Behavior Patterns and Sensitivity to Experimental Hypertension in Rats* (33450)

A. WELNER, D. BEN-ISHAY, J. J. GROEN, AND L. K. DAHL

Department of Medicine A, Hadassah Hebrew University Hospital and Medical School, Jerusalem, Israel; and Medical Research Center, Brookhaven National Laboratory, Upton, New York 11973

Attempts to develop an experimental model for the study of hypertension led to the isolation by selective inbreeding of two strains of rats with opposite susceptibility to high blood pressure (1). They were designated "Sensitive" (S) and "Resistant" (R) because of their proneness or resistance respectively to develop hypertension in response to chronic excess salt ingestion (1) as well as to other experimental procedures (2, 3). Later studies revealed that the sensitive strain differed from the resistant one in greater vascular reactivity to pressor agents (4) and in a relative aversion for salt when offered a free choice between water and saline (5). In an attempt to uncover additional differences we compared patterns of behavior in the two strains: by means of simple quantitative tests, the study revealed a marked difference in behavior between S and R. This might be relevant to the observation that proneness to hypertension in the human may be associated with certain behavior patterns (6–12).

Materials and Methods. A total of 36 female rats was used.

Group I consisted of 9 adult S and an equal number of R rats, aged 10 months. Members of this group had participated in a previous study in which they received several water and saline loads 2–3 months prior to this experiment. At the time of the study all the S rats had a variable degree of hypertension while the R rats remained normotensive (Table I). They had received a low-salt chow (0.38% NaCl) up to the age of 8 weeks and regular laboratory chow (1% NaCl) thereafter, both *ad libitum*.

Group II comprised 9 S and 9 R rats, aged 6 weeks, all experimentally naive. They had been maintained since weaning on the same low salt chow as Group I. All the individuals in this group had normal blood pressures although the average blood pressure of the 9 S rats was slightly higher than that of the 9 R's (Table II).

Water was available *ad libitum* for both groups.

The animals were kept in groups of 3 in cages made of galvanized iron of size 34 × 24 × 13 cm with floors covered by sawdust. The cages were placed on racks in the animal house in rooms lit by fluorescent light. Room temperature varied from 23–26°.

Systolic blood pressure was recorded under light ether anesthesia, by a modification of the tail microphonic method of Friedman and Freed.

Quantitative behavioral studies. Two stereotyped repetitious behavior patterns were scored: (a) "Explorations". When the lid of the cage is removed, the rat rises on its hind legs, props itself up with the forelegs on the cage wall, sticking its head out of the cage, looking around, and sniffing at the surroundings. (b) "Crossings". When the lid of the cage is removed, and an identical empty cage is placed next to it, the rat crosses back and forth between the two cages. Every crossing in either direction is scored. In order to eliminate a possible effect of the 4-day estrus cycle on behavior, the above observations were made on eight consecutive days. The complete procedure carried out between 9 and 11:00 AM was as follows: (i) The cage was removed from the rack and placed on a table. (ii) The cover was removed. (iii) Using a stop watch, the number of "explora-

* Supported in part by a grant from the Joint Research Fund of the Hebrew University—Hadassah Medical School, by Grant TW-00288-02 from the National Institutes of Health, United States Public Health Service, and by the United States Atomic Energy Commission.

TABLE I. Group I: Number of Explorations and Crossings by Adult S Rats (Hypertensive) and R Rats (Normotensive).

	Systolic blood pressure (mm Hg)		Total explorations in 8 1-min experiments		Total crossings in 8 1-min experiments	
Rat no.	S	R	S	R	S	R
1	195	110	31	72	0	5
2	195	135	27	88	0	13
3	218	140	26	77	0	8
4	155	129	20	90	0	9
5	175	136	30	93	2	14
6	150	134	32	70	1	10
7	218	138	33	81	0	11
8	198	140	33	96	0	12
9	188	135	28	83	1	15
Mean ± SD	188 ± 24.2	133 ± 9.3	28.9 ± 4.2	83.3 ± 9.2	0.4 ± 0.73	10.8 ± 3.2
p	$<.01$		$<.01$		$<.01$	

tions" of each individual was scored for 1 min. The rats were distinctly marked with dye so it was possible to keep track of every animal. (iv) An empty uncovered cage was next placed adjacent to the cage and the number of "crossings" in either direction was scored for another minute.

Comparative behavioral experiments. Two cages containing 3 R and 3 S rats respectively were placed adjacent to each other and the two lids were simultaneously removed. A comparison was made of the number of crossings that S and R individuals made from their own cage into that of the other strain.

Results. In both the old and young groups the number of explorations and crossings of the R rats far outnumbered those of the S rats (Tables I and II, Fig. 1). Statistical analysis indicated a high degree of significance of the observed differences ($p<.01$). In the crossing experiments, the majority of the S rats did not cross at all.

The comparative experiments illustrated impressively the difference in crossing behavior in both the old and the young rats: at the end of half a minute all R rats had crossed into the cage of the S rats, but none of the S rats had crossed in the reverse direction.

