Salt sensitivity as a phenotype for genetic studies of human hypertension

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Introduction

Genetic studies of hypertension are confounded by the fact that so-called essential hypertension is not a discrete entity, but rather a collection of ill-defined syndromes in which high arterial pressure is the smallest common denominator. The present review briefly discusses the potential for using salt sensitivity as a trait for defining informative sub-groups for genetic studies of hypertension.

Relationship between hypertension and salt sensitivity

There is now abundant evidence that the blood pressure response to salt intake is quite variable both in hypertensive and in normotensive individuals [1]. Thus, around 50% of hypertensives have been found to be salt sensitive, and the prevalence of this trait tends to be higher in the elderly and in blacks. Whether salt-sensitive hypertensives represent a distinct clinical subgroup more prone to cardiovascular complications, or derive greater benefits from certain therapeutic approaches, is currently unresolved [1].

Strong support for the assumption that salt sensitive individuals may be genetically prone to the development of hypertension comes from the observation that in normotensives salt sensitivity is commonly associated with a positive familial history of hypertension [2–4]. Thus, in a series of 100 consecutive young normotensive men who were investigated for salt sensitivity by an identical dietary protocol [4], we found a significant effect of salt intake on blood pressure in 25 of the 44 (57%) subjects with a positive familial history of hypertension but only in 16 of the 56 (27%) subjects with negative familial history ($\chi^2 = 8.12$, $P < 0.01$, Figure 1).

Primary and secondary forms of salt sensitivity

Although evidence from rigorous intervention studies is scarce, there can be little doubt, that a variety of secondary forms of hypertension associated with sodium retention and volume expansion will respond favourably to reduced salt intake. These include hypertension resulting from hyperaldosteronism, renal parenchymal disease, Cushing’s syndrome, use of oral contraceptives, acromegaly, and the exceptional renin or renin-substrate-producing tumour (Table 1). Salt sensitivity may also be encountered in rare mendelian syndromes of hypertension including familial glucocorticoid-remedial aldosteronism, Liddle’s syndrome, and other monogenetic forms of hypertension such as those resulting from defects in the genes encoding for 11β-hydroxylase or 11-β-hydroxysteroid dehydrogenase.

Recent demonstration that insulin resistance is associated with salt sensitivity both in lean [5] and obese normotensives [6] as well as in hypertensives [7] suggest that insulin resistance may contribute to the pathogenesis of salt sensitivity. If this is true, insulin resistance, may indeed turn out to be the most common cause of salt sensitivity.

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pressor substances [3,8], increased forearm vascular characteristics found in patients with established hypertension [10], and insulin resistance [5]. Substantial decreases in α2/β2 adrenoreceptor ratio [2], lower renin activity [10], and insulin resistance [5]. Substantial evidence from both family and twin studies show that young salt-sensitive normotensive individuals are genetically predisposed to developing high blood pressure and could therefore provide a unique opportunity for studying related physiological, biochemical, and genetic factors without the confounding presence of overt hypertension or its sequelae.

Assessment of salt sensitivity

As recently pointed out in a review of 32 clinical studies on salt sensitivity published between 1978 and 1992, a variety of protocols and definitions have been used for the assessment of salt sensitivity [12]. Nevertheless, other reviewers have found a remarkable consistency both with regard to the prevalence of salt sensitivity and the incidence of various other findings reported by different investigators using these different protocols [1].

Much concern has also been voiced regarding the reproducibility of salt-sensitivity testing. This has now been addressed in several studies that have examined the blood-pressure response to variations in salt intake in the same individual, using both dietary [4] or intravenous protocols [13,14]. Together these findings support the assumption that within the expected limitations resulting from the biological variation of the blood pressure response to any stimulus, salt sensitivity can be determined with a reasonable degree of reliability both in normotensive and hypertensive individuals.

Salt sensitivity vs familial history of hypertension

Given the relationship between salt sensitivity and familial history of hypertension, any classification based only on the response to salt intake will result in more individuals with a positive familial history of hypertension in the salt-sensitive than in the salt-resistant group. This readily explains why several findings in salt-sensitive normotensives such as increased vascular responsiveness [3,8] or insulin resistance [5] can also be demonstrated in subjects merely classified based only on the response to salt intake will result in more individuals with a positive familial history of hypertension in the salt-sensitive than in the salt-resistant group. This readily explains why several findings in salt-sensitive normotensives such as increased vascular responsiveness [3,8] or insulin resistance [5] can also be demonstrated in subjects merely classified based on the basis of a positive familial history [1]. Because of this confounding effect, it is not possible to attribute difference between such groups to either salt sensitivity or familial history per se.

The assessment of salt sensitivity, preferably by a dietary protocol, is undoubtedly more demanding than the measurement of blood pressure alone. Nevertheless, in our experience the characterization of young healthy volunteers, primarily university students, for a moderate fee has proved to be a highly practicable and efficient approach. Likewise, as evidenced by countless studies it is often easier to study the young healthy individuals. As recently pointed out in a review of 32 clinical studies on salt sensitivity published between 1978 and 1992, a variety of protocols and definitions have been used for the assessment of salt sensitivity [12]. Nevertheless, other reviewers have found a remarkable consistency both with regard to the prevalence of salt sensitivity and the incidence of various other findings reported by different investigators using these different protocols [1].

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offspring of a patient with hypertension rather than the patient itself. There is no doubt that these subjects represent a far more homogeneous group than patients with established hypertension, and the blood pressure response to salt intake in these individuals is confounded neither by antihypertensive medication nor by the presence of overt hypertension or its sequela.

How should salt sensitivity be defined for genetic studies of hypertension?

Although there is currently no universally accepted definition of salt sensitivity, it seems reasonable that any definition should be based on objective criteria such as a statistically significant change in blood pressure based on repeated blood pressure measurements rather than on an arbitrary cut-off point. Ideally, investigators should provide evidence for the reproducibility of whatever classification protocol they choose to apply.

Because virtually all forms of secondary hypertension can be considered salt sensitive, it is essential to rule out secondary causes of hypertension in each subject. It also appears advisable to limit studies to younger patients, perhaps below the age of 30. Special care must be taken to ensure that salt-sensitive cases and salt-resistant controls are of similar ages and ethnic background.

Due to the possible confounding effect of obesity, insulin resistance, and hyperinsulinaemia on the blood pressure response to salt intake, these factors should be assessed in studies of salt sensitivity. Also, given the higher prevalence of salt sensitivity among individuals with positive familial histories of hypertension, familial history of hypertension should also be taken into account.

In conclusion, as secondary causes of salt sensitivity may significantly limit the usefulness of this trait as an intermediate phenotype in patients with established hypertension, young normotensive individuals appear more suitable for studying the genetic determinants of salt sensitivity. The advantages inherent to the study of young normotensive subjects in contrast to older patients are easily stated:

1. Young normotensive individuals provide a more homogenous group than patients with essential hypertension.
2. Phenotypic characterization is confounded neither by medication nor by complications of established hypertension.
3. Follow-up studies can monitor the development of hypertension in these individuals, thereby allowing direct verification of the prospective value of genetic markers.

Undoubtedly, understanding the genetic determinants of salt sensitivity will be a major step forward in our understanding of the pathogenesis of human hypertension.

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References