The recommendation to avoid high dietary “salt” intake for the prevention and treatment of hypertension is often expressed in terms of dietary sodium. However, a consistent body of evidence suggests that the chloride component of salt is an important contributor to NaCl-induced elevations of blood pressure.1 In several rat models of salt-sensitive hypertension (Dahl salt-sensitive [S] rat, DOCA-salt hypertension, stroke-prone SHR [SHRSP], angiotensin II-induced salt-sensitive hypertension), selective dietary sodium loading, in the absence of chloride, fails to produce hypertension. In various feeding protocols, anions provided with sodium included various combinations of bicarbonate, phosphate, aspartate, glutamate, and glycinate. Overall, the failure of selective dietary sodium loading to produce hypertension in these studies was not related to group differences of body weight, net sodium balance, blood pH, or serum concentrations of sodium, potassium, or chloride.

Similarly, a limited number of clinical observations also indicate that blood pressure is not increased in humans by high dietary sodium intakes in the absence of chloride. In 1929, Berghoff et al reported that blood pressure increased in 7 hypertensive individuals on a high NaCl intake, but not on a high sodium bicarbonate intake.2 This observation was subsequently confirmed.3 Similarly, other investigators have also observed that in contrast to the increase of blood pressure induced by a high NaCl intake in hypertensive patients, blood pressure is not increased by a high sodium intake provided as sodium phosphate or sodium citrate.4 Further suggesting a modulating effect of dietary chloride on blood pressure, in hypertensive and normotensive subjects, substitution of dietary NaCl with equimolar sodium bicarbonate leads to a reduction of blood pressure.4,5 Additionally, in hypertensive humans, the reduction of blood pressure by dietary potassium is attenuated by potassium chloride compared with that of potassium citrate.6

Because the blood pressure increment in response to dietary sodium is dependent on the provision of sodium as its chloride salt, several studies have evaluated the hypothesis that blood pressure is increased by a high dietary intake of chloride, provided without sodium. Tanaka et al have previously reported that in the SHRSP, arterial pressure and incidence of stroke are increased by supplementing a normal NaCl diet with KCl but not with KHC03.7 Blood pressure was measured in chronically instrumented animals with an intra-peritoneal radiotelemetric device. Group differences of blood pressure were first discerned after 4 weeks on the diets. There were no group differences in urine protein excretion, and plasma renin activity (PRA) was higher in KCl-fed than in KHC03-fed rats. In this issue of Hypertension, this same group of investigators confirm their earlier observation that in the SHRSP, the rate of increase of blood pressure over time is specifically related to the chloride content of the diet, provided as various combinations of NaCl, KCl, and KHC03.8 An augmented rate of increase of blood pressure in rats fed NaCl plus KCl was observed within the first 12-hour dark cycle after initiating the diet. High dietary chloride intakes were associated with a reduction of urinary creatinine excretion, an increase of protein excretion, and histological evidence of renal microangiopathy. PRA did not differ among the various dietary groups.

The strength of these 2 studies is related to the repeated blood pressure measurements by telemetry in chronically instrumented animals. The results convincingly demonstrate an association between dietary chloride intake with the rate of increase of blood pressure and stroke incidence in the SHRSP. However, these observations also raise a number of questions. It is unclear if the chloride-related blood pressure increase occurs within 1 day or only after several weeks on the various diets. In addition, these results are at variance with several earlier observations that selective dietary chloride loading fails to produce hypertension. In the Dahl-S rat and the DOCA-salt hypertensive rat, selective dietary chloride loading, in the absence of sodium loading, fails to produce hypertension.1 In the SHRSP, Wyss et al reported that compared with NaCl-fed rats, the increase of blood pressure over a several-week period was delayed by selective chloride loading provided in the diet as glycine chloride and choline chloride in place of NaCl.9 In SHRSP and Dahl-S, Tobian et al reported that addition of potassium (1.36% potassium) in the form of either KCl or potassium citrate to the diet reduced blood pressure and stroke rate.10 The apparent discrepancy of the observations of Schmidlin et al with these earlier reports may be related to different experimental protocols, different rat models, and, as the authors suggest, to “genetic drift” of the SHRSP.

