Dahl Salt-Susceptible and Salt-Resistant Rats

A Review

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Dedication: This review is dedicated to Lewis K. Dahl, M.D., for his brilliant and innovative work in hypertension research.

The purpose of this article is to review comprehensively the data available on the strains of rats that were selectively bred by Dr. Lewis K. Dahl for susceptibility (S strain) or resistance (R strain)* to the hypertensive effect of high salt diet. In this review "salt" will always mean NaCl.‡

Selective Breeding

In the 1950s, Meneely and coworkers studied the effects of high salt diet on the blood pressure of rats. Meneely and Ball§ reviewed the work, showing that for a large group of rats the average blood pressure of the group was positively and linearly related to the percentage of NaCl in the diet between 0 and 10% NaCl. Moreover, they remarked that "there was quite a marked degree of individual variation" in the response of blood pressure to salt. This work was carried out on Sprague-Dawley rats that were presumably random-bred.

*A nomenclature committee of the International Society of Hypertension has stated that Dahl salt-sensitive (or salt-susceptible) rats should be designated DS and Dahl salt-resistant rats should be designated DR (see ref. 1). This nomenclature is specifically not used in this review, and its use, except as noted below, is discouraged. In Dahl's original work in 1962 and for 14 years until his death, Dr. Dahl called the strains S and R. There is no need to replace that historic precedent. The nomenclature committee specifically states that they were naming "hypertensive rat strains with stable hypertension which had been inbred (brother-sister mating) for at least 20 generations" (ref. 1). Apparently they were naming inbred strains under development at Brookhaven National Laboratory since Dr. Dahl's death in November, 1975. No fully inbred rats were supplied to investigators from the Brookhaven colony because they do not exist (yet). What was supplied were rats from colonies of S and R rats separate from the inbreeding program and maintained as Dahl had done for many years by selective breeding, avoiding inbreeding where possible. Thus, the use of DS and DR implies the use of specific inbred strains which do not exist. If and when such strains from Brookhaven become available, these specific strains of inbred S and R rats can be referred to as DS and DR.

‡Sodium in the diet is expressed in two ways in the literature, either as % Na⁺ or % NaCl. The latter assumes that all the Na⁺ is present as NaCl. % NaCl means grams of NaCl per 100 grams of food. In most of the literature reviewed, sodium was expressed as % NaCl, and so this will be used throughout the review. Where the original article gave data in % Na⁺, this will be given followed by the % NaCl so that diets can always be compared on the same basis (% NaCl = 2.54 times % Na⁺).

A survey of commercial rat chows shows that they contain close to 1% NaCl, and so "normal salt diet" will refer to 1% NaCl in the food. Two diets were introduced by Dahl during his work with S and R rats: 8% NaCl diet referred to as "high salt diet"; and 0.3 to 0.4% NaCl diet referred to as "low salt diet". Note that with this arbitrary nomenclature, low salt diet has only somewhat less than half the salt content of normal diet. Where a diet was fed that contained insufficient salt for optimum growth, this will be called sodium-deficient diet. The minimum dietary requirement of sodium for optimum growth in the rat is 0.05% Na⁺ (0.13% NaCl) (see ref. 2) and this is also an adequate minimum for reproduction (see ref. 3). On diets containing 2.8% NaCl and higher, rats grow slower than the optimum (see ref. 4).
During the 1950s, Dr. Lewis K. Dahl (fig. 1) had worked largely with the effects of salt on blood pressure in humans. In the early 1960s, he turned his attention to studies in the rat, in which he, like Meneely et al., showed that chronic excess salt ingestion leads to sustained hypertension. Taking advantage of the observation that not all rats responded to salt with similar changes in blood pressure and cognizant of the data suggesting genetic influences on blood pressure in humans, Dahl et al. were able to selectively breed rats for susceptibility (S rats) or resistance (R rats) to the hypertensive effects of high salt (8% NaCl) diet. After only three generations of selective breeding, the S and R lines were clearly separated. The blood pressures of R rats were essentially similar on control or high salt diets, but S rats responded to salt with a pronounced increase in blood pressure. Thus, the two strains yielded an interesting model for the interaction of an environmental factor (salt) with genotype.

