

# Dissecting the genetic architecture of the cardiovascular and renal stress response

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## Abstract

We review the evidence for a genetic basis of the cardiovascular and renal stress response. A bio-behavioral model of stress-induced hypertension is presented that explains how repeated exposure to stress in combination with genetic susceptibility might lead to the development of hypertension. In this model, we focus on three underlying physiological systems that mediate the stress response of the heart, vasculature and kidney: the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS) and the endothelial system (ES). We then review the evidence for a genetic influence on cardiovascular reactivity to psychological stress and stress-induced sodium retention using data from twin and family studies and a limited number of candidate gene studies. Finally, by describing the underlying physiological systems of our model and their genetic underpinning we emphasize the importance of inclusion of genetic measurements in any future studies testing the reactivity hypothesis. © 2002 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

The concept of stress reactivity has a long history in cardiovascular psychophysiology (Obrist et al., 1974). The 'reactivity hypothesis' posits that cardiovascular

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reactivity, defined as an exaggerated cardiovascular response to a behavioral or psychological challenge, may play a role as a marker or mechanism in the pathogenesis of essential hypertension (EH) and coronary heart disease (CHD) (Manuck, 1994).

A number of recent studies that focused on its measurement characteristics have strengthened the acceptance of the cardiovascular reactivity concept. They have indicated that behaviorally evoked cardiovascular reactivity is a relatively stable individual difference characteristic, relatively consistent across time and moderately stable across stressors varying in the type of underlying response system elicited (e.g. cardiac vs. vascular; active vs. passive) (Sherwood and Turner, 1995).

How convincing the evidence is for the reactivity hypothesis remains an important question. We recently reviewed prospective studies that investigated the evidence for the role of cardiovascular reactivity to behavioral/psychological stressors in the prediction of: (a) sustained increases in blood pressure (BP) and/or development of EH; (b) development of preclinical disease states, including ventricular remodeling and carotid atherosclerosis; and (c) clinical cardiovascular disease (CVD) or its progression (Treiber et al., 2002b). The emphasis on prospective, rather than cross-sectional correlational studies in this review reflected the recognition that the association between cardiovascular reactivity and CVD is potentially bi-directional (e.g. does increased cardiovascular reactivity cause EH or vice versa?). An overview of the available studies suggested that there is reasonable evidence that cardiovascular reactivity can predict the development of some preclinical states (e.g. increased left ventricular mass and BP) and perhaps even new clinical events in some EH or CHD patients.

Light (2001) recently stated, however, that the original reactivity hypothesis was youthfully naïve and needs to make way for a next generation of more complex corollaries of this hypothesis. According to Light (2001), many prospective investigations of the reactivity hypothesis have shown disappointing results, because they ignored moderating effects of genetic susceptibility and chronic stress. One example is the prospective Whitehall II study in which BP reactivity explained less than 1% additional variance in BP level 5 and 10 years later (Carroll and Smith, 2001; Carroll et al., 1995). Light et al. (1999, 2001), therefore, propose what they term the ‘Gene and Environmental Modulated Reactivity Hypothesis’. That is, individuals who exhibit high cardiovascular reactivity will be more likely to develop EH and/or CHD if they also display a high genetic susceptibility (e.g. a positive family history of EH) and/or are exposed to chronic stress (e.g. high job demand, low socioeconomic status, lack of social support).

Light’s (2001) proposal is supported by animal models of stress-induced EH and highlights the crucial role of genetic susceptibility in the reactivity hypothesis. Not only is the susceptibility to the development of EH and CHD influenced by genetic factors, as indicated by reviews of twin studies, but individual differences in cardiovascular reactivity itself appear to have a genetic basis as well (Snieder et al., 1995; Turner and Hewitt, 1992). Indeed the same genes that underlie cardiovascular reactivity may also confer susceptibility to EH and/or CHD. These reviews of the genetics of cardiovascular reactivity necessarily show their age and were somewhat

limited in scope (Snieder et al., 1995; Turner and Hewitt, 1992). For example, although largely ignored in the psychophysiological stress reactivity literature, the kidney plays an essential role in mediating the effect of stress on BP. Impaired stress-induced sodium excretion and volume regulation may lead to delayed BP recovery after stress and stimulate target organ damage development (Harshfield et al., 2002).

The main aim of this paper, therefore, is to review the current evidence for a genetic basis of the cardiovascular and renal stress response. First, we will present a theoretical model explaining how repeated exposure to stress in combination with genetic susceptibility might lead to the development of EH. In this model of stress-induced hypertension, we focus on three underlying physiological systems that mediate the stress response of the heart, vasculature and kidney: the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS) and the endothelial system (ES). Using data from twin and family studies and a limited number of candidate gene association studies, we then review the evidence for a genetic influence on the two major intermediate phenotypes of our model. These are cardiovascular reactivity to psychological stress and stress-induced sodium ( $\text{Na}^+$ ) retention, representing the cardiovascular and renal stress response, respectively. Finally, by describing the underlying physiological systems of our model and reviewing the evidence for their genetic underpinning we emphasize the importance of inclusion of genetic measurements in any future studies testing the reactivity hypothesis.

