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Dietary Sodium, Psychic Stress, and Genetic Predisposition to Experimental Hypertension[1] (39827)

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Introduction. The relative etiologic significance of dietary sodium and psychological stress in experimental and clinical hypertension remains conjectural (1). Two strains of rats have been developed in this laboratory which facilitate the examination of putative hypertensinogenic stimuli (2). One strain, the Dahl hypertension-sensitive or S strain, rapidly and predictably develops severe, usually fatal, hypertension in response to excess dietary salt ingestion. The other strain, the Dahl hypertension-resistant or R strain, responds only mildly, if at all, to the same stimulus (3). Similarly, we have recently reported that the psychological stress of chronic exposure to an aversive operant conditioning schedule involving a food-shock conflict elevated the blood pressure of S rats but not R rats (4). Since S rats are hypersensitive to excess sodium ingestion, our previous stress studies used a diet containing less than 0.4% NaCl. This was done in order to assess the effects of stress independently of the effects of sodium. Using this low-sodium diet, stress was clearly hypertensinogenic for S rats. However, the stress-induced blood pressure elevations were much less severe than the elevations previously obtained when unstressed S rats were fed diets containing 4 or 8% NaCl. Furthermore, morbidity and mortality rates were much lower in the stress experiments. We speculated that more severe hypertension might have been prevented by the relatively low amount of dietary sodium. Since the food-shock conflict results in severe food deprivation, the actual amount of ingested sodium was very low. Consequently, the present experiment examines the synergistic effects of both stimuli by exposing S rats to the chronic stress while feeding them a diet containing 2% NaCl.

Materials and methods. Thirty-five male rats, selected from the Dahl-sensitive (S) strain were used as experimental subjects. They were approximately 3 weeks post-weaning (6 weeks of age) at the time that the experimental treatment began. Complete details of the experimental procedures are available elsewhere (5). Briefly, rats were exposed for 26 weeks to one of the following five conditions. (i) Conflict: Rats in this group were placed for 6 hr daily in a standard Skinner box and were trained to press a lever according to a variable-interval (60-sec) schedule in order to obtain food pellets. Each specially made food pellet was 45 mg and was prepared from a grain-base meal containing 2% NaCl (P. J. Noyes and Co., Lancaster, N.H.). In addition to the food contingency, lever pressing periodically resulted in the brief electrification of the grid floor of the experimental chamber according to a variable-ratio schedule. Since food was not otherwise available, the rat was required to press the lever to sustain itself but, by so doing, exposed itself to electric shock. Since both food and shock delivery schedules were variable, the subject could not determine whether any particular response would result in food, shock, neither, or both. The remaining 18 hr were spent in individual home cages with ad libitum access to water, but without food. (ii) Yoked shock: Rats in this group were also placed in Skinner boxes for 6 hr daily and required to press a lever for food according to the same variable-interval schedule. However, for these rats, lever pressing was independent of shock presentation. The grid floors of the experimental chambers were arranged so that each subject in this group was yoked to a conflict subject. Each time the conflict rat was shocked, the yoked-

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shock rat was also shocked. This group served as a control for the simple application of electric shock. (iii) Yoked food: Each subject in this group was yoked to a subject in the conflict group with respect to food. These subjects were never exposed to the Skinner boxes and were never shocked. They received the appropriate amount of food as determined by conflict rats in individual home cages located in the experimental room. Since exposure to the food–shock conflict results in severe food deprivation, this group served as a control for this variable. (iv) Yoked food and shock: Each rat in this group was placed in a Skinner box but not required to press a lever for food. These chambers were arranged so that both food pellet and shock presentation were controlled by the responses of a conflict rat. Hence, each rat in the yoked-food-and-shock group received the identical amount and pattern of food and shock as a conflict rat and differed only in that it was unable to control these events. (v) Controls: Subjects assigned to this group were individually housed in the experimental room and allowed ad libitum access to food throughout the experiment. They were never shocked. The food consisted of larger pellets made from the same meal as that used to make the 45-mg pellets. Hence, control rats were also exposed to a diet containing 2% NaCl.

