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Phosducin — a candidate gene for stress-dependent hypertension

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Commentary

Repeated exposure to stress may favor, both in experimental animals and in humans, an increase in blood pressure, leading in some instances to a true hypertensive state. It is thought that stress-induced hypertension is mediated by sympathetic nervous system activation that in turn, by exerting vasoconstrictor effects and increasing heart rate (and thus cardiac output), may promote the development and progression of the hypertensive state. A new study by Beetz and colleagues in this issue of the *JCI*, which reports the results of experimental studies carried out in both mice and humans, reveals the potential role of the phosducin gene in modulating the adrenergic and blood pressure responses to stress (see the related article beginning on page 3597).

damaging immune activation triggered by HIV infection in humans (Figure 2).

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Phosducin — a candidate gene for stress-dependent hypertension

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Repeated exposure to stress may favor, both in experimental animals and in humans, an increase in blood pressure, leading in some instances to a true hypertensive state. It is thought that stress-induced hypertension is mediated by sympathetic nervous system activation that in turn, by exerting vasoconstrictor effects and increasing heart rate (and thus cardiac output), may promote the development and progression of the hypertensive state. A new study by Beetz and colleagues in this issue of the *JCI*, which reports the results of experimental studies carried out in both mice and humans, reveals the potential role of the phosducin gene in modulating the adrenergic and blood pressure responses to stress (see the related article beginning on page 3597).

Two major antecedents provide the background for the intriguing results provided by Beetz and coworkers in their study published in this issue of the *JCI* (1), which deals with the role of phosducin (*PDC*) as a novel candidate gene for stress-dependent hypertension. The first antecedent dates back several years and is represented by evidence that stress may be involved in the pathogenesis of essential hypertension (also known as primary hypertension which, by definition, has no identified cause), a relationship that was first suggested by the pioneering studies of Cannon (2) and Folkow (3). These investigators, and later other distinguished scientists (4, 5), elegantly showed that emotional stress in experimental animals may trigger the so-called "defense reaction," also known as the "fight or flight response," which is mediated by increased activation of the sympathetic nervous system and characterized by an elevation in blood pressure, an increase in heart rate, and adrenergic stimulation together with marked vasodilatation in skeletal muscle. Many of the aforementioned cardiovascular responses to stress have also been described in humans. For example, more than 30 years ago Brod and coworkers (6) reported that a mental arithmetic task elicits a pressor and tachycardic response, similarly to what has been documented in response to other stressor stimuli such as the cold pressor test, the Stroop color-word conflict test, and the mirror imaging star-tracking test (7, 8). Key to the

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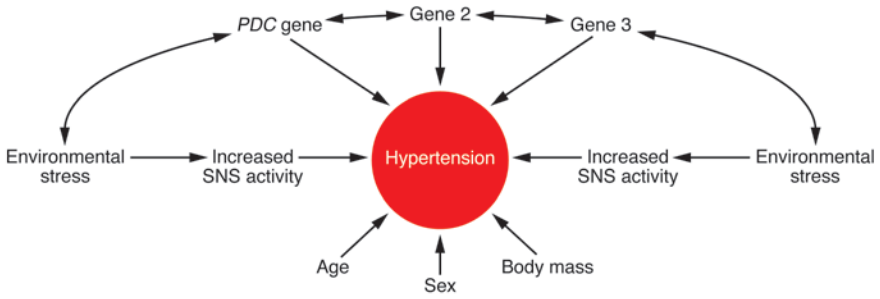

Figure 1
High blood pressure is multifactorial. This schematic illustrates the possible relationships between candidate genes, sympathetic nervous system (SNS) activation, and stress-related hypertension. In their study in this issue of the *JCI*, Beetz et al. (1) report that *PDC* likely plays a role in modulating the adrenergic and blood pressure responses to stress.

stress-related hypertension hypothesis is the concept that regular exposure to stress, as often happens in daily life, may favor the development as well as the progression of chronic blood pressure elevation in humans. A step toward embracing this hypothesis was the observation that an abnormal blood pressure response to stress at a young age may be predictive of the future development of hypertension (9, 10). The second antecedent to the study by Beetz and coworkers is a much more recent observation and refers to evidence that genetic factors may play a role in blood pressure control, in adrenergic modulation of cardiovascular drive, as well as in multiorgan responses to stress (11).