## 2. Stress-induced essential hypertension

### 2.1. *Animal models of stress-induced EH*

Studies in animal models have provided direct confirmation of the causal role of stress exposure in pathogenesis of EH. Examples are Henry's animal paradigm in mice of psychosocial EH achieved through designing social environments that enhance confrontations regarding dominance (Henry and Grim, 1990) and the borderline hypertensive rat (BHR) that develops sustained EH after weeks of daily exposure to shock avoidance tasks (Sanders and Lawler, 1992). Friedman and Iwai (1976) reported that chronic exposure to environmental stress (foot shock) resulted in persistent elevations in SBP in the hypertension-prone Dahl Salt Sensitive (DS) but not the Dahl Salt Resistant (DR) rats. These authors also demonstrated that the development of salt-induced hypertension is exacerbated by the additional repeated exposure to stress (Friedman and Iwai, 1977). These models establish that stress exposure inducing regular periods of high BP reactivity can be a critical causal factor in development of EH. However, several authors have pointed out (Light, 2001; Light et al., 1999; Harshfield and Grim, 1997) that stress exposure only leads to EH in genetically susceptible animals. For example, extensions of Henry's work from mice to rats have shown that EH in his model only develops in the most susceptible rat strains. Many strains do not develop EH, including strains that show large BP

reactivity to acute dominance confrontations (Ely et al., 1997; Harrap et al., 1984; Mormede, 1997).

## 2.2. *A biobehavioral model of stress-induced EH*

Guided by these animal models and our recent findings (Barbeau et al., 2002; Barnes et al., 2000; Jackson et al., 1999; Kapuku et al., 1999; Snieder et al., 2002; Treiber et al., 2000b) and those of others (Anderson et al., 1993; Light et al., 1999; Schneiderman and Skyler, 1996) in humans, we have revised our biobehavioral model of stress-induced EH (Treiber et al., 2002a). Our model outlines that genetic predisposition (e.g. genetic variation in SNS, RAAS and/or ES function) in concert with chronic stress exposure (e.g. low socioeconomic status [SES], high personal life stress) adversely affect BP reactivity to and BP recovery from exposure to repeated acute stress, both of which impact the progression of the development of preclinical measures of EH in youth and culminate in EH (Fig. 1). We propose that three pathways play a central role in stress-induced EH, namely the SNS, the RAAS and the ES.

Others (Light, 2001; Light et al., 1999) have defined genetic susceptibility in their model in terms of a positive family history of EH and CVD. However, an increasing number of candidate genes will become available with the recent completion of the first draft of the human genome (Peltonen and McKusick, 2001). We, therefore, argue that common variation in these genes (polymorphisms) can and should be directly measured to improve insight in regulation of physiological pathways leading to susceptibility for stress-induced EH.

Our model will be important in guiding hypothesis testing, but we acknowledge that it is by no means comprehensive. Other biological systems and risk factors might mediate the influence of stress on development of EH, such as the hypothalamic pituitary adrenal axis, parasympathetic autonomic reactivity and serotonin function in the central nervous system. Studies that have measured indices of these systems (corticosteroid levels, respiratory sinus arrhythmia and serotonin metabolites, respectively) indicate the importance of genetic variation in these systems as well (Bartels et al., 2002; Inglis et al., 1999; Snieder et al., 1997; Williams et al., 2001). Others emphasize the effect of the early environment in the vulnerability to stress (Francis et al., 1999).

## 2.3. *Role of the SNS, the RAAS and the ES*

As shown in Fig. 1, our model proposes that, when exposed to repeated acute social and environmental stress such as verbal/physical conflict with law/authority figures or family members, unfair treatment, neighborhood instability/crime, discrimination, residential overcrowding, etc. (Anderson and Armstead, 1995; Anderson et al., 1992; Clark et al., 1999; Farley and Allen, 1989), increased SNS activity occurs that, in turn, results in the release of catecholamines, norepinephrine and epinephrine. Both norepinephrine and epinephrine have positive inotropic and chronotropic influences on the heart. This results in increased heart rate and

