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Central and Peripheral Norepinephrine Concentrations in Rat Strains Selectively Bred for Differences in Response to Stress: Confirmation and Extension[1]

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LIANG, B. AND D. A. BLIZARD. *Central and peripheral norepinephrine concentrations in rat strains selectively bred for differences in response to stress: confirmation and extension.* PHARMAC. BIOCHEM. BEHAV. 8(1) 75–80, 1978. – Inbred rats from the Maudsley Reactive (MR) strain had lower concentrations of norepinephrine in hypothalamus, heart, and spleen, and lower total catecholamines in adrenal than inbred Maudsley Non-Reactive rats (MNRA line). In contrast, they had a higher concentration of telencephalic NE than MNRA rats. These results confirmed previous findings obtained on rats maintained by non-systematic breeding within the two lines. Comparisons were also made between MR and a second Maudsley Non-Reactive strain (MNR). Rats of the two Non-Reactive lines (MNRA, MNR) have been bred from the same foundation population and selected for the same behavioral characteristics, but have been genetically isolated from each other for many generations. It was found that MR rats showed differences from MNR rats in hypothalamic and peripheral (but not telencephalic) NE concentrations similar to those seen in MR/MNRA comparisons. Since rats of the two Non-Reactive lines differ appreciably from MR rats in open-field defecation (the criterion on which they were selected), their differences from MR rats in a neurochemical system involved in sympathetic function suggests that this system may be functionally related to well established behavioral and physiological differences between the lines.

Maudsley Reactive and Maudsley Non-Reactive strains Stress Norepinephrine Autonomic nervous system Affective illness Genetic models

THE Maudsley Reactive (MR) and Maudsley Non-Reactive (MNR) rat strains were originally selectively bred for differences in open-field defecation (OFD) and have been characterized on many other behavioral tests [10,12]. MR rats perform less efficiently than MNR rats on escape-avoidance conditioning [11,22] and show greater response suppression in a CER test than MNR rats [27]. In addition, a well established drinking response is suppressed by electric shock to a greater degree in MR rats [20]. Finally, MR rats exhibit greater susceptibility to frustrative non-reward than MNR rats [26]. Measures of autonomic nervous system response to mild [3] and more intense stress [4,6] also indicate a greater reactivity in MR rats. Taken together, these behavioral and physiological differences are considered by Gray [15] and Broadhurst [10] to indicate that MR rats are more susceptible to stress than MNR rats.

Pertinent to differences in autonomic function, recent results indicate a difference in the central and peripheral noradrenergic systems of the Maudsley strains [28]. Specifically, Maudsley Non-Reactive rats (MNRA line) [13] had higher norepinephrine (NE) levels in heart, spleen, adrenal and hypothalamus than Maudsley reactive (MR) rats. In addition, turnover of NE in heart was significantly faster in MNRA rats. In this experiment, subjects were derived from a colony of the strains maintained by nonsystematic breeding within the two lines. The purpose of the present study was to discover if the main findings were replicable in close relatives of the inbred lines. In addition, biochemical comparisons of MR rats with rats from two separate MNR lines were made [13]. If neurochemical differences already found between MR and MNRA lines were also seen in comparisons of MR and the other Non-Reactive line (MNR), this would lend additional support to the idea that the behavioral and physiological differences between the Maudsley strains are based on

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fundamental differences in central and peripheral noradrenergic function.

METHOD

Animals

Male rats from the Maudsley Reactive (MR) and both Maudsley Non-Reactive strains (MNR and MNRA) were supplied from the colony maintained by Dr. Gordon M. Harrington, Department of Psychology, University of Northern Iowa, Cedar Falls, IA 50613. Contrary to the information in Festing and Staats [13] which suggests that MNRA are hooded rats, animals in these three strains are all albino. MNRA is non-agouti (aa) and MNR agouti (AA). They have been separated since about the 8th generation of inbreeding [8] (see [17, 18, 19] for a comparison of these lines). These animals were maintained in our laboratory for approximately three months before use in this experiment. During this time a number of non-intrusive measures such as home-cage food and water intake and digestive transit time [31] were taken from them several weeks before use in this experiment. They were housed in single cages with Purina Lab Chow and tap water available ad lib. The diurnal cycle consisted of 15 hr light/ 9 hr dark. Their approximate age at sacrifice was as follows: MR, 7 months; MR, 7 months; MNRA, 5–1/2 months; MNR, 7 months.