Discussion. The study showed that two strains of rats with opposite, genetically de-

TABLE II. Group II: Number of Explorations and Crossings by Young S Rats (Normotensive) and R Rats (Normotensive).

	Systolic blood pressure (mm Hg)		Total explorations in 8 1-min experiments		Total crossings in 8 1-min experiments	
Rat no.	S	R	S	R	S	R
1	132	115	24	94	0	8
2	134	120	20	67	9	22
3	126	116	10	51	0	18
4	120	120	14	57	2	6
5	128	124	20	52	1	19
6	128	114	29	52	5	18
7	128	112	26	46	0	11
8	130	122	26	41	1	11
9	120	122	26	38	0	10
Mean ± SD	127.3 ± 4.8	118.3 ± 4.2	21.7 ± 6.3	55.3 ± 16.8	2.0 ± 3.1	13.6 ± 5.6
p	$<.01$		$<.01$		$<.01$	

termined susceptibilities to experimental hypertension also differed markedly in their behavior to a change in their environmental situation. When the rats were observed unobtrusively in their cages with the lid on, there was no noticeable difference in activity between members of the two strains. They moved intermittently through the cage, cleansed, trimmed, and scratched themselves, sneezed, and dug in the sawdust in similar

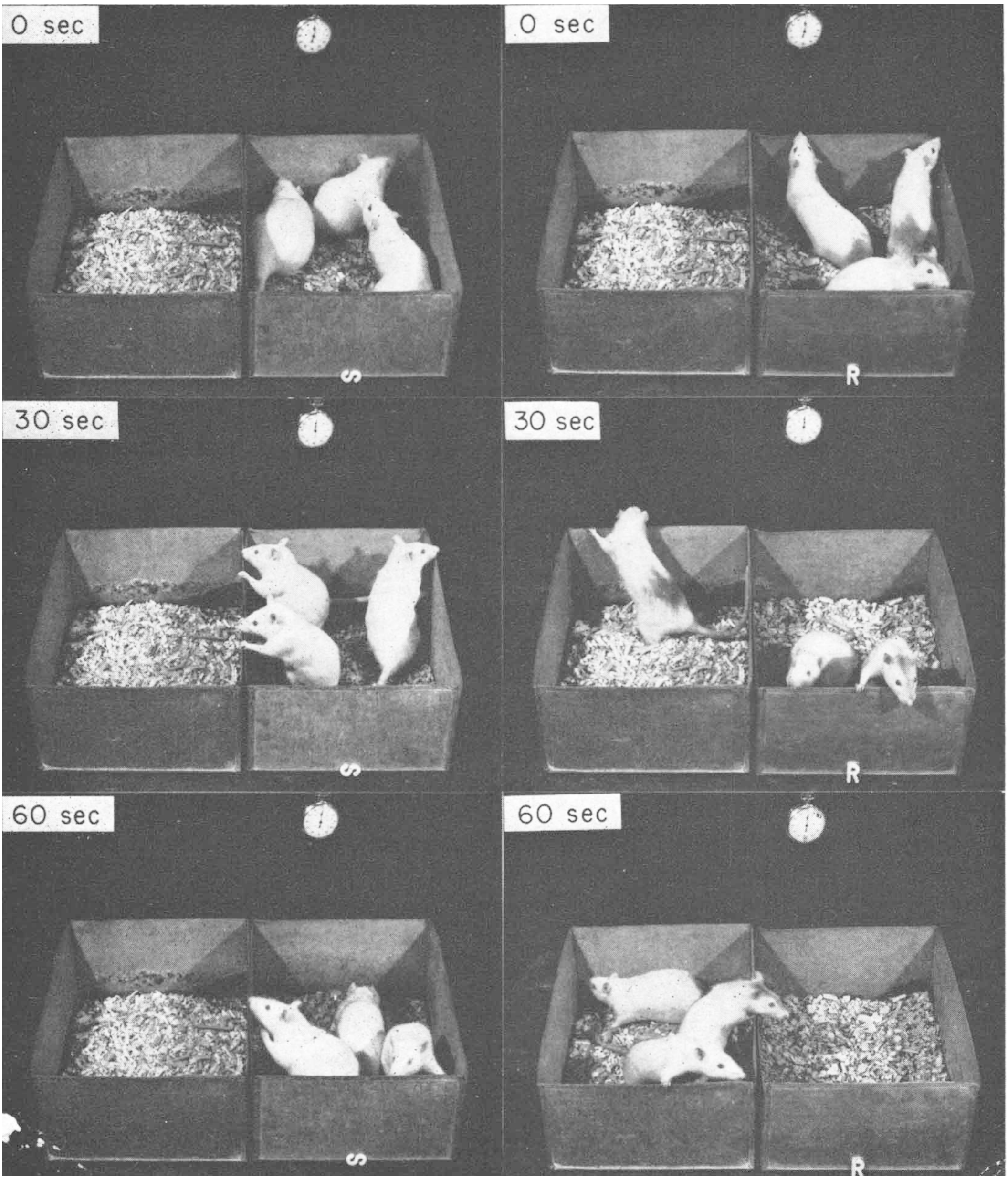

FIG. 1. "Crossing" behavior by adult members of S strain (left) and R strain (right) rats. None of the S rats "crossed" into the adjacent box during the 1-min test period whereas all of the R animals did so. While all of the adult S rats were hypertensive and none of the adult rats was, the difference in behavior pattern also prevailed among young, normotensive animals from both strains.

ways. When the lid was removed, both strains showed an enhanced activity but this was much more marked in the R rats as shown by the unequivocally higher frequency of "exploring" and "crossing" in that strain.