Each week, subjects were weighed and systolic blood pressures were measured by tail plethysmography while the rats were lightly anesthetized with ether (6).

Results. Weights. The weekly group mean body weights are presented in Fig. 1. The control subjects fed a 2.0% NaCl diet exhibited a growth curve similar to that usually observed in S rats given a low-sodium diet containing less than 0.4% NaCl. Yoked-shock animals required to obtain food via the variable-interval schedule could not nearly maintain normal body weights. The variable-ratio 60-sec schedule permits reinforcement on the average of once each minute for 6 hr. However, in order to obtain the maximum of 360 pellets or 16.2 g (360 × 0.045 g), the subject would have to almost constantly lever-press throughout the 6-hr session. Rats in this group averaged approximately 250 pellets or about 11 g/day

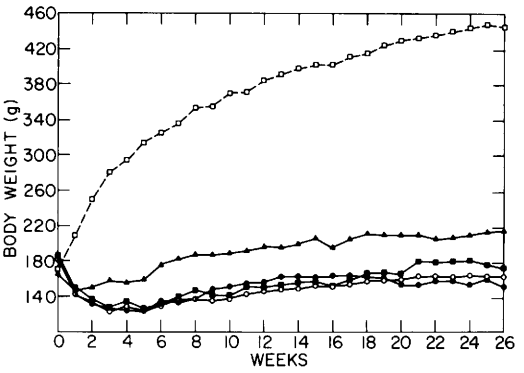

FIG. 1. Mean body weights of: conflict rats (○——○——○); yoked-shock rats (▲——▲——▲); yoked-food rats (●——●——●); yoked-food-and-shock rats (■——■——■); and control rats (□–□–□).

throughout the experiment. In contrast, the conflict rats exposed to this schedule, but with the associated shock contingency, averaged approximately 150 pellets or 7 g/day. As the experiment progressed, both conflict rats and yoked-shock rats developed more efficient response strategies and slightly increased the number of pellets obtained. Yoked-food rats and yoked-food-and-shock rats received food according to the performance of conflict rats. Consequently, their food intakes were approximately equal and, as expected, the mean body weights of these three groups were approximately equal.

Blood pressure. As indicated in Fig. 2, there was considerable week-to-week variability in all groups. Despite this, an analysis of variance revealed highly significant main effects for treatment ($P < 0.01$) and for weeks ($P < 0.01$). Likewise, the treatment by weeks interaction was significant ($P < 0.01$). Post hoc comparisons, using the Tukey Honest Significance Difference technique (7), indicated that conflict-exposed rats had significantly higher blood pressures than any of the other groups over the duration of the experiment. Despite occasionally large differences of some weeks, there were no statistically significant differences among any of the other conditions.

Discussion. These results confirm our previous reports in that chronic exposure to a food–shock conflict did cause moderate but sustained elevations in blood pressure in the strain genetically susceptible to hyper-

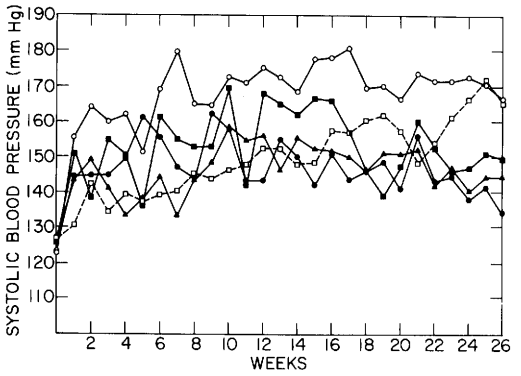

FIG. 2. Mean systolic blood pressures of: conflict rats (○——○——○); yoked-shock rats (▲——▲——▲); yoked-food rats (●——●——●); yoked-food-and-shock rats (■——■——■); and control rats (□--□--□).