Blood pressure is a polygenic trait, meaning that there are multiple genetic loci with effects on blood pressure. When starting from a genetically heterogeneous base population, the technique of selective breeding acted to concentrate in the salt-susceptible or salt-resistant strains, respectively, the alleles with effects to increase or decrease blood pressure response to salt. Although it is often recognized that the extreme sensitivity of the S to salt is unique, the extreme resistance of the R rat is equally unique. R rats should not be considered a "normal" control strain equivalent to random-bred, unselected rats. In this context it is well to recognize that it is the whole spectrum of blood pressure, from high to low, that is genetically regulated and that hypertension in the genetic context is a rather arbitrary, albeit very convenient, designation.

It was estimated using quantitative genetic techniques that approximately 2-4 loci were involved in controlling the blood pressure response to salt in S and R rats. The theoretical formulas from which such estimates were calculated were based on genetic assumptions that in practice are less than perfectly met. Thus, the result of 2-4 loci influencing salt susceptibility in S and R rats is approximate. To date only one of these loci has been definitively described in biochemical genetic terms (see below under Endocrine Factors). There is no evidence for sex-linked genes.

In the original selective breeding experiments to produce S and R rats, brother-sister matings (i.e., inbreeding) were made for the first few generations. Subsequently, selection was continued but purposeful...
inbreeding was avoided (Dahl, personal communication). As of 1975, the S and R rats in the Brookhaven colony were not inbred strains, although they were sometimes referred to as such in the literature. An inbred strain is one for which brother-sister matings have been made for 20 or more generations. This theoretically leads to homozygosity at almost 100% of genetic loci, thus fixing the characteristics of the strain. Since 1975, inbreeding programs with S and R rats have been initiated at Brookhaven and in my laboratory.

General Characteristics of the Strains

When S rats were placed on a high salt (8% NaCl) diet at weaning (21–23 days of age), they rapidly developed hypertension and all died by the 16th week of salt feeding. With similarly treated R rats, blood pressure remained in the normotensive range, and 80% of the animals survived to the 48th week on high salt.9 The age at which high salt diet was started partly determined the magnitude of the blood pressure response in S rats. When given high salt at weaning, S rats developed fulminating hypertension (above 200 mm Hg) within 6 weeks. If high salt feeding was delayed until 3 months of age, the hypertension developed less rapidly and blood pressure went to about 185 mm Hg by 16–20 weeks.12

Studies by Meneely et al. using regular laboratory rats showed that supplemental potassium prolonged survival rate in rats on high salt diets.5 10 Using S rats, Dahl et al.4 found that for diets with the same amount of NaCl blood pressure was reduced by increasing potassium content. On diets with different absolute concentrations of NaCl and KCl, but with identical Na⁺/K⁺ molar (M) ratios, animals on the higher absolute NaCl intake had higher blood pressures. Thus, both the Na⁺/K⁺ M ratios and the absolute amount of Na⁺ in the diet are important determinants of the final blood pressure.

There is a widespread misconception that S rats become hypertensive only when placed on high NaCl diets. In fact, on normal rat chow that contains 1% sodium in S rats. Serum sodium and potassium were higher than R.16 Skeletal muscle sodium and potassium concentrations responded similarly in S and R to treatment with deoxycorticosterone.17 Thus, there is no evidence that S rats become hypertensive because of excess sodium retention.

The usual practice with S and R rats is to vary the NaCl content of the food and provide water ad libitum. Both strains eat the same amount of food on either high (8% NaCl) or low (0.4% NaCl) diets.18 19 If, however, the rats are provided with both water and saline solutions to drink, the S rats will consume significantly less saline.20

In an interesting demonstration of the high salt content of processed baby food, Dahl et al.21 showed that S rats fed such food developed hypertension and died. Control S rats on 0.4% NaCl rat chow had relatively normal blood pressures and lived significantly longer.