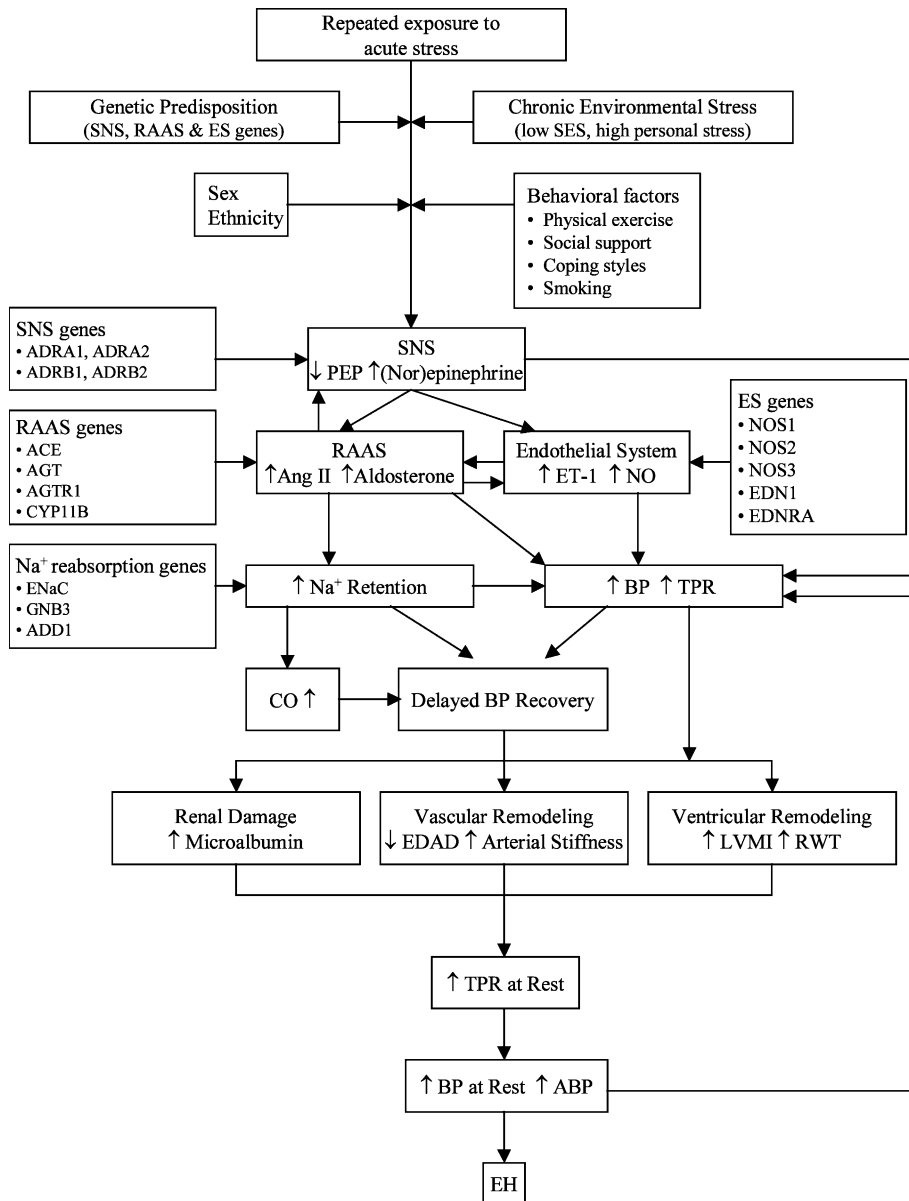


Fig. 1. Beobehavioral model of stress-induced hypertension. SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; ES, endothelial system; SES, socioeconomic status; PEP, pre-ejection period; Ang II, angiotensin II; ET-1, endothelin-1; NO, nitric oxide; Na<sup>+</sup>, sodium; BP, blood pressure; TPR, total peripheral resistance; EDAD, endothelial dependent arterial dilation; LVMI, left ventricular mass indexed by body size; RWT, relative wall thickness; ABP, ambulatory blood pressure; EH, essential hypertension; ADRA1, α1-adrenergic receptor gene; ADRA2, α2-adrenergic receptor gene; ADRB1, β1-adrenergic receptor gene; ADRB2, β2-adrenergic receptor gene; ACE, angiotensin converting enzyme gene; AGT, angiotensinogen gene; AGTR1, angiotensin II type-1 receptor gene; CYP11B2, aldosterone synthase gene; NOS1, nitric oxide synthase-1 NOS2, nitric oxide synthase-2; NOS3, nitric oxide synthase-3; EDN1, ET-1 gene; EDNRA, ET-1 receptor A gene; ENaC, Epithelial Na<sup>+</sup> Channel gene; GNB3, G-protein β3-subunit gene; ADD1, α-adducin gene.

decreased pre-ejection period (PEP), commonly measured indices of SNS arousal. Norepinephrine causes vasoconstriction throughout the vascular system via excitation of smooth muscle cells. Epinephrine causes vasoconstriction in some vessels, particularly those of the skin, and vasodilation in others, especially those of the skeletal musculature (Brück, 1983; Genest et al., 1977; Hypertension Primer (eds. Izzo and Black, 1999)). Ethnicity, gender, ineffective coping resources and deleterious lifestyle behaviors (e.g. sedentary behavior, smoking) may act as moderators of this response.

The ES is a dynamic interface that contributes to the control of vascular smooth muscle function via production of vasoactive substances such as nitric oxide (NO), a potent vasodilator, and endothelin-1 (ET-1), a potent vasoconstrictor. SNS arousal along with physiological stimuli such as transmural pressure, increased flow and shear stress potentiate the release of these vasoactive substances, as well as angiotensin II (Ang II) (Davies et al., 1995; Horkey et al., 1994; Lemne et al., 1994; Lerman et al., 1990; Luscher and Vanhoutte, 1990). Ang II directly induces release of ET-1 (Imai et al., 1992), which in turn potentiates the vasoconstrictor response to Ang II and potentially norepinephrine (Haynes et al., 1994; Yoshida et al., 1992). Our findings in youth (Treiber et al., 2000b, 2002c) and those of others in adults (Fyhrquist et al., 1990; Noll et al., 1996) indicate that acute behavioral challenges (e.g. video game, cold pressor, mental arithmetic) result in increased release of ET-1 which is associated with increases in BP and total peripheral resistance (TPR). Decreased effectiveness of NO due to decreased production, more rapid inactivation and/or decreased sensitivity of smooth muscle (Panza et al., 1993; Taddei et al., 1996) in combination with greater production of ET-1 compared with NO release (Jackson et al., 1998; Treiber et al., 2002c) may play an important role in the increased vasoconstrictive tone in response to acute behavioral challenges.

As depicted in Fig. 1, the RAAS is activated via SNS arousal, as well as ES activity (Hypertension Primer (eds. Izzo and Black, 1999)). Ang II is released which increases BP via direct vasoconstriction, and results in further activation of the SNS and potentiation of the effect of norepinephrine. Ang II induces increased aldosterone production and their combined effects influence volume homeostasis through stimulating thirst centers and proximal tubular reabsorption of  $\text{Na}^+$ . This increase in  $\text{Na}^+$  and water retention leads to a rise in cardiac output and delayed BP recovery. The augmented  $\text{Na}^+$  retention enhances vasoconstrictive effects of norepinephrine on peripheral vasculature, which further increases BP via increased TPR (Anderson et al., 1992; Mark et al., 1975; Nilsson et al., 1985).

