Behavior and Sensitivity to Experimental Hypertension
II. Lack of Correlation Between Certain Behavior Patterns and Hypertension in Two New Strains of Rats[1] (37697)

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We have previously reported significant differences in behavior patterns in rats of the Brookhaven strain, that were selectively bred for their propensity and resistance, respectively, to hypertension (1, 2). Members of the hypertension-prone S strain were less inquisitive when facing a change of environment (1) and less aggressive in their reactions to pain and thirst (2). The available data allowed no conclusion as to whether the disparate behavior traits had been fortuitously selected by inbreeding, or whether there was a meaningful connection between certain behavior patterns and the predisposition or resistance to hypertension.

In an attempt to critically answer that question, two sets of experiments were carried out:

By selective inbreeding, we have obtained two unique strains of rats which differ in their inquisitive or "explorative" behavior in the same manner as do R and S rats of the Brookhaven strain. These rats, that we have designated as "Explorers" and "Nonexplorers" were tested for their susceptibility to desoxycorticosterone (DOCA)–salt hypertension. Concomitantly, we have studied the explorative behavior in another colony of rats selected for their sensitivity and resistance respectively, to DOCA–salt hypertension. These rats have been designated as H for hypertensive and N for normotensive (3). The results presented here show a complete dichotomy between explorative behavior and susceptibility to hypertension in rats.

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Material and Methods. Quantitation of behavioral pattern. To quantify differences in behavior between the rats, we used the "exploration score" as previously described (1). The exploration score (abbreviated score, hereafter) equals the number of times an individual rat will rise on its hind limbs and stick its head out of the cage during 1 min following removal of the cage lid. The animals were kept in groups of 3 in cages made of galvanized iron, size 34 × 24 × 13 cm with floors covered by sawdust. Each rat was distinctly marked with dye which enabled us to clearly follow the movements of an individual animal. The test was repeated for 4 consecutive days, and the results of four 1-min measurements were averaged for each animal.

Separation of Explorer and Nonexplorer rats. Rats of both sexes from the Hebrew University "Sabra" strains were tested as above and their score determined. Animals with a score of 6 or above were designated as "Explorers" while those with a score of 2 or less were designated as "Nonexplorers." Five pairs of each group constituted the parental generation (P). Beginning with the first generation and throughout 6 subsequent generations, we continued brother–sister mating, selecting those siblings with the highest score in the Explorer strain and with the lowest score in the Nonexplorer strain.

Experiment 1. In this study, male and female rats from the 7th generation of these two strains were used. At the age of 2 months, the score and systolic blood pressure were determined. The animals subsequently underwent left nephrectomy and were subjected

TABLE I. Susceptibility to DOCA–Salt Hypertension in Explorer and Nonexplorer Rats.

	Group[a]	No. of rats	Systolic B.P. Before	Systolic B.P. After DOCA	Exploration score/min
Males	E	20	126 ± 9[b]	153 ± 16	6.3 ± 2.1*
	NE	22	127 ± 12	158 ± 17	1.4 ± 0.8
Females	E	11	128 ± 9	167 ± 15	7.5 ± 1.3*
	NE	20	120 ± 9	154 ± 2	2.1 ± 1.0

[a] E, explorers; NE, nonexplorers.

[b] Values are mean ± standard deviation. Significance of difference between Explorer and Nonexplorer rats, when present, is shown as: * $p < 0.01$.

to a DOCA–salt regimen as previously described (3). Briefly, the regimen consisted of the administration of DOCA in oil, 2.5 mg/rat sc, 3 times a week to a total amount of 22.5 mg and drinking 0.9% NaCl instead of water. A *post-DOCA* blood pressure measurement and score were also obtained on each rat, on the first day following cessation of treatment.

Experiment 2. In this experiment, we used male and female members of the 9th generation of the DOCA-hypertension-prone (H) and DOCA-hypertension-resistant (N) strains developed in this laboratory (3). These strains were also originally derived from the Hebrew University "Sabra" strain, by selective inbreeding of animals that showed respectively the highest or the lowest sensitivity to DOCA–salt as outlined above. The blood pressure prior to and following DOCA–salt was determined as was their score.

Since the score of an individual was virtually unchanged by DOCA in either one of the two experiments, only the post-DOCA data are presented in the results. Blood pressure was measured by the microphonic method of Friedman and Freed, under light ether anesthesia. Statistical analysis was made by Student's t test.

Results. Experiment 1: Susceptibility to DOCA–salt hypertension in Explorer and Nonexplorer rats. Table I summarizes the observations in 31 Explorer and 42 Nonexplorer rats.