Our results suggest, therefore, that the observed difference in behavior between the strains was not simply one of movement in general but in the reactions to a change in the environment. Under the circumstances of these experiments the R rats showed more "inquisitiveness" and "interest in the outer world." It appeared as if the S rats were more, and R rats less, inhibited in their tendency to explore the new environment offered to them. One might paraphrase the human psychological terminology by describing the behavior of the R rats as more "extrovert" or "aggressive" and that of the S rats more "introvert" or "timid." Whatever the interpretation of the behavior, the finding of a correlation between behavior and predisposition to hypertension opens possibilities for explanation and further work.

Since the young normotensive S rats behaved like the hypertensive adults, elevated blood pressure is not plausible as a determinant of these different behavioral patterns in the two strains. On the basis of available data, it is not yet possible to correlate the behavioral differences with the sharply differing capacities to develop hypertension. It is possible that the propensity for hypertension and a certain behavior pattern are two genetic components that happen to occur together in the same strain, without being causally related.

There are some observations in human beings suggesting that certain behavior patterns, including impaired mobility, are associated with hypertension. In patients with chronic poliomyelitis and other deformities, a parallelism between immobility and high blood pressure has been observed (13). We are reluctant to ascribe to subtle differences in response to environmental "stress" a cardinal role in explaining the opposite tendencies to hypertension in these two strains; powerful psychological stresses over long periods failed to induce hypertension in the strain susceptible to hypertension (14). A genetic study of these two strains is now under way that will indicate whether or not the propensity (or resistance) to experimental hypertension is transmitted by single or multiple genes. Preliminary data indicate that this is a polygenic trait. Behavior characteristics in mammals are genetically controlled and there is considerable evidence to suggest that they, too, are transmitted by polygenic inheritance (15). Such multifactorial inheritance of both the trait for (or against) hypertension and that of behavior might enhance the probability of coincidental selection. No definitive conclusion is possible at this time as to whether these behavioral differences play a meaningful role in the sharply different proclivities to experimental hypertension.

Summary. Rats from two inbred strains with opposite genetic predispositions to hypertension had different behavior patterns after a standard change in their environment. After removal of the cage lid, the number of "explorations" and "crossings" between two adjacent cages were consistently higher in the strain resistant to hypertension than in the strain prone to hypertension ($p<.01$). This difference in behavior was present in young rats before experimental hypertension was produced indicating that the behavioral pattern was not the result of the hypertension. It is not yet clear that these behavioral differences play a direct role in the sharply different proclivities to hypertension present in the two strains of rat.

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Received July 26, 1968. P.S.E.B.M., 1968, Vol. 129.

High Altitude Hyperuricemia (33451)

LUIS A. SOBREVILLA AND FERNANDO SALAZAR (Introduced by Alberto Hurtado)
Universidad Peruana Cayetano Heredia, Instituto de Investigaciones de la Altura, Lima, Peru

Since the original observations of Viault, it is known that permanent residents at high altitude develop an adaptive polycythemia, and later the studies of Hurtado *et al.* (1) have shown an absolute increase in the circulating red cell mass and a slightly diminished total plasma volume. The occurrence of hyperuricemia in association with polycythemic states is well known (2) and the relationship between hyperuricemia and renal function has been extensively examined in primary hyperuricemia (3).

Since a potentially harmful role for excessive levels of serum urate has been suggested (4), we decided to study a group of subjects living permanently at 4200 m in Cerro de Pasco, Peru, to determine the occurrence and extent of hyperuricemia in this polycythem-

TABLE I. Hematocrit, Serum Urate, and Creatinine in 15 Male Subjects Living at Cerro de Pasco (14,000 ft).

Subject	Age	Hematocrit (%)	Urate (mg/100 ml)	Creatinine (mg/100 ml)
J.S.S.	22	50.5	6.94	1.6
E.C.C.	21	54	5.19	0.8
R.F.M.	30	60	10.30	1.7
R.A.D.	29	68.6	6.13	1.4
M.J.M.	36	60	6.04	1.4
A.C.F.	46	58.7	6.66	1.1
L.M.R.	29	55.5	6.70	1.3
D.C.Z.	31	76	9.14	1.7
P.C.S.	33	65.2	6.48	1.6
P.L.N.	25	60.5	6.88	1.5
J.P.C.	32	67	8.26	1.1
R.D.R.	26	55	6.92	1.4
C.I.P.	35	52.5	7.19	1.4
V.T.P.	37	62.5	6.65	1.0
E.A.C.	41	53	7.24	1.2
Mean	31.5	59.90	7.11	1.34
SEM		1.75	0.34	0.07