Open–Field Tests

Open-field tests were carried out on these animals approximately 2 months before sacrifice to ensure that the usual differences in open-field defecation seen between MR and MNR lines were demonstrable in these samples. The open-field test consisted of a white-walled, circular arena 32.75 in. in diameter. It was illuminated at a level of approximately 30 ft candles from a photoflood suspended over the center of the field. Each animal was removed from its home-cage, carried in a holding cage to the nearby experimental room and placed in the open-field for 2 min. Its activity was automatically recorded following a method of Giulian and Silverman [14] and the number of boli excreted in a 2 min period recorded.

Tests were carried out on 4, consecutive days. On Days 1 and 2, half of the rats in each group were tested 3 hr before lights off and on Days 3 and 4, 1–1/2 to 2 hr after lights off. The reverse order of exposure to light and dark phases of the diurnal cycle was followed for the remaining animals. In both cases, test order on a given day was balanced across strains. This test procedure, i.e., comparison of exposure to the open-field during light versus dark phases of the diurnal cycle, was adopted in the context of another experiment and, since there were no differences in open-field behavior between light vs dark exposure, will not be discussed here.

Biochemical Studies

All rats were decapitated 1–4 hr before light offset with order of killing balanced across strains. Brains were removed immediately and divided into telencephalic, hypothalamic and brain-stem portions as described previously [28].

Hearts were cut free of the great vessels and connective tissues; spleens and adrenal glands were also removed and their surrounding fat layers excised.

All tissues were frozen on dry ice until assay.

Norepinephrine Assay

After weighing, all tissues except brain-stem were homogenized in 0.4 N perchloric acid. Catecholamines were then isolated following the procedure of Roth and Stone [23]. After centrifugation the pH of the supernatant was adjusted to 8.5 and passed twice over an alumina column. After washing with 20 ml distilled water, the NE was eluted from the column by washing with 1.5 ml of 0.2 N perchloric acid, followed by 1.5 ml of 0.1 N perchloric acid.

NE was oxidized according to a modification of the Anton and Sayre [2] procedure. After oxidation, the fluorescence from the trihydroxyindole derivative of NE was read at 395/505 nm on an Aminco-Bowman spectrophotofluorometer.

To calculate recovery, a known amount of NE was added to one of 2, duplicate samples of the tissue being assayed and the fluorescence obtained from each sample then compared. The recovery ranged from 70–80% and the final tissue NE concentration in each case was corrected appropriately.

Comparisons of tissue quenching were made for each tissue in the 3 strains by adding a known amount of NE to a duplicate of a tissue sample for each strain before oxidation. The increment in fluorescence produced by the addition of NE was compared to each strain. Tissue quenching was found to be of comparable magnitude in each case.

Brain stem NE was assayed by the technique of Maickel *et al.* [21]. This procedure was selected because brainstems were also assayed for 5–HT. The results of this analysis are reported elsewhere [5].

RESULTS

NE Concentrations in Brain Samples

The differences between the three strains in each brain area were evaluated by one-way analysis of variance. *T*-tests were used as follow-up tests to locate the precise source of variation.

In hypothalamus there was a trend for rats of both MNR lines to have higher NE concentrations than MR rats ($F(2,23) = 2.728$, $p<0.10$). Because this trend paralleled our previous results in hypothalamus [28], *t*-tests were run to compare individual groups. One-tailed tests were deemed appropriate for these comparisons because the previous findings predicted the direction of the differences between the lines. In the present experiment MNRA and MNR rats had significantly higher hypothalamic NE than MR rats (MNRA vs MR, $t = 2.06$, df 16, $p<0.05$; MNR vs MR, $t = 1.95$, df 16, $p<0.05$, one-tailed tests). There were no differences between the two MNR lines.

Thus, in three independent experiments ([28], and the present study) MNRA rats have had higher hypothalamic NE concentrations than MR animals ($p<0.01$; $p<0.05$, one-tailed, $p<0.05$, one-tailed). The difficulty in demonstrating this difference definitively in a consistent manner is associated with the small absolute size of the hypothalamic tissue samples. Because tissue weight is used to express NE in μg per gram of tissue variability in hypothalamic dissections has a greater effect on group variability in tissue NE concentrations than is the case with larger tissues where dissection variability is negligible in relation to the absolute size of the tissue.

