Genetic influence on brain catecholamines: high brain noradrenaline in salt-sensitive rats

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Summary

1. Rats genetically sensitive to salt-induced hypertension showed higher levels of plasma noradrenaline and adrenaline than rats genetically resistant to hypertension.
2. The hypertension-sensitive rats had higher hypothalamic noradrenaline and lower adrenaline than resistant rats.
3. In response to a high salt diet brain-stem noradrenaline increased in sensitive rats and resistant rats exhibited a decrease on the same diet.

Key words: brain stem, catecholamines, hypothalamus, salt sensitivity.

Introduction

Dahl salt-sensitive rats develop severe hypertension on a high salt diet but remain normotensive on a low salt diet, whereas Dahl salt-resistant rats remain normotensive on either diet (Dahl, Heine & Tassinari, 1962). Studies using the techniques of parabiosis and renal homografts (Dahl & Heine, 1975), as well as studies indicating reduced natriuretic capacity of the kidneys of salt-sensitive rats compared with salt-resistant rats (Tobian, Lange, Azar, Iwai, Koop & Coffee, 1977), have suggested that renal factors may be primarily responsible for the differential susceptibility to hypertension. However, evidence has accumulated which implicates both peripheral (Takeshita & Mark, 1978; Friedman, Tassinari, Heine & Iwai, 1979b) and central (Ikeda, Tobian, Iwai & Goossens, 1978; Saavedra, Del Carmine, Iwai & Alexander, 1979) nervous system factors as being at least partially responsible for the development of hypertension in salt-sensitive rats.

All of the studies, concerning nervous system involvement in the Dahl model, to date, have examined mature salt-sensitive and salt-resistant rats after a fixed period on either a high or low salt diet. The purpose of the present study was an examination of some central and peripheral catecholamine levels accompanying changes in blood pressure on graded amounts of dietary salt and at different time intervals after excessive salt intake.

Methods

The first study examined circulating noradrenaline (NA) and adrenaline levels in response to diets differing in sodium content. Weanling (21 days of age) salt-sensitive and salt-resistant rats were fed a diet containing 0.3, 1.0, 4.0 or 8.0% (w/w) NaCl. After 5 weeks, each rat was lightly anaesthetized with ether and the blood pressure was measured indirectly by tail plethysmography. Immediately after blood pressure determination, a mid-line incision was made and a blood sample (10 ml) was obtained from the abdominal aorta of each rat. The heparinized blood samples were treated and subsequently assayed for catecholamines according to Anton & Sayre (1962).

The second experiment examined hypothalamic and brain-stem catecholamine levels at different intervals after the initiation of a high salt diet. Salt-sensitive and salt-resistant rats were placed on a diet containing 8.0% (w/w) NaCl at 2 weeks post-weaning (35 days of age) and killed 0, 2, 6, 8, 10 or 12 weeks later. In all cases, indirect blood pressures were obtained 24 h before killing. The rats were decapitated, at which time the brain was quickly excised, chilled in ice, dissected along natural demarcation lines into cortex, hypothalamus and brain stem (Glowinsky...
& Iversen, 1966) and frozen. Simultaneously, the heart and adrenals were quickly removed, rinsed, weighed and immediately frozen. Tissues were subsequently assayed for NA and adrenaline. The present study presents only results obtained from hypothalamic and brain-stem tissue.

Results

All results were analysed by using a two-way analysis of variance procedure. In the first study, the expected blood pressure pattern emerged. As indicated in Table 1, salt-sensitive rats exhibited significantly higher blood pressures than salt-resistant rats. The significant strain and diet interaction was due to the increased blood pressure of salt-sensitive rats on the 4.0 and 8.0% NaCl diets and the absence of such an effect in salt-resistant rats. The blood pressure results were not closely paralleled by changes in either plasma NA or adrenaline. As can be seen in Table 1, salt-sensitive rats had higher plasma NA levels in every dietary condition resulting in a statistically significant effect. However, the absence of a significant strain and diet interaction indicates that the magnitude of this difference remained fairly constant. Similarly, although there appeared to be more variability, salt-sensitive rats had significantly higher adrenaline levels than salt-resistant but the strain and week interaction was not significant.

Table 2 presents the results of the second experiment. For clarity of presentation, only the results obtained in weeks 0, 2, 6 and 12 are presented. The statistical analysis, however, included the data from weeks 4, 8 and 10 as well. Once again, the blood pressure data were generally as expected although the hypertension evinced by salt-sensitive rats after 12 weeks' exposure to the 8.0% NaCl diet was less than expected. Salt-sensitive rats had higher concentrations of NA in the hypothalamus than salt-resistant rats each week. The rise in hypothalamic NA in salt-sensitive rats at 2 weeks was not maintained nor was the less dramatic fall in salt-resistant rats at the same interval. Hence, although there was a very significant strain effect, the strain and week interaction failed to reach statistical significance. The results of the hypothalamic adrenaline concentrations were in the opposite directions. Overall, salt-sensitive rats had significantly lower levels than salt-resistant

| TABLE 1. Blood catecholamine levels in Dahl salt-sensitive and Dahl salt-resistant rats
| Results are means for six samples individually assayed. |
| NaCl in diet (%) . . . . . . 0-3 1-0 4-0 8-0 |
| | Sensitive/Resistant | Sensitive/Resistant | Sensitive/Resistant | Sensitive/Resistant |
| Systolic blood pressure (mmHg) | 120/108*†‡ | 120/108*†‡ | 160/111*†‡ | 207/114*†‡ |
| Plasma noradrenaline (ng/ml) | 2.6/1.9* | 3.4/1.5* | 3.6/2.1* | 3.7/2.0* |
| Plasma adrenaline (ng/ml) | 10.7/10.9* | 11.2/10.8* | 10.7/10.6* | 11.6/10.6* |