Collectively, animal and human studies have demonstrated that this complex interactive involvement of the SNS, RAAS and ES all contribute to increased TPR mediated BP reactivity to stress (reviewed in Anderson et al., 1992; Folkow, 1990; Julius and Nesbitt, 1996; Sherwood and Turner, 1995; Weinberger et al., 1982). Importantly, when these vasoactive systems experience repeated exposure to behavioral challenges, dysregulation of their function can occur and problems are encountered in appropriately activating and/or turning off in efforts to return to previous levels of cardiovascular function (McEwen, 1998; McEwen and Seeman, 1999).

#### 2.4. Development of preclinical measures of essential hypertension

The recurrent exaggerated increases in BP and TPR responses to stress are associated with concomitant increases in cardiac and vascular wall tension and intravascular shear stress (Folkow, 1990; Julius and Nesbitt, 1996). It is hypothesized that over time this leads to secondary renal and cardiovascular structural adaptation, that is, renal damage and vascular and ventricular remodeling, to help normalize wall tension (Folkow et al., 1958; Julius and Nesbitt, 1996; Weber et al., 1994).

Increased urinary microalbumin is an index of renal damage (Bigazzi et al., 1994). Urinary microalbumin has been found to be increased in early stages of EH (Bianchi et al., 1999; Mogensen, 1999; Parving et al., 1974). Further, studies have found that renal damage, as indicated by increased urinary microalbumin, is relatively independent of other target organ damage and does not necessarily occur in parallel with BP related changes to the vasculature or the heart (Mogensen, 1999; Palatini et al., 1997). To our knowledge, the relationship between BP reactivity and change in urinary microalbumin over time has not been examined.

A functional measure of vascular remodeling is diminished endothelium-dependent arterial dilation to reactive hyperemia (EDAD) (Celermajer et al., 1992). Decreased EDAD is an index of endothelial dysfunction, a relatively early event in the pathogenesis of CVD (Luscher and Vanhoutte, 1990). In youth and adults, decreased EDAD of femoral or brachial arteries to reactive hyperemia has been associated with elevated resting BP, smoking, hypercholesterolemia and has differentiated individuals with and without CVD or EH (Anderson and Armstead, 1995; Anderson et al., 1995; Celermajer et al., 1994a,b, 1992; Luscher and Vanhoutte, 1990). In line with our model (Fig. 1), we (Kapuku et al., 2000; Treiber et al., 1997, 2001) and others (Sherwood et al., 1999) recently found an association between exaggerated BP and/or TPR reactivity to acute laboratory challenges and decreased EDAD in normotensive youth and adults.

Increased arterial stiffness is another functional manifestation of vascular remodeling related to vascular smooth muscle hypertrophy and increased collagen deposition (Folkow, 1990). Increased arterial stiffness has been associated with increased resting BP in youth (Riley et al., 1986). Consequences of increased arterial stiffness include LVH, stroke, renal failure and coronary artery disease (Cockcroft and Wilkinson, 2000; Cockcroft et al., 1997). To date, the relationship between BP reactivity and prospective changes in arterial stiffness has not been evaluated.

An early sign of ventricular remodeling is increased left ventricular mass indexed by body size (LVMI) and relative wall thickness (RWT) which over time may lead to left ventricular hypertrophy (LVH) (Devereux and Roman, 1992). This is of particular interest, since LVH is the strongest known predictor, other than advancing age, of cardiovascular morbidity and mortality (Casale et al., 1985; Koren et al., 1991; Levy et al., 1990). In agreement with our model (Fig. 1), BP and TPR reactivity to laboratory challenges have been associated with increased LVMI and/or LVH in youth and adult studies (Daniels et al., 1990; Gump et al., 1999; Hinderliter et al., 1996). Our findings in longitudinal studies of youth indicated that BP reactivity accounted for 7–15% of the variance in the prediction of LVMI 2–3

years later and differentiated those who developed LVH (Kapuku et al., 1999; Murdison et al., 1998; Papavassiliou et al., 1996).

In summary, as shown in Fig. 1, these morphological and functional alterations are hypothesized to lead to elevations in resting TPR and BP, as well as ambulatory BP (ABP), which further leads to increases in BP reactivity. A vicious cycle ensues which contributes to the pathogenesis of EH.

### 3. Heritability of the cardiovascular stress response

#### 3.1. Twin studies

A role for genetic factors in stress reactivity finds support in studies showing that a family history of hypertension in normotensive subjects is associated with higher BP reactivity to laboratory stressors (Fredrikson and Matthews, 1990). However, a weakness of these studies is that many failed to verify the family history of disease. An additional problem is that the relation between family history of EH and increased cardiovascular reactivity may be explained by shared environmental rather than genetic factors. Twin studies are able to efficiently discriminate between these alternative explanations (Spector et al., 2000).

Turner and Hewitt (1992) reviewed ten published studies that explored the genetic and environmental origins of individual differences in heart rate and BP reactivity to psychological challenge (not including the cold pressor task) by employing the classic twin study methodology. Their conclusions were that, (1) BP responses are moderately heritable (heritability [ $h^2$ ] range = 0.40–0.85; median  $h^2 = 0.63$ ), and (2) there is very little evidence of shared environmental influence.

A later review by Snieder et al. (1995) that specifically focussed on BP reactivity, but did not limit itself to psychological stressors (i.e. studies investigating the cold pressor test were included) expressed caution in interpreting available twin studies (see also the discussion in Hewitt and Turner, 1995). First, studies used different methods to estimate heritability. Second, there was wide variation in the age and sex composition of the twin samples in the studies. Third, interpretation was hampered by the use of different stress tasks across studies. Furthermore, some studies had very small sample sizes. Although Snieder et al. (1995) found that heritability estimates for BP reactivity are less consistent than for resting BP levels, they arrived at essentially the same conclusions. That is, BP reactivity is moderately heritable and the influence of shared environment appears negligible.