Sensitivity of S Rats to Other Forms of Experimental Hypertension

The S rat is more sensitive than the R rat to hypertension induced by several experimental procedures. These include deoxycorticosterone plus 7.3% NaCl in food,22 adrenal regeneration plus 1% NaCl to drink, and cortisone given to adrenalectomized rats drinking 0.85% saline.23 Obviously, with these techniques the excess salt feeding included in the protocols confounds the claim that salt-sensitive rats are more prone to steroid-induced forms of hypertension. But, in fact, if deoxycorticosterone is administered without excess salt, S rats do show significantly increased blood pressure while R rats do not.17 The S rats are also more prone than R to develop hypertension in experiments that omit excess salt but that involve clipping of the renal artery,22 injection of cadmium,24 25 or psychological stress.26 In early studies on “stress,” electric shocks were administered independent of the rats’ behavior and no elevations in blood pressure occurred.37 However, with the appropriate conflict between the necessity to obtain food and to avoid electric shock, S rats did respond with increased blood pressure,28 29 and this response was greater in S than R.36

Kidney

The kidney has been the focus of considerable attention in S and R rats. This interest largely arises from the renal cross-transplantation experiments of Dahl et al. If the kidney from an S rat is transplanted into an R rat from which both original kidneys have been removed, the R rat develops higher blood pressure than R rats with transplanted R kidneys or R rats with unilateral nephrectomy. Conversely, an R kidney transplanted into an S rat ameliorates the blood pressure rise seen in S rats with transplanted S kidneys or S rats with unilateral nephrectomy.30 32

Early attempts to identify some abnormality of renal function between S and R rats were unsuccessful. Using clearance methods on unanesthetized rats, Benlishay et al.33 found that the glomerular filtration rate and renal plasma flow were similar in S and R. The natriuretic and diuretic response to a hypertonic saline load was also equal in the two strains.34 In contrast, when the saline load was given as an isotonic solution, S rats excreted significantly more sodium and water than R rats.35 This difference was present in young rats before the development of markedly increased blood pressure in S rats.

It has been reported that S rats have 15% fewer glomeruli than R. Following 20–30 days of high salt to induce mild hypertension in the S rats, the S compared to R showed increased single nephron blood flow,
increased single nephron glomerular filtration rate, and decreased resistance at the afferent and efferent arteriolar segments. These data were interpreted as adaptive changes to the reduced number of glomeruli. Recently it was found that S rats responded to acute administration of dexamethasone with a markedly greater diuresis and proteinuria than R. Since glucocorticoids act by increasing glomerular plasma flow rate, this result implies differences in glomerular function between S and R.

Using an autoperfused kidney preparation, Fink et al. have found that the renal vascular resistance of rats on a low salt diet was less in S than R rats. Following 4 weeks of 8% NaCl diet fed to 8- to 10-week-old animals, R rats had decreased renal vascular resistance and an increased slope of their pressure-renal blood flow curves (i.e., a greater change in blood flow for a given change in pressure) compared to R rats on a 0.4% NaCl diet. In contrast, the S rats did not change their renal vascular resistance or renal pressure-flow curves in response to salt. This was interpreted to mean that S rats did not decrease renal vascular resistance in response to high salt intake and therefore S renal vascular resistance was inappropriately high on high salt intake. Another interpretation, also discussed by the authors, is that the S renal vasculature was already dilated on a low salt diet and could not respond further to salt. The latter interpretation is more compatible with the micropuncture studies.

Tobian et al. have studied Na+ and water excretion using isolated perfused kidney preparations from S and R rats raised for 8 weeks on 8% NaCl. Kidneys were perfused with blood from normal Sprague-Dawley rats. At any given renal perfusion pressure, R kidneys excreted more urine and sodium than S. Thus, in S rats, the pressure-natriuresis curve was shifted to the right relative to R. Girardin et al. performed similar experiments with S and R rats before and after high salt (8% NaCl) diet. They concluded that there was no preset abnormality of the pressure-natriuresis curve in S rats until after S-rat kidneys had been exposed to high blood pressure for 7 weeks. This suggests that an abnormal pressure-natriuresis curve may result from the significant vascular lesions that are known to occur in S rats with elevated pressure (see below). The point is not settled, however, because Tobian et al. were careful to compare S and R rats with similar blood pressures and still found differences in pressure-natriuresis curves.