The control blood pressure levels before uninephrectomy and DOCA were not different in the two strains. Administration of DOCA–salt for 3 weeks resulted in marked but comparable rises in blood pressure in both strains.

The score, shown in the last column, was evidently considerably higher in the Explorer than in the Nonezplorer rats ($p < 0.01$). Thus, a high or low score, respectively, appeared to be unrelated to resistance or susceptibility to DOCA–salt hypertension in these rats.

Experiment 2: Exploration score in DOCA-sensitive (H) and DOCA-resistant (N) rats. Table II lists the data obtained in 43 DOCA-sensitive (H) and 39 DOCA-resistant (N) rats.

The control blood pressure measured prior

TABLE II. Exploration Score in DOCA-Sensitive (H) and DOCA-Resistant (N) Rats.

	Group	No. of rats	Systolic B.P. Before	Systolic B.P. After DOCA	Exploration score/min
Males	N	19	127 ± 6*[a]	134 ± 7*	4.1 ± 1.7
	H	22	137 ± 8	186 ± 19	4.2 ± 1.2
Females	N	20	111 ± 7*	120 ± 6*	5.1 ± 1.1
	H	21	121 ± 8	170 ± 19	5.7 ± 1.3

[a] Values are mean ± standard deviation. Significance of difference between N and H rat, when present, is shown as: * $p < 0.01$.

to any treatment was significantly higher in the DOCA-sensitive-H than in the DOCA-resistant-N rats ($p < 0.01$). This observation has been reported in a previous study (3).

Following uninephrectomy and DOCA treatment, H rats of both sexes became markedly hypertensive, whereas the blood pressure of the N rats remained normal.

The score presented in the last column was virtually identical in the DOCA-sensitive-H, and DOCA-resistant-N rats of either sex.

Thus, a genetically-determined sensitivity or resistance to DOCA-salt hypertension seemed to be unrelated to differences in behavior as measured respectively by a low or a high exploration score.

Discussion. The present study was prompted by our previous observation of markedly different behavior patterns in the Brookhaven strains of rats with opposite, genetic predisposition to hypertension. Recent studies in these animals have shown that the propensity or resistance to hypertension is transmitted by multiple genes (4). Other studies in mammals indicate that behavior patterns are also genetically transmitted, apparently by polygenic inheritance (5). It seemed relevant to determine whether inheritance of susceptibility to hypertension and of certain behavior patterns were causally related or a mere coincidental clustering of two genetic components. In the Explorer and Nonexplorer rats, we have been able to segregate a genetic difference in behavior, similar to that described in rats of the Brookhaven strains (1). Yet, unlike the latter two strains, the Explorer and Nonexplorers did not differ in their blood pressure prior to and following DOCA administration (6).

In the DOCA-resistant (N) and the DOCA-sensitive (H) rats, we have been able to isolate a disparate susceptibility to experimental hypertension similar to that described in the Brookhaven strain, yet the N and H strains showed no measurable difference in behavior pattern, as this is exemplified by their exploring score.

We have now studied three different groups of rats, each group of which consists of two strains with genetically determined differences in (a) behavior, (b) blood pressure, or (c) both. In the initial study with the two Brookhaven strains, opposite predispositions to hypertension were also associated with significantly different behavior patterns (1, 2). In Experiment 1 of the present study, we observed two other strains with similar blood pressure responses to DOCA–saline but significantly different genetically determined behavior patterns. And, finally, in Experiment 2 of this latter study, we tested two more strains with opposite, genetically determined predisposition to DOCA–saline hypertension, but similar explorative behavior patterns.

The use of the "exploratory score" as a meaningful parameter for measuring behavior in general, may be questioned. Yet, in a previous study we found this parameter most helpful in quantitating differences with respect to a particular pattern of behavior, between hypertension-prone (S) and hypertension resistant (R) rats of the Brookhaven strain (1). On the basis of additional data obtained in two different settings, we conclude that this particular pattern of behavior is not linked to a predisposition for or against hypertension.

While the present study does not support a hypothesis in which behavior plays a primary role in the pathogenesis of hypertension, it would be premature to draw a general conclusion on the connection between behavior and susceptibility to hypertension.

Summary. A possible relationship between certain inherited behavior patterns and susceptibility to hypertension was studied in rats. An "exploration score" was devised to quantify explorative behavior.

Susceptibility to DOCA–salt hypertension was similar in two strains that had been selectively bred for their disparate explorative behavior. Conversely, explorative behavior was similar in two other strains, selected for their respective susceptibility and resistance to DOCA–salt hypertension. Inheritance of a hypertensive trait appears therefore to be unrelated to inheritance of a specific explorative behavior in these rats.

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