In general, recent findings from our Georgia Twin Study corroborated and extended these earlier studies by studying a multiethnic cohort. We observed similar heritability estimates (range: 0.43–0.75) for BP and heart rate response to acute psychological stress in both European American and African American youth (Treiber et al., 2000a).

Collectively, two overarching conclusions can be drawn. First, evidence of moderate heritability (0.40–0.60) typically means two things. Genetic influence is important, but so too is environment, which accounts for the remaining proportion

of the variance. The second conclusion is that since shared (or common) environmental influence ( $c^2$ ) is minimal, environmental influence occurs primarily via variation in nonshared environments ( $e^2$ ), i.e. environmental influences unique to the individual.

### 3.2. Family studies

The few family studies reported to date have generally found low, or unstable, familial correlations, and quantitative genetic model fitting has not been attempted. Ditto (1987) investigated similarities in 36 sibling pairs (aged 18–21) in cardiovascular reactivity to four different stress tasks: a conceptual task, a mental arithmetic task, an isometric handgrip task and a cold pressor task. Only one significant sibling correlation was found: this was for DBP reactivity to the cold pressor task (0.40). Matthews et al. (1988) conducted a study in which 145 families were measured using serial subtraction, mirror image tracing, and an isometric handgrip task. Only the correlation of SBP reactivity to the isometric handgrip was significant for parent-offspring as well as sibling pairs. Snieder et al. (1995) found small but significant parent-offspring correlations for SBP reactivity to a reaction time task ( $r = 0.11$ ) and a mental arithmetic task ( $r = 0.13$ ). No significant correlations were found for DBP reactivity.

Ditto and France (1990) compared correlations in a group of 30 young (mean age: 26) and 30 middle-aged (mean age: 52) spouse pairs. Spouse correlations in BP reactivity to a mental arithmetic and an isometric handgrip task were small and did not increase as a function of the number of years living together. This suggests that the influence of a common environmental factor is small or even non-existent, thereby offering support for the second conclusion of Turner and Hewitt (1992) that shared environment plays only a minor role in determining individual differences in BP reactivity.

To better understand the contribution of major gene influences to individual differences in cardiovascular reactivity, Cheng et al. (1997) performed a segregation analysis on BP responses to a mental arithmetic task. The study population consisted of 1451 adults who were members of 81 Utah pedigrees. They found that major gene effects controlled DBP, but not SBP reactivity to the mental arithmetic task. The best fitting model was a major codominant model with a gene frequency of 0.10 and significant age and sex effects.

### 3.3. Multivariate twin studies

Recent twin studies of cardiovascular reactivity have moved away from merely calculating heritabilities based on measurements of single traits or single time points. Many study protocols use multiple tasks and measure multiple response traits that show a certain degree of interrelatedness that may be due to the pleiotropic action of genes and/or common environmental influences. Extensions of the classical twin study to more complex multivariate designs involving multiple variables are needed to shed light on these questions.

Ditto (1993), for example, used bivariate model fitting in his twin data to investigate whether common genes could explain associations between resting and reactivity values of heart rate and BP and associations between cardiovascular reactivity to different stressors. Genetic effects on reactivity were relatively independent of those affecting resting heart rate and BP, but significant overlap of genetic influences was found on heart rate and BP responses to the two active coping tasks.

In another twin sample, Busjahn et al. (1996) conducted bivariate model fitting and found both common and specific genetic influences on BP levels at rest and during the cold pressor test. However, genetic influences on BP at rest and BP reactivity to the cold pressor were entirely independent, suggesting that different (sets of) genes contribute to BP reactivity to the cold pressor and BP level at rest. A similar result was reported by Maes et al. (2000) in a large sample of 317, 11-year old white twin pairs from the Medical College of Virginia Twin Study. They found that a separate set of genetic factors accounted for 20% of the variance in SBP during an isometric handgrip test only. These results were contradicted by yet another study of 160 adolescent twin pairs (Boomsma et al., 1998). Multivariate analysis of BP levels at rest and during a reaction time and mental arithmetic task indicated that the same genetic and environmental influences are expressed during rest and stress conditions. Increases in BP heritability estimates were seen during stress, however. This amplification of genetic influences under stress support the view that use of laboratory challenges (or dynamic measures of BP regulation in general, such as ambulatory BP) may improve the ability to identify genes involved in BP regulation.

As mentioned above, a review of twin studies (Snieder et al., 1995) indicated that BP reactivity might be moderately heritable, but inconsistent results were observed across studies and different tasks. The reason for the inconsistency in heritability estimates could lie in the less reliable determination of reactivity measures compared with the reliability of levels. Reactivity is calculated as the difference between two levels (task-rest), which increases the error term. This has been recognized in the stress reactivity literature where studies now often aggregate cardiovascular change scores across tasks (Kamarck et al., 1992) and measures (e.g. Light et al., 1999) to increase the reliability of the findings. Preliminary results of the Medical College of Virginia Twin Study show the utility of these principles. Multivariate analyses of multiple visits substantially reduced the effect of measurement error through the construction of a latent cardiovascular reactivity variable underlying these multiple visits. Heritability estimates as high as 85% were found for these latent cardiovascular reactivity constructs (Maes et al., 2001).