In any case, it is important to know what lesions have been described in S and R kidneys. Jaffé et al. reported that, as S rats develop hypertension, they develop focal tubular collapse, focal tubular dilation, glomerular scarring, and proliferation of muscleelastic tissue at arteriolar branch pads. As hypertension progressed, the lesions progressed in distribution and severity with larger areas of tubular collapse or dilation, and protein casts. Glomerular scarring and proliferative lesions at the branch pads became severe, and degenerative changes in arterioles were seen. The severity of the lesions correlated well with blood pressure, and discernible lesions were seen even with only mild elevations of blood pressure in the S rats in the range 130-150 mm Hg (fig. 9 of ref. 43). In my own experience, significant renal lesions are seen with blood pressures in the 150-160 mm Hg range. There are significant correlations among blood pressure, renal lesions, and urinary protein excretion even in mildly hypertensive S rats. Control R rats in these experiments uniformly lacked significant renal pathology. However, because Tobian et al. were careful to compare S and R, it is worth emphasizing that lesions at the renal vascular branch pads are evident in S rats even with modest elevation in blood pressure. Branch pads are valve-like structures in the normal rat which in the kidney are present only where the interlobular arteries give rise to afferent arterioles that supply the juxtamedullary glomeruli. The efferent vessels from juxtamedullary glomeruli of course supply the renal medulla. It is interesting that mildly and moderately hypertensive S rats have a reduced renal papillary plasma flow compared to R. Whether this is a physiologic effect or a pathologic effect due to branch pad thickening has not been investigated.

Urinary kallikrein excretion has been uniformly reported to be lower in S than R rats. urinary kallikrein is known to be stimulated by mineralocorticoids. S rats have a net mineralocorticoid excess due to increased production of 18-hydroxy-11-deoxycorticosterone (see Endocrine Factors below). Low urinary kallikrein at first appears inconsistent with the higher mineralocorticoid status. It was found, however, that urinary kallikrein excretion of S rats did not increase in response to exogenous mineralocorticoid. The mineralocorticoid treatment did of course increase blood pressure, and in this short-term experiment, the S rats developed mild renal lesions and proteinuria. S rat urinary kallikrein did increase normally in response to a sodium-deficient diet, a situation where increases in blood pressure and renal damage would be minimized. Thus, low urinary kallikrein in the S rat might be secondary to renal damage. The developmental pattern for urinary kallikrein excretion is compatible with this suggestion. There was no difference in urinary kallikrein excretion between young S and R rats (6 weeks old). Differences in urinary kallikrein between S and R developed concomitantly with increased blood pressure and increased urinary protein excretion in S over R rats. Moreover, it has been found that S rats early in the development of hypertension and concomitant with the development of proteinuria excrete in their urine a kallikrein-binding protein. Initial evidence suggests that this binding protein could be a kallikrein inhibitor originating from the plasma.

Urinary prostaglandin E2, excretion is and in vitro renomedullary synthesis of prostaglandin E2 are lower in S than R. These changes are difficult to interpret because in most species prostaglandin E2 is a renal vasoconstrictor but in the rat it may be a vasodilator. If, however, lower vasoconstrictor activity in the S-rat kidney should not to potentiate hypertension.
The S rats have unequivocally lower plasma renin activity, lower renal renin activity, and lower juxtaglomerular granularity than R rats. Plasma and renal renin activity in both strains respond appropriately to changes in NaCl intake, but a difference between S and R remains regardless of diet. The strain difference in plasma renin activity was present as early as 39 to 42 days of age; small differences in blood pressure were also present at this young age. S pressures being higher than R. Perfused S kidneys also released less renin than perfused R kidneys. A possible inhibitory action of S-rat plasma on hog renin in vitro has been reported. R-rat plasma had no such activity. The substance(s) responsible for this have never been pursued. The pH profile of plasma renin activity has also been shown to differ in S and R rats.

No evidence for a mutation in the (Na+,K+)-ATPase molecule was found in comparing the enzyme from S and R rats. Renal (Na+,K+)-ATPase has been measured in renal microsomes. In young S and R rats with minimal changes in blood pressure, there was no difference between strains in renal microsomal (Na+,K+)-ATPase activity. In 6-month-old rats fed a normal 1% NaCl diet, S rats had long-standing hypertension and also reduced renal microsomal (Na+,K+)-ATPase activity which was attributed to possible renal damage. Although the pH optima were the same, the slope of the pH curves above pH 7.0 were different. It was possible to type individual rats as either S or R on the basis of the pH profile of their plasma renin activity, and this characteristic was independent of changes in plasma renin induced by alteration of salt intake. The cause of this phenomenon is unknown, but could involve molecular differences in renin or renin substrate.