Based on this background, Beetz and colleagues, in their current study (1), test the hypothesis that the *PDC* gene may be involved in the development of some clinical forms of hypertension, such as those thought to be dependent on stress, via an involvement of sympathetic neural factors (Figure 1). The study is technically appreciable — it relies on state-of-the-art methodologies to assess human genetic profiles and takes advantage of a unique and highly demanding investigational approach based on collection of data both in experimental animal models and in humans.

Assessment of cardiovascular responses to stress: an evolving concept

In the vast majority of published studies aimed at assessing human cardiovascular responses to laboratory stressors, blood pressure, heart rate, and other hemodynamic variables have usually been evaluated during the performance of a single laboratory stressor. A major disadvantage of this approach is the poor reproducibility of the blood pressure and heart rate responses to stress within a single individual (8). The same is true for other stressor stimuli, which therefore makes it difficult to determine the representative blood pressure response to stress in a given individual based on the performance of a single stressor test. Currently, it is recommended that the assessment of human reactivity to stress be based on the evaluation of the average responses to a given procedure repeated at least twice in the same experimental session.

Two further problems should be mentioned regarding the assessment of human cardiovascular responses to laboratory stressors. The first problem involves the lack of any relationship among the hemodynamic responses elicited in a given individual by different laboratory stressors (8). This means that it is extremely difficult, if not impossible, to define the patterns of a subject's reactivity to stress by evaluating the hemodynamic responses to a single specific test. The second problem is even more complex, which is the fact that the reactivity to laboratory stressors does not necessarily represent the reactivity of subjects to the daily stresses of life (8). The aforementioned limitations should thus be taken into account when planning studies aimed at clarifying the interrelationships between a given genetic trait and cardiovascular responses to stress. Finally, it is important to remember that researchers still debate whether and to what extent the blood pressure responses to stress, even when assessed according to state-of-the-art methodologies, may predict the future development of hypertension. This concept was stressed in the 2007 European Society of Hypertension/European Society of Cardiology guidelines for the management of hypertension (12), which underline the caution needed when interpreting stressor responses as markers of future hypertension.

Evaluating neuroadrenergic contribution to stress-related hypertension

PDC is a 33-kDa cytosolic regulator of G protein–mediated signaling and is known to be present in the retina, the central nervous system, and pineal gland (13) and, as shown by Beetz et al. (1), is also present in sympathetic ganglia but not in the heart, blood vessels, or kidney. As regulators of G protein signaling have been shown to be involved in cardiovascular function, Beetz et al. hypothesized that *PDC* may represent a candidate gene involved in the development of hypertension, and their studies were aimed at determining the possible relationships between *PDC* gene deletion and markers of adrenergic function. The authors first examined mice with a targeted deletion in the *Pdc* gene ($Pdc^{-/-}$ mice) and evaluated norepinephrine and epinephrine turnover from isolated cardiac tissue as well as by direct assessment of the vaso-

Table 1
Assessment of sympathetic cardiovascular function

Variable measured	Technique used	Sensitivity of the approach	Degree of difficulty
Heart rate	Electrocardiogram	Satisfactory	Easy
Plasma norepinephrine	HPLC	Good	Moderately difficult
Norepinephrine spillover	Radiolabeling	Excellent	Difficult
Heart rate variability	Power spectral analysis	Satisfactory	Easy
Muscle sympathetic nerve traffic	Microneurography	Excellent	Difficult

constrictor responses to endogenous and exogenous adrenergic neurotransmitters. Interestingly, they found that while cardiac morphology and function did not differ between *Pdc*$^{-/-}$ and wild-type mice, blood pressure was significantly elevated in the *Pdc*$^{-/-}$ animals. This hypertension was not the result of increased vasoconstriction or vascular remodeling in the *Pdc*$^{-/-}$ animals. The authors went on to show that exposure of both wild-type and *Pdc*$^{-/-}$ animals to stress (postoperative stress or transfer to novel environments) resulted in greater increases in blood pressure in *Pdc*$^{-/-}$ mice. Administration of the antihypertensive drug prazosin, which blocks vasoconstrictory α_1 adrenoceptors, lowered blood pressure to similar levels in wild-type and *Pdc*$^{-/-}$ animals, indicating that the hypertensive state in *Pdc*$^{-/-}$ mice was the result of increased sympathetic nervous system activity (or "sympathetic tone"), which the authors went on to show involved increased electrical activity of sympathetic neurons — specifically, increased potassium channel currents that facilitate faster repolarization.