tension. Exposure to electric shocks or food deprivation did not result in long-term elevations in blood pressure although food-deprived rats did exhibit increases for several weeks. These observations are analogous to those previously reported in S rats similarly exposed but given a low-salt diet (5). Rats exposed to both food deprivation and electric shock, but without conflict, exhibited dramatic fluctuations in blood pressures which were generally higher than those of S rats exposed to either aversive stimulus alone but lower than those of conflict-exposed rats. Once again, this pattern is strikingly similar to that obtained in our previous studies using a low-salt diet.

The addition of 2% NaCl to the diet of stressed S rats did have an effect. A comparison of data previously obtained in our laboratory on S rats exposed to the conflict procedure, but on a low-salt diet, with the present data of S rats similarly stressed but on a 2% NaCl diet, is revealing. Beginning at the 12th experimental week and throughout the rest of the 26-week test period, the rats fed 2% NaCl had average systolic blood pressures approximately 10 mm Hg higher. A similar directional trend was evident in the other stressed groups, with rats given 2% NaCl having slightly higher blood pressures. Control rats given 2% NaCl also had a mean systolic blood pressure approximately 10 mm Hg higher than previously tested control rats fed a low-salt diet.

The addition of 2% NaCl to the diet of stressed S strain rats did not, however, result in blood pressure elevations as severe as those exhibited by unstressed S rats fed diets containing 4 or 8% NaCl (8). S rats exposed to an 8% NaCl diet typically exhibit average systolic blood pressures well over 200 mm Hg within 8 weeks, followed by significant mortality rates. Similar, although less severe, effects are noted with a 4% NaCl diet.

There does appear to be an interaction of genotype with sodium intake and psychological stress in the development of hypertension. We have recently obtained data from R strain rats exposed to the food-shock conflict using a 2% NaCl diet. There was no evidence throughout the 26-week test period of blood pressure elevations in these subjects (Friedman and Iwai, unpublished observations).

In this experiment animals exposed to the food-shock conflict developed higher blood pressures than all the other groups, clearly indicating that this type of stress synergistically interacts with the 2% NaCl diet. However, despite the combination of genetic predisposition, chronic psychological stress, and moderate sodium ingestion, we failed to obtain elevations in blood pressure comparable to those shown by genetically susceptible rats allowed ad libitum access to a salt diet containing 4 or 8% NaCl. Similarly, previous experimental attempts by others using unselected animal populations have usually reported stress-induced blood pressure elevations less pronounced and less persistent than those reported by investigators using stimuli such as the Goldblatt clamp or other physiologic insults. The relative subtlety of stress in the present study must be interpreted keeping in mind that the animal model used was specifically bred for susceptibility to sodium and that the particular stress situation employed results in severe food deprivation. Both factors may have prevented the expression of more serious stress-induced hypertension. Although it appears that psychological stress can interact with other putative hypertensinogenic stimuli to produce long-term elevations in blood pressure, the etiologic significance of stress, viz-a-viz these other stimuli, in the pathogenesis of experimental hypertension

still remains conjectural. However, it should be noted that even modest elevations, such as those observed here, may have profound pathophysiologic effects.

Summary. Rats with a genetic susceptibility to hypertension were exposed for 26 weeks to the stress of a chronic food–shock conflict while being fed a diet containing 2% NaCl. The rats developed modest elevations in blood pressure. These elevations were greater than those previously observed in conflict-exposed rats fed a very-low-sodium diet and much greater than those observed in unstressed rats fed 2% NaCl ad libitum. However, the elevations in blood pressure were less severe than those usually exhibited by genetically similar rats fed a diet containing 4 or 8% NaCl without the superimposition of psychological stress. The results suggest that, although psychological stress can synergistically interact with sodium, its hypertensinogenic potency remains conjectural.

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