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Endocrine Glands

It has been shown that adrenalectomy in S rats prevents the development of hypertension induced by high salt diet. This shows that adrenal function is necessary for salt-induced hypertension, but by itself does not establish that abnormal adrenal function in S rats causes the hypertension. But, in fact, the pattern of steroids secreted by S and R adrenal glands are markedly different. S adrenals show increased 18-hydroxylation of deoxycorticosterone (DOC) to form 18-hydroxy-11-deoxycorticosterone (18OH-DOC) compared to R adrenals. This higher 18-hydroxylation per unit weight of the S adrenal was exactly offset by a lower 11β-hydroxylation of DOC to form corticosterone (B) in S compared to R. Total utilization of DOC precursor was identical between the strains, it was just the proportion going to 18OH-DOC or corticosterone that was altered. This gave rise to characteristic ratios of 18OH-DOC/B for S and R rats, which allowed unambiguous separation of S and R strains on the basis of the in vitro incubation of the adrenal. Salt feeding had no effect on these characteristic steroid patterns.

Genetic studies have shown that the characteristic steroid patterns of S and R rats are controlled by a single genetic locus with two alleles inherited by codominance. The locus was eventually named Hyp-I for hypertension locus number 1 for reasons given below.

Initially, the genetic data on the Hyp-I locus presented an enigma. The increment in 18-hydroxylation in S compared to R was equal to the decrement in 11β-hydroxylation. Thus, equal and opposite effects were apparently produced on the two enzymes, 18-hydroxylase and 11β-hydroxylase, by a single gene. Detailed biochemical studies show that the assumption that 18-hydroxylation and 11β-hydroxylation are catalyzed by separate enzymes is wrong. The S-rat cytochrome P-450 for 18-hydroxylation had an identical Warburg’s partition constant to that of S-rat cytochrome P-450 for 11β-hydroxylation, implying that the two reactions were catalyzed by the same enzyme. Similarly, the partition constant of R-rat P-450 for 18-hydroxylation was identical to the partition constant of R-rat P-450 for 11β-hydroxylation, again implying one enzyme for the two hydroxylations. The S and R partition constants differed drastically, however, implying the
existence of a mutant form of a single cytochrome P-450 for 18- and 11 β-hydroxylation between the two strains. Moreover, the S and R genotypes at Hyp-1 segregated with the characteristic S and R partition constants for the enzyme. This constitutes genetic proof that the same enzyme catalyzes both 18- and 11 β-hydroxylation of DOC. Subsequently, pure cytochrome P-450 for 11 β-hydroxylation was isolated from bovine adrenals; this enzyme also catalyzed 18β-hydroxylation. The obvious rationalization for the equal and opposite effects in the S and R rats for 18- and 11β-hydroxylation between the two strains is that, when a given form of P-450 (S or R) binds a DOC molecule, the molecule is hydroxylated at either the 18- or the 11β-position. If a molecule of DOC is 18-hydroxylated, it detaches from the enzyme and is not 11β-hydroxylated or vice versa. Therefore, a genetically mutated P-450 with increased constants for the enzyme constiutes genetic evidence that the same enzyme catalyzes both 18- and 11β-hydroxylation. The obvious rationalization for the equal and opposite effects in the S and R rats for 18- and 11β-hydroxylation between the two strains is that, when a given form of P-450 (S or R) binds a DOC molecule, the molecule is hydroxylated at either the 18- or the 11β-position. If a molecule of DOC is 18-hydroxylated, it detaches from the enzyme and is not 11β-hydroxylated or vice versa. Therefore, a genetically mutated P-450 with increased 18β-hydroxylase activity (S rats) necessarily has a complementary reduction in 11β-hydroxylase activity.

Alleles at the Hyp-1 locus were shown to segregate with an increment in blood pressure in salt-fed F1 rats derived from an S × R cross. This is powerful genetic evidence that the Hyp-1 locus causes differences in blood pressure. It was concluded from the genetic experiments that the Hyp-1 locus accounted for a blood pressure difference of about 16 mm Hg between S and R rats in the environment of a high salt diet. Since blood pressure in the S and R model is known to be under polygenic control, the remaining difference in blood pressure between the strains is obviously due to the other (unidentified) genetic loci.