Several potential mechanisms may account for the contribution of chloride to salt sensitivity of blood pressure.1 In Dahl-S rats, DOCA-salt rats, and in humans, plasma volume is higher on a high NaCl intake than when sodium is provided with anions other than chloride, although net sodium balances do not differ. This suggests that the anion ingested with sodium affects the distribution of sodium between the intracellular and extracellular...
Compartments. Additionally, in experimental models, sympathetic nervous system activity is greater in rats fed NaCl than in rats receiving sodium without chloride.

Chloride reabsorption in the cortical segment of the loop of Henle is greater in Dahl-S than in Dahl-salt-resistant (R) rats when both are examined at equivalent renal perfusion pressures. This finding is present before exposure to a high NaCl diet and before the onset of hypertension. Enhanced reabsorption of water and chloride in the loop of Henle may contribute to the blunted natriuretic capacity and hence to hypertension in Dahl-S rats. Perhaps relevant to this observation, hypertension also occurs in an inherited clinical syndrome, pseudohypoaldosteronism type II, (Gordon syndrome), possibly as a consequence of increased chloride reabsorption in the thiazide-sensitive segment of the distal renal tubule. In the Dahl-S rat, if chloride delivery to the loop is related to dietary chloride intake, decreased renal tubular reabsorption of chloride may account for the failure of nonchloride salts of sodium to increase blood pressure.

Schmidlin et al suggest that a renal hemodynamic effect of chloride accounts for the blood pressure elevation in SHRSP on high chloride intakes. This would be consistent with the relatively rapid increase of blood pressure (first 12-hour dark cycle) in these animals. In vivo, in isolated perfused kidneys, and in kidneys perfused in situ, hyperchloremia results in renal vasoconstriction and a decline in glomerular filtration rate as a consequence of tubuloglomerular feedback. Schmidlin et al suggest that tubuloglomerular feedback is activated by increased chloride delivery to the macula densa in chloride-fed animals, resulting in increased renal afferent arteriolar resistance, reduced renal blood flow and glomerular filtration rate, and increased systemic arterial pressure.

Although considerable evidence indicates that renin release is inhibited by increased chloride delivery to the macula densa or increased chloride transport across the thick ascending limb of the loop of Henle, in the studies of Schmidlin et al, PRA either did not differ or was actually higher in SHRSP on the higher chloride intakes. The authors suggest that the elevation of PRA in KCl-fed rats is a consequence of enhanced vasoconstriction of the renal afferent arteriole in response to chloride.

If chloride in some way increases blood pressure, it might be reasonable to hypothesize that blood pressure is decreased by chloride deprivation. However, both clinically and experimentally, it is difficult to identify instances of selective chloride deficiency in the absence of sodium deficiency. Generally, these are combined deficiencies associated with volume contraction and either normal or low blood pressure. One example of selective chloride deprivation has occurred in infants fed chloride-deficient, but not sodium-deficient, formulas. The consequences are metabolic alkalosis, increased urinary potassium excretion, and hypokalemia. Other examples include Bartter syndrome and several variants of classic Bartter syndrome. These are inherited kidney disorders associated with salt wasting, hypokalemia, metabolic alkalosis, and increased renin secretion. Inactivating mutations in genes encoding ion channels and transporters that mediate salt transport in the thick ascending limb of the loop of Henle have been identified in these syndromes. Among the different variants of Bartter syndrome, these include: the sodium-potassium-chloride cotransporter (NKCC2), the potassium channel (ROMK), one of the chloride channels (CIC-Ka), brattin (an essential subunit for the chloride channels CIC-Ka and CIC-Kb), and a digenic disorder attributable to mutations in the genes that encode the chloride channels CIC-Ka and CIC-Kh. This latter disorder is also associated with deafness caused by loss of function of these chloride channels, which are also expressed in the inner ear.

In summary, the chloride ion is necessary for the expression of elevated blood pressure by dietary NaCl. In contrast to previous observations of others, the recent report of Schmidlin et al suggests that dietary chloride, independent of dietary sodium, increases arterial pressure and PRA in SHRSP. These observations will require confirmation, and understanding the apparent discrepancy with earlier reports will require additional study. Further studies will also be required to determine if dietary chloride increases blood pressure by some mechanism other than by increasing renal tubular reabsorption of sodium and chloride. From a practical perspective, the experimental manipulations of selectively increasing either sodium or chloride dietary intakes do not reflect usual dietary patterns, because most sodium and chloride are consumed as NaCl.

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Contributions of Sodium and Chloride to NaCl-Induced Hypertension
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