Kamarck et al. (1994) employed a multivariate statistical approach and developed a 2-factor model representing vascular and cardiac influences on reactivity to stress. They found this model to be consistent across samples, testing sessions and sets of tasks and concluded that individual differences in cardiovascular reactivity to mental stress may be characterized by a stable, 2-dimensional pattern of response. However, multivariate analyses of their twin data (82 MZ and 55 DZ pairs) indicate that this phenotypical 2-dimensional pattern is not found for the underlying genetic and environmental influences, because the genetic (but not the unique environmental)

effects could be simplified to a single common factor (Pogue-Geile et al., 1996). As this result might be due to sample size limitations, larger twin studies are needed to further test the genetic architecture of the cardiovascular stress response.

### 3.4. *Twin studies of ambulatory BP*

There has been a growing realization in the cardiovascular psychophysiological literature that cardiovascular reactivity to laboratory stress may be of limited predictive value for reactivity to stress in real life (see for a review, e.g. van Doornen and Turner, 1992). In a real life setting, higher ambulatory values are likely to be found in individuals with more frequent exposure to stressors. Thus, use of ambulatory monitoring of the cardiovascular system is important as a means to gain insight into adverse health effects of stress in people's everyday life. The value of ambulatory BP (ABP) measurements is further illustrated by studies showing that ABP is a better predictor of target organ damage (Pickering and Devereux, 1987) and cardiovascular morbidity and mortality (Ohkubo et al., 2000; Verdecchia, 2000; Verdecchia et al., 2001) than BP measured in the clinic. Therefore, application of ambulatory measurements is also strongly advocated for the quantitative genetic investigation of consequences of stress in real life. More specifically, as an extension to the laboratory-field generalization studies Hewitt and Turner (1995) propose a multivariate twin design to test for the presence of additional genetic and environmental influences on ABP over and above those influences on laboratory BP.

Although several studies have examined ABP in twins, the sample sizes of the initial studies have been small. Degaute et al. (1994) evaluated 24 h ABP in a hospital research setting with 28 MZ and 16 DZ pairs of young adult males. The small sample size and the presentation of 33 different measures makes interpretation of results difficult, but overall evidence suggested heritability on some characteristics of the 24-h profiles for DBP. Somes et al. (1995) examined the heritability of ABP in 38 pairs of MZ twins, 17 pairs of same-sex DZ twins and 11 pairs of opposite-sex DZ twins. Heritability estimates of 0.22 and 0.34 were observed for 24-h SBP and DBP, respectively. Fagard et al. (1995) measured 24-h ABP in 26 MZ and 27 DZ male twin pairs aged 18–38 years. Using model fitting techniques, heritability ranged from 0.51 to 0.73 for 24-h, daytime and nighttime SBP and DBP comparisons. The remaining variances were typically accounted for by unique environment (range = 0.27–0.40). In a recent study of a large sample of 150 MZ and 122 DZ twin pairs Vinck et al. (2001) measured conventional and ambulatory BP and compared heritability estimates in three age groups: 18–29, 30–39 and  $\geq 40$  years. Heritabilities were similar (around 50%) for laboratory and ambulatory (daytime and nighttime) SBP and DBP and no significant differences between age groups were found.

Thus, there is a relative paucity of adequately powered twin studies on ambulatory measures. Evaluations of genetic and environmental influences on ambulatory versus laboratory BP as suggested by Hewitt and Turner (1995) still await realization, although the data needed to conduct such a study is now becoming available (Vinck et al., 2001).

### 3.5. Candidate gene studies

Although more than 150 candidate genes for EH have been postulated with projections of exponential increases resulting from the recent completion of the human genome project, to date only a few studies have investigated the influence of specific candidate genes on cardiovascular levels during stress and cardiovascular responses to stress.

The  $\beta$ 2-adrenergic receptor contributes to BP regulation by mediating peripheral vasodilation and polymorphic variation in this gene may, therefore, influence the BP response to stress. Li et al. (2001) found an association between the Arg16Gly polymorphism of the  $\beta$ 2-adrenergic receptor gene (ADRB2) and SBP and DBP under resting conditions and during mental arithmetic and cold pressor stress. Response of DBP to both stressors was significantly associated with this polymorphism as well. McCaffery et al. (2002) studied the Arg389Gly and Arg16Gly polymorphisms in the  $\beta$ 1-adrenergic receptor gene (ADRB1) and the ADRB2, respectively. Associations were observed for both polymorphisms with SBP and DBP at rest and an association with DBP reactivity for the ADRB1 polymorphism only.

These results were extended in data from our Georgia Twin Study. We investigated the relationship between the Arg16Gly and Gln27Glu polymorphism of the  $\beta$ 2-adrenergic receptor gene and BP at rest and in response to postural change, social stressor interview and car driving simulation in a multiethnic cohort of youth (Snieder et al., 2002). We studied 395 European American and 275 African American twins from the SouthEastern United States (mean age:  $14.6 \pm 3.0$ ; range: 10.0–25.9). In European Americans, carriers of the Gly allele of the Arg16Gly polymorphism showed significantly higher SBP levels at rest, during social stressor interview and car driving. European American carriers of the Glu allele of the Gln27Glu polymorphism showed significantly higher levels of both SBP and DBP at rest and during postural change. The only significant finding in African Americans was a higher resting DBP in Glu carriers. No associations were found between these polymorphisms and cardiovascular reactivity (i.e. change scores) to any of the stressors. The findings thus suggest that vasodilatory related genetic factors may play an important role in control of BP levels at rest and during stress, particularly in European American youth.