In telencephalon the significant F ratio, $F(2,24) = 6.667$,

TABLE 1

NE LEVELS IN TELENCEPHALON, HYPOTHALAMUS AND BRAIN STEM μg OF NE/GM OF TISSUE

	MR	N	MNRA	N	MNR	N		
Telencephalon	0.2821 ± 0.0141	9	0.2282 ± 0.0095	8	0.2873 ± 0.0110	8	MR vs MNRA MR vs MNR MNRA vs MNR	$p<0.01$ NS $p<0.01$
Hypothalamus	1.5257 ± 0.1187	9	1.8384 ± 0.1058	8	1.9153 ± 0.1469	8	MR vs MNRA MR vs MNR MNRA vs MNR	$p<0.05$* $p<0.05$* NS
Brainstem	0.7609 ± 0.0435	8	0.6798 ± 0.0232	8	0.7479 ± 0.023	9	MR vs MNRA MR vs MNR MNRA vs MNR	$p<0.1$ NS $p<0.05$

*1 - Tailed test.

TABLE 2

NE LEVELS IN HEART, SPLEEN AND ADRENAL GLANDS* μg OF NE/GM OF TISSUE

	MR	N	MNRA	N	MNR	N		
Heart	0.6295 ± 0.02	10	0.7866 ± 0.04	8	1.0004 ± 0.03	8	MR vs MNRA MR vs MNR MNRA vs MNR	$p<0.01$ $p<0.001$ $p<0.01$
Spleen	1.077 ± 0.0787	10	1.9247 ± 0.0759	8	2.1332 ± 0.11	8	MR vs MNRA MR vs MNR MNRA vs MNR	$p<0.001$ $p<0.001$ p NS
Adrenal Glands	39.623 ± 1.1566	10	45.6964 ± 0.9384	8	46.4714 ± 1.6532	9	MR vs MNRA MR vs MNR MNRA vs MNR	$p<0.001$ $p<0.01$ p NS

*The level reported here represents the total catecholamine level per pair of adrenals.

$p<0.005$, reflected the following significant differences between the three groups: MR rats had higher NE levels than MNRA (t = 2.97, df 15, $p<0.01$) thus confirming a trend previously noted in Slater *et al.* [28]; MNR rats also had significantly higher telencephalic NE than MNRA animals (t = 4.00, df 15, $p<0.01$). Finally, MR and MNR animals did not differ in telencephalic NE concentrations.

In brainstem, the F value was not statistically significant, $F(2,22) = 1.89$, $p<0.20$. Table 1 summarizes these data.

Peripheral NE Concentrations

F ratios indicated significant differences for all three peripheral tissues (Heart, $F(2,23) = 30.37$, $p<0.001$; Spleen, $F(2,23) = 31.53$, $p<0.001$; Adrenal, $F(2,24) = 9.24$, $p<0.005$). MNRA rats had higher peripheral NE concentrations in heart (t = 3.27, df 16, $p<0.01$) and spleen (t = 6.42, df 16, $p<0.001$) and higher adrenal catecholamines t = 4.18, df16, $p<0.001$) than MR rats (Table 2). These results were all repeated in MNR/MR comparisons (Heart, t = 8.67, df 14, $p<0.001$; Spleen, t = 7.9, df 14, $p<0.001$) and adrenal catecholamines (t = 3.56, df 17, $p<0.01$) than MR. With the exception of heart where MNR rats had significantly higher NE levels (t = 3.91, df 14, $p<0.01$) than MNRA rats, the 2 MNR lines did not differ in peripheral NE concentrations (Table 2). (The levels of adrenal catecholamines in both strains are unusually high (Table 2). This tendency was not seen in the previous study [28]. However, upon careful examination we could not find any fault with various aspects of our assay procedure and we are therefore reporting these values.)

Open–Field Defecation

MR rats defecated significantly more than MNRA (X^2 = 6.45, df = 1, $p<0.025$) and MNR (X^2 = 6.82, df = 1, $p<0.01$) rats in the open-field. This difference was observed in both light and dark phases of the diurnal cycle. There were no differences in the defecation scores between MNRA and MNR rats (Table 3). Because occasional technical problems spoiled a significant proportion of activity scores, these data were not analyzed.

Body Weight

MR rats weighed significantly more than both MNRA and MNR rats at sacrifice. There were no significant differences between MNR groups (Table 4). In evaluating these differences it should be remembered that MNRA rats were approximately 1–1/2 months younger than the MR and MNR rats.