* Significant strain effect, P < 0.05.
† Significant diet effect, P < 0.05.
‡ Significant strain and diet interaction, P < 0.05.

| TABLE 2. Tissue catecholamine levels in Dahl salt-sensitive and Dahl salt-resistant rats
| Results are means for three samples individually assayed. |
| Time on 8% (w/w) NaCl diet (weeks) . . . . . 0 2 6 12 |
| | Sensitive/Resistant | Sensitive/Resistant | Sensitive/Resistant | Sensitive/Resistant |
| Systolic blood pressure (mmHg) | 123/99*†‡ | 129/101*†‡ | 172/113*†‡ | 169/100*†‡ |
| Hypothalamic noradrenaline (ng/g) | 3.16/2.57* | 4.05/2.03* | 3.52/2.36* | 3.46/2.47* |
| Hypothalamic adrenaline (ng/g) | 2.27/2.69* | 2.35/2.04* | 1.34/2.28* | 1.60/1.60* |
| Brain-stem noradrenaline (ng/g) | 0.83/0.83* | 1.06/0.69* | 0.93/0.67* | 1.07/0.64* |
| Brain-stem adrenaline (ng/g) | 0.65/0.66* | 0.53/0.52* | 0.24/0.34* | 0.21/0.27* |

* Significant strain effect, P < 0.05.
† Significant strain effect, P < 0.05.
‡ Significant strain and weeks interaction, P < 0.05.
rats. Once again, there was no significant strain and weeks interaction. Brain-stem NA was the same in salt-sensitive and salt-resistant rats at week 0. However, in response to the high salt diet, salt-sensitive rats evinced an increase whereas salt-resistant rats showed a decrease. Salt-sensitive rats tended to maintain relatively high levels whereas salt-resistant rats tended to maintain relatively low levels. This resulted in a statistically significant strain effect and a significant strain and weeks interaction. As was the case with hypothalamic tissue, the direction of the strain difference was opposite for NA and adrenaline. Overall, salt-sensitive rats had significantly lower adrenaline levels in brain stem than salt-resistant rats although considerably more week-to-week variability existed. There was a definite trend toward lower brain-stem adrenaline levels in both lines, but the strain and week interaction was not significant.

Discussion

The relationship between central and peripheral catecholamine concentrations and salt-induced hypertension appears to be complicated. The results of the present study suggest that some central and peripheral catecholamine differences between salt-sensitive and salt-resistant rats are dependent on genetic factors but do not closely parallel blood pressure changes. In the present study, for example, the difference in plasma NA and hypothalamic NA between salt-sensitive and salt-resistant rats in the baseline state did not appreciably change during salt feeding and the development of hypertension. On the other hand, brain-stem NA rose in salt-sensitive rats in response to the high salt diet and salt-resistant rats showed a decrease. Hence, this difference appears to be due to differential responsiveness of the two strains to the hypertensinogenic stimulus. It is not yet possible adequately to determine the relevance of these peripheral and control catecholamine differences to salt-induced hypertension. Clearly, the longitudinal approach of the present study can be elucidating. However, more precise anatomical dissection may be more informative, given the complex constellation of results reported by Saavedra et al. (1979).

Two additional theoretical issues bear mention. For those indices which differentially change in response to excess salt ingestion in salt-sensitive and salt-resistant rats, it becomes important to determine if the difference is actually due to differential responsiveness to salt per se. Changes occurring in salt-sensitive rats but not in salt-resistant rats may be secondary to elevations in blood pressure irrespective of the aetiological stimulus. Another point concerns the nature of physiological and biochemical indices which correlate with the genetic predisposition to hypertension but that do not necessarily parallel the development of the high blood pressure. We have previously demonstrated that certain behavioural characteristics distinguish salt-sensitive rats from salt-resistant rats in the normotensive state. This is analogous to some of the peripheral and central catecholamine differences reported here and by others (Saavedra et al., 1979). A careful genetic cross study of the relationship between the behavioural and cardiovascular phenotypes, however, indicated that the relationship between the two variables was not genetic but was fortuitous (Friedman, Haber & Iwai, 1979a). Hence, the relevance of the correlations obtained between catecholamine levels and genetically determined blood pressure responsiveness to salt ingestion remains to be determined.

Acknowledgments

This work is supported by the U.S. Department of Energy (Contract DE-AC02-76CH00016) and PSH Grant HL-14913.

References