Williams et al. (2001) evaluated the impact of a promoter polymorphism of the serotonin transporter gene (5HTTLPR) on cardiovascular reactivity to mental stress. Individuals with one or two long 5HTTLPR alleles showed higher levels of the major serotonin metabolite 5HIAA in the cerebrospinal fluid, as well as greater BP and heart rate responses to the mental stress protocol. Thus, these findings suggest that the 5HTTLPR polymorphism affects serotonin function in the central nervous system, which appears to result in an increased cardiovascular response to stress.

Although this review focuses on cardiovascular reactivity to behavioral and psychological challenges, several prospective studies have demonstrated that excessive BP responses to dynamic exercise may also be a risk marker for future

EH and CVD related mortality (Palatini, 1998). Rivera et al. (2001) reported a significant association between a codon ten polymorphism in the transforming growth factor  $\beta 1$  (TGF- $\beta 1$ ) gene and SBP at rest and during exercise in European Americans but not in African Americans. It would be interesting to test whether these results can be replicated for BP levels during psychological stress.

#### 4. Heritability of the renal stress response

As mentioned earlier, stress-induced SNS arousal activates the RAAS and stimulates proximal tubular reabsorption of  $\text{Na}^+$ , which increases  $\text{Na}^+$  and water retention leading to a rise in cardiac output and BP. To our knowledge, there are no published twin studies concerning stress-induced  $\text{Na}^+$  retention as determined by changes in urinary  $\text{Na}^+$  excretion. However, several lines of evidence suggest that genetic variability is important in renal  $\text{Na}^+$  handling and its response to stress (Harshfield and Grim, 1997).

##### 4.1. Genetics of $\text{Na}^+$ balance

First, a series of studies in the 1970s and 1980s by Grim, Luft, Weinberger and colleagues provided evidence for a genetic basis of salt sensitivity (defined as an increased BP response to salt intake). They observed that African Americans and first-degree relatives of patients with EH excreted salt in an attenuated fashion, i.e. were more salt sensitive than European Americans and people without a family history of EH (Luft, 2000, 2001). A twin study found genetic influences on urinary and fractional excretion of  $\text{Na}^+$  amongst a range of other heritable indicators of renal function (Grim et al., 1979). In another study of the same group, significant familial resemblance in BP response to dietary salt restriction in normotensive individuals provided additional evidence for the genetic influence on salt sensitivity (Miller et al., 1987).

These early results have been confirmed by a number of further twin studies. Whitfield and Martin (1985) reported a heritability of 50% for the fractional excretion of  $\text{Na}^+$ . Kagamimori et al. (1996) observed a heritability of 0.45 for urinary  $\text{Na}^+$  levels from among 35 MZ and 19 DZ twin pairs aged 6–14 years old. Nowson et al. (1997) found a heritability of 54% for the  $\text{Na}^+/\text{H}^+$  antiporter/exchange activity as measured in human cheek epithelial cells. Some earlier twin studies suffered from small sample sizes, but a recent large study of > 300 twin pairs reported heritabilities of 0.43 and 0.52 for 24 h  $\text{Na}^+$  excretion and fractional excretion of  $\text{Na}^+$ , respectively (Swaminathan et al., 2002).

##### 4.2. Genetics of stress-induced $\text{Na}^+$ response

Koepke and his colleagues (Koepke and DiBona, 1985; Koepke et al., 1988) performed a series of studies where they subjected inbred strains of rats susceptible

to development of EH (e.g. the DS and the Spontaneously Hypertensive Rat [SHR]) to a stressful stimulus (brief intermittent bursts of air directed at the dorsum of the head). The stress increased BP, heart rate, renal sympathetic nerve activity and decreased urinary  $\text{Na}^+$  excretion in these genetically susceptible strains but not in the normotensive control strains (Wistar–Kyoto rats).

Light et al. (1983) found the same variability in response for humans exposed to a series of psychological stressors for a 1 h period. Subjects were divided into high and low heart rate reactors and a positive or negative family history of EH. The high reactors with a family history of EH retained sodium during the testing period, which was associated with an increase in heart rate, suggestive of common SNS activation. In contrast, the other groups showed a functional increase in  $\text{Na}^+$  excretion (to compensate for the higher stress BP). A study by Harshfield et al. (1991) found that subjects who increased  $\text{Na}^+$  retention in response to a 1 h behavioral challenge showed continued elevation of BP into the recovery period and an uncoupling of the RAAS. Furthermore, this response pattern was more common in individuals with a positive family history of EH. A recent pilot study from our laboratory involving 15 MZ and 20 DZ twin pairs revealed much higher twin correlations in MZ (0.68) as compared with DZ twins (0.17) for changes in urinary  $\text{Na}^+$  excretion to a laboratory stress evaluation, indicating genetic influence (Harshfield et al., 2000).

Thus, the evidence points to the importance of a genetic influence on renal handling of  $\text{Na}^+$  and its response to stress, warranting the search for the specific genetic variants responsible for this effect.

## **5. Genetic influence on the SNS, the RAAS and the ES**

We propose that the genetic variability in the cardiovascular and renal stress response has its origin in genetic variation underlying SNS, RAAS and ES function. This hypothesis is supported by studies showing genetic influences on (hormonal) indices of these systems.

For example, both circulating catecholamines and urinary catecholamine excretion are influenced by heritable factors (Miller et al., 1980; Williams et al., 1993). Another study directly measured sympathetic impulse traffic in the peroneal nerve of nine pairs of MZ twins and eight pairs of age-matched subjects without family relationship. The findings indicated that the strength of sympathetic outflow to muscle is controlled genetically (Wallin et al., 1993). Likewise, indices of the RAAS such as plasma renin activity, plasma aldosterone concentrations and urinary aldosterone excretion show heritable effects (Grim et al., 1979; Manatunga et al., 1992). Wang et al. (1997) investigated the heritability of plasma NO metabolite levels and found that 30% of the variance could be explained by genetic factors. To our knowledge, no such studies have been performed for ET-1 levels.