Tissue/Body Weight Ratios

Because of the significant differences in body weight

TABLE 3

MEAN OPEN-FIELD DEFECATION IN MR, MNRA AND MNR RAT STRAINS

	MR	N	MNRA	N	MNR	N	
Open Field Defecation	2.563	12	0.36	10	0.23	13	MR vs MNRA $p<0.025$ $\chi^2 = 6.45$, df, 1 MR vs MNR $p<0.01$ $\chi^2 = 6.82$, df, 1

TABLE 4

TISSUE WEIGHT/BODY WEIGHT RATIO (G/G BODY WEIGHT)

	MR	N	MNRA	N	MNR	N	Statistics
Body Wt.	363.429 ± 5.327	9	342.857 ± 7.673	8	334.1 ± 5.391	8	MR vs MNRA $p<0.05$ MR vs MNR $p<0.001$ MNRA vs MNR $p<0.1$
Spleen Wt./Body Wt.	0.00226 ± 0.0000763	9	0.001534 ± 0.000051	8	0.00167 ± 0.000042	8	MR vs MNRA $p<0.001$ MR vs MNR $p<0.001$
Heart Wt./Body Wt.	0.00286 ± 0.0000737	9	0.003132 ± 0.0000639	8	0.003212 ± 0.0001185	8	MR vs MNRA $p<0.02$ MR vs MNR $p<0.05$
Kidney Wt./Body Wt.	0.00653 ± 0.000101	9	0.00797 ± 0.000177	8	0.007143 ± 0.000179	8	MR vs MNRA $p<0.001$ MR vs MNR $p<0.02$ MNRA vs MNR $p<0.02$
Adrenal Wt./Body Wt.	0.0001399 ± 0.0000052	9	0.0001253 ± 0.00000348	8	0.000119 ± 0.00000471	8	MR vs MNRA $p<0.05$ MR vs MNR $p<0.02$
Brain Wt./Body Wt.	0.0044 ± 0.0001401	9	0.004866 ± 0.0001284	8	0.004912 ± 0.0001575	8	MR vs MNRA $p<0.05$ MR vs MNR $p<0.05$

Adrenal weight represents the weight of one pair of adrenal glands.

between the strains, tissue weights were corrected for differences in body weight (Table 4).

F ratios were statistically significant for all tissues (Spleen/body wt, $F(2,24) = 41.68$, $p<0.001$; Heart/body wt, $F(2,24) = 4.456$, $p<0.025$; Kidney/body wt, $F(2,23) = 21.20$, $p<0.001$; Adrenal/body wt, $F(2,24) = 5.535$, $p<0.025$; Brain/body wt, $F(2,24) = 4.056$, $p<0.05$). These reflected the following group differences: MR rats had larger spleens per gram of body weight than MNRA ($t = 7.46$, df 16, $p<0.001$) and MNR rats ($t = 6.55$, df 17, $p<0.001$); and larger adrenals per gram of body weight than MNRA ($t = 2.19$, df 16, $p<0.05$) and MNR rats ($t = 2.9$, df 17, $p<0.02$). MNRA rats did not differ from MNR on either of these measures.

In three other tissues both MNR lines had heavier organs relative to body weight than MR rats (Brains, MNRA vs MR, $t = 2.38$, df 16, $p<0.05$; MNR vs MR, $t = 2.43$, df 17, $p<0.05$; Hearts, MNRA vs MR, $t = 2.71$, df 16, $p<0.02$; MNR vs MR, $t = 2.587$, df 17, $p<0.05$; Kidneys, MNRA vs MR, $t = 7.28$, df 16, $p<0.001$; MNR vs MR, $t = 2.99$, df 17, $p<0.02$). Only in kidneys did MNRA and MNR differ. MNRA rats had larger kidneys per gram of body weight than MNR rats ($t = 3.27$, df 15, $p<0.02$).

The present data on heart/body weight and brain/body weight ratios (both MNR lines heavier than MR) confirm and extend the previous comparison of MNRA and MR lines [28]. The previous data indicated that spleens and adrenals of MR rats tended to be heavier per gram of body weight but only at marginal levels of significance. The present data with larger groups of rats suggest that spleens and adrenals of MR rats are significantly heavier than both MNRA and MNR lines when body weight differences are taken into account.

DISCUSSION

Confirmation of Previous Findings

These data confirm the existence of a difference in the central and peripheral noradrenergic systems of the MR and MNRA rat strains. Specifically, in hypothalamus, heart and spleen MNRA had higher NE levels than MR rats and also had higher adrenal catecholamine content than MR rats. In the previous experiment MR rats exhibited a tendency toward higher NE levels in both telencephalon and brain stem samples. This trend was statistically significant in telencephalon in the present study but not in brainstem.