Because of the effects of the Hyp-1 locus, S rats have 2 to 3 times higher peripheral plasma levels of 18OHD-DOC than R rats, but the plasma concentrations of corticosterone and DOC are not different between the strains. Adrenals of S rats are about 15% to 20% heavier in S than R. This situation probably arises as a consequence of corticosterone levels being regulated by the pituitary. ACTH-induced compensatory hypertrophy of the S adrenals presumably occurs to make up for their less efficient production of corticosterone per unit weight of adrenal. This, of course, can only exacerbate the total overproduction of 18OHD-DOC which occurs at a higher rate per unit weight of adrenal in the S rat. Corticosterone, but not 18OHD-DOC, causes feedback regulation of ACTH. Since there is no underutilization of DOC precursor, excess DOC secretion does not occur.

Plasma aldosterone is significantly lower in S than R, possibly as the consequence of the mineralocorticoid activity of 18OHD-DOC causing suppression of the renin-angiotensin system. Aldosterone in S and R rats responds normally to a sodium-deficient diet and, more important, aldosterone secretion is suppressed by excess salt intake in S as well as in R rats. It has been argued that on low salt intakes the net mineralocorticoid status of the rat is dominated by aldosterone. As aldosterone is suppressed by salt, however, the net mineralocorticoid activity is more and more dominated by steroids from the inner adrenocortical zones, which are secreted independently of salt intake. Since these include 18OHD-DOC, which is higher in S than R, the net mineralocorticoid activity calculated for S on high salt approaches 1.5 times that calculated for R on a high salt diet. Thus, there is some rationale for an interaction between the Hyp-1 locus and salt on blood pressure. Injections of 18OHD-DOC into unilaterally nephrectomized rats drinking 1% saline caused a modest (15–20 mm Hg) increase in blood pressure after 3 weeks of administration.

Mineralocorticoid receptors in the kidneys of S and R rats have been studied. The concentration of receptors and their affinities for aldosterone or 18OHD-DOC were the same for the two strains. Although blood pressure responses to exogenous mineralocorticoid are greater in S than R, this is probably not due to an increased effect of the mineralocorticoid on S rats at the level of the kidney because distal tubular hypertrophy and skeletal muscle potassium depletion were equivalent in S and R rats.

There is no evidence for sex linkage of the genetic effects on blood pressure, meaning that none of the genetic loci controlling blood pressure is located on the X chromosome. Sex steroids do, however, exert effects. Intact S females respond to 8% NaCl diet with a slower increase in blood pressure than S males, although both sexes eventually reach the same high level. Castration of S males has no effect on blood pressure response to salt, but castration of S females altered their blood pressure response so that it was like that of S males. Contraceptive steroids given to female S rats had complex interactive effects with salt. On 0.38% NaCl diet, contraceptive steroids significantly lowered blood pressure, but on 4% NaCl diet contraceptive steroids significantly increased blood pressure.

About 85% of the R rats from Dahl’s original stock (Brookhaven colony) had a curious anatomical change in their pituitary glands. This consisted of marked accumulation of a proteinaceous fluid (histologically referred to as colloid) in the pituitary cleft (Rathke’s cleft). This characteristic was rarely seen in S-rat pituitaries. Gel electrophoresis of the proteins in the pituitary cleft showed a pattern similar to serum proteins but with the addition of four proteins that were unique to the colloid. Two of these proteins (MW 52,000 and 63,000) were isolated and shown to cross-react immunologically with rat albumin. Peptide mapping of one of these showed strong homology with rat albumin, suggesting that it was a fragment of albumin. Pituitaries of R rats showed much greater protease (esteropeptidase) activity than pituitaries of S rats. This proteolytic activity may account for the unique colloid proteins that are probably proteolytic fragments of plasma proteins.

The accumulation of pituitary colloid was shown to be an inherited trait, but the genes involved had not been fixed by selection for blood pressure response to salt in the Brookhaven colony. Following inbreeding of R rats, two sublines were obtained, one with and one without pituitary colloid accumulation. Genetic studies showed that accumulation of one of the unique
Pituitary colloid proteins was largely controlled by a single genetic locus (Pc for pituitary colloid). Although inverse correlations between blood pressure and colloid accumulation were seen in segregating F2 populations derived from crosses of S and R rats in two separate experiments, definitive associations of blood pressure and the Pc locus were not obtained. Lacking in these experiments is any knowledge of a molecule with an effect on blood pressure. In retrospect, it seems possible that the data obtained on pituitary colloid accumulation may have arisen as a consequence of loose linkage of the Pc locus to another locus actually involved in blood pressure regulation.