PDC dysregulation and cardiovascular abnormalities

Beetz et al. (1) also observed that, over time, blood pressure dysregulation in *Pdc*$^{-/-}$ mice brought about structural and functional changes in the vasculature and heart that are similar to those observed in humans with essential hypertension. To evaluate the role of *PDC* in human blood pressure phenotypes, the authors undertook a gene-association study in two different human populations, individuals of African-American or French-Canadian descent. A linkage block containing *PDC* was associated with both wake and stress response blood pressure phenotypes in both populations. Stress phenotypes were induced, for example, by subjecting individuals to a mental arithmetic task or in response to standing. SNPs in the human *PDC* gene were linked with stress-dependent blood pressure responses in the African-American population. Individuals homozygous for the G allele of a *PDC* SNP (rs12402521) had blood pressure levels 12–15 mmHg higher than levels in humans with the A allele. Thus from this set of data it appears that *PDC* represents a candidate gene not only for retinopathies, as previously documented (14, 15), but also for some forms of cardiovascular disease such as essential hypertension.

PDC and human sympathetic function

The approaches employed in the present study (1), along with the nerve traffic recording technique (16), represent the most sophisticated and sensitive methodologies currently available to assess neuroadrenergic function in different experimental animal models. On the other hand, the assessment of sympathetic activity in humans is based on sets of 24-hour ambulatory blood pressure measurements (e.g., blood pressure values during the waking state, at rest, or in response to having to perform a mental arithmetic task). As such, these human studies lack a direct measure of adrenergic cardiovascular drive. Assessment of neural sympathetic cardiovascular function in humans is certainly a demanding and difficult task that requires sophisticated methodologies and expertise (Table 1) (17). However, in future studies, the sympathetic responses to stress in these populations may be more specifically assessed by measuring heart responses during the mental arithmetic test or in response to the other stressors employed. Although heart rate is the result of a balance of parasympathetic and sympathetic effects on the activity of the cardiac sinus node, evidence has been provided that a good correlation exists between resting heart rate and other direct indices of adrenergic cardiovascular drive, such as direct recording of efferent muscle sympathetic nerve traffic and venous plasma norepinephrine levels (18). Similar relationships have been reported in the assessment of heart rate responses to stress (19). The information obtained by collecting heart rate data may thus be of help in understanding the link reported here by Beetz et al. (1) between genetic abnormalities in the *PDC* gene and sympathetic function.

Although the results of this study — which suggest that *PDC* has potential as a therapeutic target in the treatment of stress-induced hypertension — are of major scientific and clinical relevance, future studies will be required to better delineate the effect of *PDC* on blood pressure and sympathetic tone in humans before specific recommendations can be made regarding any related therapeutic intervention. Future research will thus have to focus on the three major and complex areas of investigation addressed by the present study, namely assessment of cardiovascular responses to stress, evaluation of human adrenergic function, and definition of the role of genetics in the pathogenesis of essential hypertension.

Role of candidate genes in the pathogenesis of hypertension

Despite the large number of studies on the pathophysiology of hypertension published in the past decade, it should be recognized that, at present, the role of genetic factors in the etiology of human hypertension remains ill defined. This is due to a variety of confounding factors, including (a) the heterogeneity of the populations studied; (b) the importance of non-genetic risk factors such as age, gender, lifestyle, and environment; (c) the difficulty in assigning pathophysiological function to hypertension-associated SNPs; and (d) the difficulty in performing longitudinal studies. Recently, however, some new insights into the complex relationship among genes, sympathetic factors, and stress-related hypertension have been reported. Subjects with a deficiency in genes encoding the melanocortin 3 and 4 receptors are characterized by low blood pressure and hemodynamic and biochemical signs of reduced sympathetic tone (20). Conversely, genetic variations in neuropeptide Y receptors as well as in renalase activity appear to be associated with high blood pressure (21–23). Finally, we have recently shown that in hypertensive patients with metabolic syndrome, sympathetic overdrive is linked to the gene encoding the α_{1A} adrenoceptor (24). Taken together, the findings suggest that some hypertensive clinical states may be characterized by a genetic background that is linked to sympathetic abnormalities.

Conclusions

In conclusion, the study by Beetz and coworkers (1) provides new and interesting insights into the complex relationships between genetic background, sympathetic neural factors, and stress-related hypertension. Future studies will be needed to clarify the therapeutic implications of the aforementioned findings.

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