitum*. Systolic blood pressure was measured under light ether anesthesia, by the tail microphonic method of Friedman and Freed. The care of the animals was reported before (6).

Expt. 1, aggression induced by thirst. The purpose of this study was to test in a semiquantitative way the aggression of thirsty S and R rats when they were compelled to compete for drinking water. The experiments were carried out in 22 rats aged 10–12 weeks. Their blood pressures at the time of the study were normal, although the S group already had significantly higher values than the R (S:127 mmHg ± 5; R:116 mmHg ± 5:$p<.001$). All experiments were carried out in the morning following a 24-hr period without food or fluid. In the first set of observations control data were obtained by placing each animal alone in a cage in which water was available. The moment the animal began to drink, a stop watch was set and during the next 2 min the actual time the animal drank water was recorded. Usually the animal would not drink uninterruptedly, but would stop occasionally for several seconds; accordingly, the "control drinking time" was always less than 2 min. Two days later, pairs of similarly treated rats were placed in a cage, and after letting them get acquainted with their new surroundings, a bottle of water was placed on the lid, its nozzle protruding into the cage. Usually both animals would reach for the bottle almost simultaneously. In a few instances when one rat did not seem to notice the water, the bottle was removed and replaced several times until both animals were obviously aware of its presence.

The rats would invariably engage in a vivid dispute for the water. Each animal would try to get hold of the nozzle and take a few drinks while pushing aside its rival with the forelimbs. Occasionally one of the contenders would prevail while the other rat would wait for some time but more often, both animals would keep on fighting while taking turns at the bottle. Sometimes both animals would drink in concert for various lengths of time. The animals were distinctly marked with dye so they could be identified. Two

[1] Grant TW-00288-02 from the National Institutes of Health, USPHS, and by the United States Atomic Energy Commission, and

[2] By a grant from the Joint Research Fund of the Hebrew University Hadassah Medical School, Jerusalem, Israel.

TABLE I. Intergroup Competition: Drinking Time in 22 Fasting Rats, Grouped in S–R Pairs.[a]

	Control drinking time (sec); strain:		Drinking time (sec) in presence of contender; strain:	
Pair no.	S	R	S	R
1	112	115	45	100
2	110	112	55	95
3	115	113	71	107
4	106	110	69	82
5	108	107	70	80
6	105	112	50	85
7	111	115	72	90
8	113	111	106	90
9	106	108	45	90
10	108	98	70	62
11	116	107	65	91
Av ± SD	110	110	65	89
	±3.7	±4.8	±17	±12
Significance	NS		$p < .01$	

[a] Actual time (sec) during a 2-min (120 sec) period in which thirsty rats drank water. Control time established with individual rats tested alone.

observers with stop watches recorded the actual drinking time for each rat over the 2-min period. The duration of the drinking time was directly related to the animal's ability to keep its opponent away. Intergroup behavior was observed in 11 S–R pairs. Intragroup behavior was observed in 8 R–R and 8 S–S pairs. In the latter studies, 8 R and 8 S rats were studied. Each animal was paired twice, each time with another member of its own strain in the following order: 1 vs. 2, 2 vs. 3 . . . 8 vs. 1.

Results. Table I summarizes the drinking pattern observed in 22 animals, grouped in 11 S–R pairs. The "control drinking time" of each animal is presented in column 1. Members of the two strains, when allowed to drink unobtrusively, had an average "control drinking time" of 110 seconds. The introduction of a competing partner caused a marked reduction in drinking time in individuals of both strains. However, the effect of interference was significantly more pronounced in the S rats ($p<0.01$). This difference is readily explained by the observation that R was the "dominant" partner, in 9 out of 11 pairs.

The intergroup behavior pattern is presented in Table II for 8 R–R, and 8 S–S pairs. In each group the average drinking time for both partners was remarkably similar. Though values obtained in the R–R group tended to be lower than in the S–S group, the difference was not significant.

Expt. II, aggression induced by pain. This study was undertaken to determine whether painful stimuli evoked different aggressive reactions in the sensitive and resistant rats. A group of 40 rats, 20 of each strain, aged 4–6 months, was used. The animals had been subjected to several water and saline loadings 2–3 months prior to this study. All the S had a variable degree of hypertension, while the R rats were normotensive. The rats were randomly paired in 20 R–S pairs. Each pair was placed in an empty cage, size 34 × 24 × 13 cm, and allowed to familiarize themselves with the new surroundings for several minutes. A standard Mohr pinchcock clamp was then put on the tip of the tail of one of the animals for 30 sec while the other rat was left untouched. In 10 pairs the tail of an R rat was pinched and in the other 10 pairs the S rat was so treated. The reaction to the painful stimulus evoked several patterns of behavior: Some animals would squeak and move around in an attempt to get

TABLE II. Intragroup Competition: Drinking Time in 16 Fasting Rats Grouped in 8 S–S and 8 R–R Pairs.[a]