The secretion and pressor effects of antidiuretic hormone (ADH) have been studied in S and R rats. On low salt intake, urinary excretion of ADH and plasma ADH concentrations are similar for S and R. On high salt intakes, urinary ADH excretion and plasma ADH increase significantly more in S than R. Matsuguchi et al. concluded that this increased plasma ADH did not contribute to hypertension in salt-fed S rats because treatment with a compound that selectively blocks the pressor effect of ADH had no effect on blood pressure. If the renin-angiotensin system is blocked with captopril, than a specific inhibitor of the pressor effect of ADH does lower blood pressure significantly more in S than R rats. Whether this should be interpreted to mean that ADH participates in elevating blood pressure in the S rat is a moot point.

Serum thyroxine and triiodothyronine are the same in S and R rats. Both hormones are suppressed by feeding 8% NaCl diet and both are suppressed equally in S and R. Therefore, no role for the thyroid in the hypertension of the S rat is evident.

**Nervous System**

If S rats are treated with either guanethidine or 6-hydroxydopamine to destroy the sympathetic nervous system, then salt-induced hypertension is reduced or fails to occur. Ganglionic blockade abolished the blood pressure difference between S and R rats fed high salt diet for 4 weeks. Lesions of the paraventricular nuclei, paraventricular nuclei: plus suprachiasmatic nuclei, or the anteroverentral third ventricle (AV3V) region reduced or prevented the rise in blood pressure of S rats fed a high salt diet. Lesions of the suprachiasmatic nuclei enhanced the blood pressure response of S rats to salt.

Results of ablation or blocking experiments that reduce blood pressure do not necessarily mean that overactivity of the nervous components that are blocked are causally involved in salt-induced hypertension in the S rat. Such experiments may mean only that normal activity of the nervous components involved are required for blood pressure responses to develop, that is, the particular nervous component may be permissive. Other work, however, suggests more than a permissive role for the nervous system. Takeshita and Mark studied a perfused hindlimb preparation in which they were able to demonstrate an increased neurogenic component to vascular resistance in S compared to R rats. Sympathetic denervation caused a significant decrease in vascular perfusion pressure in S rats on high salt (8% NaCl), but not in S rats on low salt (0.4% NaCl), or R rats on either salt intake. Sympathetic nerve stimulation increased perfusion pressure more in S rats on a high salt diet than in S rats on low salt or in R rats on either salt intake. These results were probably not due to structural changes in blood vessels since perfusion pressures of hindlimbs during maximal vasodilation with papaverine were similar for S and R rats on both high and low salt diets.

It has been reported that the pressor responses of S rats were slightly greater than R in response to intracerebroventricular administration of angiotensin II or hypertonic saline. It was suggested that this difference was not due to structural changes in blood vessels because the rats were fed low salt (0.3% NaCl), although the S rats had significantly higher pressures than R (approximately 130 vs 115 mm Hg). This suggestion appears justified, at least for the hindlimb blood vessels, where a similar difference in pressure apparently generated no structural changes. Increasing the potassium content of the diet decreased the pressor responses to intracerebroventricularly administered angiotensin II or hypertonic saline by about 5 mm Hg without altering the basal blood pressure levels on the low salt (0.3% NaCl) diet. Thus, the claim was made that the beneficial effect of high potassium diet in the presence of high sodium may have a central nervous system component, although no tests were made on high NaCl diets.

There is an abnormality of baroreflex control of the heart rate in S compared to R rats. Gordon et al. gave bolus injections of phenylephrine and determined the slope of the lines relating blood pressure and pulse interval (heart rate). The slope of these plots (baroreflex slope) was greater for R than S, that is, for any change in blood pressure the heart rate changed more in R than S. This difference was present with rats on a low salt diet where basal blood pressure differences were minimal, suggesting that the difference in baroreflex slopes was not a response to hypertension. Feeding high salt had no apparent effect on the difference in baroreflex slopes between strains, but it did "reset" the reflex in S rats by shifting the line for S rats to the right, that is, a higher pressure was now required in S rats to cause a given pulse interval (heart rate). Gordon et al. favored an interpretation of their results relating the "defect" in baroreflex sensitivity of S rats to a neural component rather than, for example, to a difference in the arterial distensibility.