Thus, similar biochemical and morphological (see RESULTS) data have been obtained on lines maintained by random breeding within each line [28] and on close relatives of the progenitor lines (the present study). This suggests that the differences in the NE system are stable features of these lines and are probably genetically fixed within them. In addition, the present data are obtained from rats which were singly-caged whereas subjects of the previous study were group-housed. Thus, the similarity of

the 2 sets of findings suggests that the differences in the NE system of these strains are not dependent on strain differences in social behavior (e.g., different levels of social stress, etc.).

Reliability of the Behavioral/Neurochemical Correlation

The existence of 2 MNR lines (MNRA and MNR) which both differ in similar fashion from MR rats in open-field behavior [19] provides an opportunity to test the reliability of the correlation between the NE system and behavior found in the original study. For example, if differences between MR and MNRA rats observed in the previous study are also seen between MR and MNR animals, the possibility that the correlation has functional significance would be strengthened. On the other hand, if MR/MNRA differences are not upheld in MR/MNR comparisons, then less confidence could be attached to the possibility of an etiologic relationship between the NE system and behavior. Therefore, the finding in the present study that both MNR rat strains exhibited higher levels of NE in heart and spleen and higher adrenal catecholamines than MR rats supports the hypothesis that genetic selection for differences in response to stress involves the peripheral sympathetic system. Rats from both MNR lines also had higher hypothalamic NE than MR rats. This suggests, as for the peripheral tissues, that the hypothalamic noradrenergic system may be involved in behavioral differences between the strains. Additional support for the concept of a functional correlation between the NE system and behavioral differences between the MR and MNR lines was the general lack of a significant difference between the two MNR groups perhaps indicating a close parallel between the genetic complement of the 2 strains. The single exception to this parallel, that MNR rats had higher cardiac NE than MNRA rats, may indicate the presence of genetic factors which distinguish the strains in this organ.

Certain MR/MNRA differences seen in the previous study were not seen in MR/MNR comparisons in the present experiment. For example, the tendency toward higher NE concentrations in telencephala of MR rats vs MNRA rats seen in the previous study, was confirmed in the present experiment but was not seen in MR/MNR comparisons. In addition, there was a tendency (albeit non-significant) in both experiments for MR rats to have higher brainstem NE than MNRA rats. This trend was not seen in the present study in MR/MNR comparisons. Hence, it would appear from these findings, that NE levels in telencephalon and brainstem are probably not crucial to the expression of behavioral differences between these strains.

Psychopharmacological Evidence

An additional line of evidence which supports the concept that MR/MNR differences in behavior are functionally related to differences in their CA systems are the results of a number of psychopharmacological studies. These suggest that the response of these strains to drugs which affect central CA systems is profoundly different. Thus, Broadhurst [9] found that the performance of MR rats on escape – avoidance conditioning was facilitated more by pretreatment with reserpine than that of MNR rats. In fact, at the highest dose-level used, MR rats performed better than MNR animals, the reverse of the usual strain difference. In a later experiment Gupta and Holland [16] showed that MR rats exhibited a greater increase in inter-trial crossing during escape-avoidance conditioning following treatment with an autonomic depressant (methylpentynol) but were less responsive to amphetamine administration than MNR rats on the same measure. In a separate series of experiments [24,25] Satinder has shown that MNR rats show a depression in performance of escape-avoidance conditioning following d-amphetamine administration whereas MRs show a marked improvement at certain dose-levels. Although the results of different investigations using amphetamine are not consistent with each other, resolution of the discrepancies may lie by allusion to the use of different isomers of amphetamine by the various investigators. For example, Gupta and Holland [16] did not specify which variant of amphetamine they used. Since the various isomers of amphetamine have different behavioral effects [30], their use by different investigators could quite conceivably account for the different effects reported by Gupta and Holland [16] and Satinder [24,25].

Although the focus of this paper is on the differences between MR and MNR strains in their NE systems, the possible contribution of other neurochemical differences between the lines to their differences in behavior should not be overlooked. Recently, differences in hypothalamic DA between MR and MNRA strains have been demonstrated [7]. MR rats have higher hypothalamic DA than MNRA rats. Antelman and Caggiula [1] have recently proposed a significant interaction between NE and DA systems, thus the inverse correlation of these transmitters in MR and MNR strains may constitute a valuable opportunity to explore their interaction. Previous experiments have shown that MR rats have higher 5–HT levels than MNR rats in some brain regions [29]. However, data obtained from the subjects of the current experiment and reported elsewhere [5] indicates that the difference in central 5–HT only shows up in MR/MNRA comparisons but not in MR/MNR comparisons. Thus, the possible involvement of the central 5–HT system in MR/MNR behavioral differences is weakened.

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