A New Player in Circulatory Adaptation to Orthostatism

Better to Play With Than Without Him

Francois Alhenc-Gelas

As exemplified by arterial hypertension, discovery of monogenic forms of common cardiovascular disorders can unravel the critical role of known molecules and molecular interactions in homeostasis.[1] Relevance of these peculiar genetic defects to the common forms of the disease may be limited as far as cause is concerned but needs to be considered, for both pathophysiological and clinical issues. The topic is further illustrated in this issue by the first description of monogenic forms of orthostatic hypotension (OH) caused by deficiency in cytochrome CYB561.[2]

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OH and the Sympathetic Nervous System

OH is a frequent disorder, at least in mild form, caused by circulatory maladaptation to the effect of gravity on standing. Prevalence has been reported to be high in elderly subjects, but the condition is less frequent in young adults.[3] Sequestration of blood in lower parts of the body reduces ventricular preload, stroke volume, and blood pressure, depending in part on capacity of the venous compartment and lack of muscular effect on venous return. If this is combined with preexisting hypovolemia or deficiency in neurohormonal counter-regulatory mechanisms, large drops in blood pressure may occur and blood flow delivery to organs, especially the brain, is compromised. OH should be seen as a potentially serious condition that may remain asymptomatic if moderate but can also result in discomfort, syncope, brain infarction, arrhythmia, and death. Iterative episodes of brain ischemia can also aggravate cognitive disorders. Treatments are not always satisfactory.[4,5]

The sympathetic nervous system (SN) plays a major role in circulatory adaptation to orthostatism. The system can indeed be activated quickly through arterial baroreceptors and act quickly through noradrenaline release increasing arteriolar resistance and heart rate and restoring cardiac output and organ perfusion pressure. Other vasoconstrictor systems are involved, like the renin–angiotensin system, which is physiologically related at its 2 ends, control of renin secretion and action of angiotensin II to the SN, and vasopressin which acts more on the long term.[4] Impairment of SN activity is a key pathogenic feature in most, if not all orthostatic syndromes, such as those observed in neurological diseases, uncontrolled diabetes mellitus with peripheral neuropathy, and during treatment with sympatholytic drugs, as well as in OH without a definite, recognizable cause and called idiopathic.

Primary defects in SN activity may occur as a consequence of congenital deficiency in enzymes involved in monoamine synthesis and metabolism, their cofactors or transporter systems. Patients experiencing these deficiencies often present with severe neonatal or early childhood neurological symptoms because of accumulation of precursors and defect in end products in several brain areas.[6] However, when mutations result mainly in reduction of noradrenaline synthesis, as is the case in deficiency in dopamine β-hydroxylase, the enzyme responsible for the synthesis of noradrenaline from dopamine, the SN seems to be the main sufferer. Early-life symptoms may be present, but the condition is often diagnosed later when an orthostatic syndrome with OH develops.[7,8] Interestingly, a mirror form of orthostatic intolerance with tachycardia and without OH has been described in subjects deficient in norepinephrine transporter having excess circulating noradrenaline because of impaired reuptake.[9]

Genetic Deficiency in CYB561

van den Berg et al[2] report severe, familial, neurogenic orthostatic syndromes resembling dopamine β-hydrolase deficiency but caused by biallelic defective mutations in the gene coding for CYB561, a cytochrome involved in ascorbate metabolism in nerve cells. One of the 2 affected families carried a missense mutation in exon 3, whereas the other had a point nonsense mutation in exon 2, in both cases presumably resulting in loss of functional protein and biological activity. Cytochrome b561 is known to function as a transmembrane electron carrier restoring intravesicular level of ascorbate by reducing dehydroascorbate generated during dopamine hydroxylase action.[10] Ascorbic acid is a cofactor for dopamine β-hydroxylase in vesicles of sympathetic nerve terminals and adrenal chromaffin cells (see Figure 1 in van den Berg et al[2]). Deficiency in CYB561 results in decreased bioavailability of ascorbic acid in vesicles and consequently inhibition of dopamine β-hydroxylase activity. Accordingly, catecholamine levels are low in plasma of affected subjects and in brain of mice deficient in CYB561.

These clinical observations provide interesting information, for both physiologists and clinicians:

First, they document the critical role of CYB561 in catecholamine biosynthesis and in cardiovascular and metabolic homeostasis. No other redox system was able to substitute for this cytochrome. The physiological role of CYB561 in the circulation could not have been easily recognized by studying CYB561-deficient mice, albeit continuous recording of blood

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pressure and heart rate in these animals may have provided some clues.

The study also underlines the role of ascorbic acid in the biosynthesis of catecholamines and the consequences of a decrease in its local bioavailability. Circumstantial evidence suggests that severe ascorbate deficiency may present clinically with OH,[11] but bioavailability of ascorbate has not been systematically investigated in OH.

Some clinical features in CYB561-deficient patients are worth commenting on.

Orthostatic maladaptation and hypoglycemia can be attributed to defect in SN activity, but no clinical symptom attributable to loss of CYB561 in the brain is reported in the patients, despite widespread cerebral expression of the *CYB561* gene. Phenotype is similar to dopamine β-hydroxylase deficiency, underlining the prominent role of noradrenaline depletion.

Severe renal insufficiency occurred in the 2 CYB561-deficient patients in 1 family. Causality between SN deficiency and renal failure can be suspected, but mechanisms remain undocumented. Renal ischemic episodes are likely to have played a role. Role of dysregulation of the renin–angiotensin system in patients with SN deficiency and OH should not be overlooked. Renin secretion is activated during hypotension in part through sympathetic renal nerve stimulation. Angiotensin II maintains glomerular filtration. Suppression of this regulation may compromise renal function.[12] Renal function should be monitored in SN deficiency and OH.[13]

L-dihydroxyphenylserine (Droxidopa) used here for treatment is used in patients with dopamine β-hydroxylase deficiency and also, but with weaker pathophysiological rationale, in other forms of OH. L-dihydroxyphenylserine is converted to noradrenaline by cytoplasmic L-aromatic-amino-acid decarboxylase. This treatment was considered efficient in the CYB561-deficient patients but eventually became unsatisfactory because of intolerance. L-dihydroxyphenylserine has been reported to be generally well tolerated in clinical trials.[14] However, the drug is eliminated by the kidney and renal insufficiency can reduce tolerance.

Relevance to Orthostatic Syndromes

Relevance of the present cases to other forms of OH is unknown. The defective mutations leading to symptomatic CYB561 deficiency reported by van den Berg et al[2] in 2 families are most likely recessive, heterozygote subjects remaining apparently asymptomatic. These mutations have not been described before, and their prevalence in population is likely to remain low, especially at homozygote state, even if no consanguinity was documented in the 2 affected families. CYB561 deficiency has not been described before. Accordingly, the condition is likely to be very rare, as is also the other, physiologically and clinically related genetic form of OH, primary dopamine β-hydroxylase deficiency.[8] However, the present study documents that a new gene, the *CYB561* gene, is causally involved in OH and suggests studying this gene in OH patients and searching for mutations, especially is there is familial antecedent and dopamine β-hydroxylase level in blood is normal.

The study shows that the CYB561–ascorbate interaction plays a critical role in SN activity and deficiency in the cytochrome results in severe circulatory maladaptation to orthostatism. CYB561 is a potential player in pathological situations with gain of function of SN, like neurogenic hypertension, postural tachycardia syndrome, and neuropsychiatric disorders.

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Disclosures

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