Pettinger et al. have studied the properties of α-receptors in S and R rats. Renal α1- and α2-receptor densities were higher in S than R. High salt diet caused an increase in renal α1-receptors in S but not in R rats. Renal α1-receptor density was unchanged by salt feeding. The higher renal α1-receptor densities were not a result of hypertension per se because renal α1-receptor density was not increased by DOCA-salt or renal hypertension in normal rats. Whether increased α-recep-
tor density is a genetically mediated cause of salt sensitivity in the S rats remains to be determined by genetic analysis.

R rats show more exploratory behavior and greater aggressive behavior than S rats. The relationship of this behavior to blood pressure is obscure, and the difference could have arisen from genetic drift (i.e., chance selection of behavior patterns).

Cardiovascular System

Ganguli et al. have described the early changes in some hemodynamic parameters when rats were placed on a high salt diet. After 3 days on high salt, R rats showed an 18% increase in cardiac output, a 14% decrease in peripheral resistance, and no change in blood pressure. At 7 days of salt feeding, the cardiac output and peripheral resistance in R rats were back to the levels seen in control rats on a 0.3% NaCl diet, and blood pressure remained unchanged. S rats responded very differently, with a 10% increase in cardiac output, a 10% increase in peripheral resistance, and a 20% increase in blood pressure after 3 days on a high salt diet. At 7 days on high salt, cardiac output had returned to the control value but blood pressure and peripheral resistance remained elevated.

When pressor agonists are given intravenously, S rats respond with a greater increment in blood pressure than R. This is true with angiotensin, norepinephrine, phenylephrine, and vasopressin. In these experiments, this difference in pressor response was seen with rats on low salt (0.4% NaCl) diets, where differences in blood pressure between strains were minimal and thus structural adaptations of the vasculature (smaller arteriolar lumens) and subsequent hyperresponsiveness on this basis would be minimal. Whether there was always complete absence of structural adaptation is a moot point. In the case of Gordon et al., the strain difference in response to norepinephrine or serotonin. Membrane potentials of tail arteries and aorta were increased by salt feeding in S but not R rats. This was interpreted to be a secondary response to hypertension.

Exercise

Forced treadmill running has a pronounced effect on the blood pressure of salt-fed S rats. If running is started soon after weaning, concomitant with salt feeding, the onset of hypertension was delayed 8 weeks and the mortality rate was reduced. This beneficial effect of exercise was less effective when exercise was started at a later age.

Drug Treatment

A thiazide diuretic was not at all effective in preventing an initial marked rise of blood pressure in 6-week-old S rats where treatment was started concomitant with feeding 8% NaCl diet. Continued thiazide treatment of the salt-fed rats did, however, eventually normalize the blood pressure. In another experiment, thiazide diuretic was started at weaning and continued for 14 weeks on 0.3% NaCl diet. When the rats were then switched to a 8% NaCl diet with continued thiazide treatment, the marked rise in blood pressure occurring in the nonthiazide-treated S rats was prevented in the thiazide-treated group. Thus, there appears to be a complex interaction between the age at which thiazide and salt are started and blood pressure response.
The calcium antagonist nifedipine, when administered to hypertensive S rats on high salt, lowered blood pressure into the normal range and maintained it there for 12 weeks, in spite of continued high salt intake. If nifedipine treatment was started with the high salt diet, the development of hypertension was prevented. In contrast, the converting enzyme antagonist captopril had no effect on salt-induced hypertension in S rats.

Conclusions

The blood pressure response to salt (NaCl) in Dahl salt-susceptible (S) and salt-resistant (R) rats is inherited as a polygenic trait. The genetic loci involved not only alter the blood pressure response to salt but also alter blood pressure responses to other experimentally induced forms of hypertension. Experimental evidence indicates important roles for the kidney, adrenal cortex, nervous system, and unidentified humoral factors in regulating blood pressure in S and R rats. Only in the adrenal cortex has a genetic locus, which is involved in regulating blood pressure, been identified.

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