	Strain			Strain	
Rat no.	S	S	Rat no.	R	R
1 vs. 2	66	101	1 vs. 2	60	53
2 vs. 3	100	57	2 vs. 3	88	83
3 vs. 4	69	77	3 vs. 4	57	67
4 vs. 5	67	64	4 vs. 5	62	50
5 vs. 6	57	76	5 vs. 6	60	55
6 vs. 7	100	76	6 vs. 7	51	65
7 vs. 8	61	66	7 vs. 8	69	44
8 vs. 1	78	80	8 vs. 1	103	102
Av ± SD	75	75		69	65
	±17	±13		±18	±19
Significance	NS			NS	

[a] See Table I.

hold of their tail, or retreat meekly to a corner without interfering with the other rat. Other animals would fiercely attack their partner, run over it, bite it, and pursue the onslaught as long as the clip was on. The intensity and the number of attacks during the observation period of 30 sec were scored arbitrarily from 0 to 4, giving a semiquantitative estimation of the aggressive response.

Results. The score for the 10 pairs in which the S rat was pinched, averaged 0.8 ± 1; in the other 10 pairs where the R rat was pinched, the score was 3.6 ± 0.51. The difference is highly significant ($p < .001$).

Discussion. The foregoing study lends further support to previous observations of a marked difference in behavior in two strains of rats with different susceptibility to hypertension. In an earlier report we have suggested that rats which were sensitive to hypertension (S) had a tendency to be more inhibited in their motor behavior than the resistant (R) ones (6). That concept has now been extended by showing difference in the aggressive behavior between S and R animals, under certain experimental conditions.

In the drinking experiments the S rats were consistently less aggressive than the R when faced with the necessity to fight for access to drinking water. The possibility was considered that the decreased aggressiveness in S was due to a difference in body fluids or to a better tolerance to water deprivation in this strain. Though body fluids were not actually determined, the changes in body weight, urine volume, and blood osmolality following complete fasting, did not suggest a better adaptation to water deprivation in the S strain (unpublished observation). Alternatively the difference in combativeness could be ascribed to a higher thirst threshold in the S. This possibility, is however not supported by the observation that S rats tended to drink more than the R rats, when matched with a member of their own strain.

In the second set of experiments, in which an aggressive reaction was evoked by a painful stimulus, the difference between the strains was again clearly demonstrated. While all R would attack immediately and repeatedly, the S rats would usually not interfere with the other partner or, at most, would stage an abortive attack. The difference in aggressiveness could be due, at least in part, to a different threshold to pain, and further studies might elucidate this question. However, since a submissive behavior was previously observed in experiments where no painful stimuli were involved (6), we are inclined to ascribe the reactions to thirst and pain to the same pattern of behavior, rather than postulate a higher threshold for both pain and thirst in the S rats. Since a "submissive" behavior was clearly present in young normotensive as well as in adult hypertensive animals, it is unlikely to have been caused by the hypertensive state. The available data allowed no conclusion as to whether such behavior could predispose to high blood pressure. Because the two strains were obtained by selective inbreeding, one may conclude that these behavior patterns are genetically "clustered" with the respective predilection for or against development of experimental hypertension. Whether this clustering is merely a matter of chance or whether it is related to a genetic complex of more fundamental importance is not known.

Summary. Aggressive reactions were evoked by thirst and pain in rats belonging to two strains with opposite genetic susceptibility to experimental hypertension. Members of the sensitive strain were consistently less aggressive than those of the resistant strain. This pattern of behavior was found both in young normotensive and adult hypertensive rats of the sensitive strain. It appears that selective inbreeding has resulted in certain behavior patterns being genetically "clustered" with the predilection for or against development of experimental hypertension. It is not known whether this is due to chance or whether it is related to a genetic complex of more fundamental importance.

The authors are indebted to Dr. L. K. Dahl for his generous supply of animals, and for his reviewing of the manuscript of this paper.

1. Dahl, L. K., Heine, M., and Tassinari, L., J. Exptl. Med. **115**, 1173 (1962).

2. Dahl, L. K., Heine, M., and Tassinari, L., Nature **194**, 480 (1962).

3. Dahl, L. K., Heine, M., and Tassinari, L., J. Exptl. Med. **118**, 605 (1963).

4. Dahl, L. K., Heine, M., and Tassinari, L., J. Exptl. Med. **122**, 533 (1965).

5. Wolf, G., Dahl, L. K., and Miller, N. E., Proc. Soc. Exptl. Biol. Med. **120**, 301 (1965).

6. Welner, A., Ben-Ishay, D., Groen, J. J., and Dahl, L. K., Proc. Soc. Exptl. Biol. Med. **129**, 886 (1968).

Received May 5, 1969. P.S.E.B.M., 1969, Vol. 132.