## 6. Future directions

### 6.1. Focus on candidate genes of SNS, RAAS and ES function

We suggest that future studies investigating genetic influences on the cardiovascular and renal stress response should measure polymorphic variation in candidate genes underlying the SNS, the RAAS and the ES (see Fig. 1). A major advantage of this approach is that rather than studying the effect of candidate genes in isolation, they are studied within the framework of a model describing the interrelated physiological networks underlying BP regulation in response to stress.

A small selection of such candidate genes are. (1) For the SNS: the  $\alpha$ 1- and  $\alpha$ 2-adrenergic receptor genes (ADRA1, ADRA2) and the  $\beta$ 1- and  $\beta$ 2-adrenergic receptor genes (ADRB1, ADRB2). (2) For the RAAS: the genes for angiotensin converting enzyme (ACE), the angiotensin II type-1 receptor (AGTR1), aldosterone synthase (CYP11B2) and angiotensinogen (AGT). (3) For the ES: the ET-1 gene (EDN1), the gene for the ET-1 receptor A (EDNRA) and the genes for the three types of nitric oxide synthase (NOS1, NOS2, NOS3). In addition to the genes underlying these physiological systems, there are a number of relevant candidate genes that directly influence  $\text{Na}^+$  reabsorption in the kidney. Examples are the genes for (subunits of) the Epithelial  $\text{Na}^+$  Channel (ENaC), the G-protein  $\beta$ 3-subunit (GNB3) and  $\alpha$ -adducin (ADD1) (Luft, 2000, 2001; Munroe and Caulfield, 2000).

### 6.2. Detection of novel pathways and candidate genes: the promise of animal models

The study of animal models of EH shows great promise for the elucidation of the underlying physiological pathways involved in stress-induced EH as well as its genetic basis. The DS rat, for example, provides a useful model for studying the salt-sensitive, low renin EH, as found in many African Americans. Preliminary data from our laboratory indicate that DS rats exposed to chronic environmental stress (recurrent unpredictable, unavoidable exposure to high velocity bursts of air to the head) for 18 days show a higher acute SBP response, a slower BP recovery after stress and blunted endothelium dependent vasodilation compared with DR animals. We expect that continued chronic stress exposure will induce sustained EH, which will be accelerated by a high salt diet.

Although genetic mapping of quantitative trait loci (QTLs) for complex cardiovascular traits has been relatively straightforward in animal models, the identification of QTLs on the molecular level has proven far more challenging (Flint and Mott, 2001). However, key advances in gene expression profiling using microarray technology and the efficient production of congenic and transgenic disease models have brought gene identification within reach. Although none of the many QTLs for BP in rats have so far been translated into genes, recent success was reported for an insulin resistance gene (Aitman et al., 1999).

Our own preliminary data using microarray analysis show that gene expression in the renal inner medulla in response to a high sodium diet differed between the DR and DS rat. The DS animal showed a diminished transcriptional response to the high

salt diet (Jackson et al., 2000). Furthermore, the same gene expression data indicated that a component of the glutathione pathway is up-regulated in the DR animal. Glutathione participates in the endogenous free radical scavenging pathway and the increased basal expression in the DS rat is consistent with a higher level of free radical production even without induction of hypertension. This may indicate a role for oxidative stress in mediating the salt-dependent hypertension in the DS rats. The observed diminished transcriptional response may indicate that the DS rat lacks the necessary adaptive genetic response to maintain normal BP on a high salt diet. Comparison of gene expression in DS and DR animals may reveal whether similar mechanisms may be important under conditions of chronic environmental stress.

The DS rat has been used extensively in evaluating the genetically defined risk for salt-sensitive hypertension. Recently, Cowley et al. (2000, 2001) have provided evidence that rat chromosome 13 and 18 contain loci that play an important role in determining the influence of sodium intake upon arterial pressure. Garrett et al. (2000) recently published QTLs for BP that differ between the DS and SHR. Three QTLs were detected, one on each of rat chromosomes 3, 8, and 9. For the chromosome 3 QTL the SHR allele increased BP, and for chromosomes 8 and 9 the DS allele increased BP. This study also found that DS and SHR are not different for the previously described prominent BP QTLs on chromosomes 1, 2, 10, and 13. Many of these rat QTLs will probably be located on different human chromosomes, but the anticipated completion of the genome sequence of rat and mouse in 2003 will facilitate translation of such findings to the Human Genome through comparative mapping (Stoll et al., 2000). Novel candidate genes identified in this fashion will be tested and integrated into our model of stress-induced EH.

## **7. Summary and conclusions**

We developed a bio-behavioral model of stress-induced hypertension that explains how repeated exposure to stress in combination with genetic susceptibility might lead to the development of hypertension. In this model, we focus on three underlying physiological systems that mediate the stress response of the heart, vasculature and kidney: the SNS, the RAAS and the ES. Several lines of evidence point to a genetic basis of the two major intermediate phenotypes of our model: cardiovascular reactivity to psychological stress and stress-induced  $\text{Na}^+$  retention, representing the cardiovascular and renal stress response, respectively. We propose that polymorphic variation in candidate genes underlying the SNS, the RAAS, the ES and  $\text{Na}^+$  reabsorption in the kidney are at least partly responsible for these genetic influences. Any future studies testing the reactivity hypothesis should include either a general measure (e.g. family history of EH) or specific measures (specific polymorphic variants) of genetic susceptibility to the development of stress-induced EH and its sequelae.

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