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Molecular Aspects of Gitelman's Syndrome Angiotensin II Signaling Alteration

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DESCRIPTION

Gitelman's Syndrome (GS) is a rare inherited tubulopathy characterized by hypokalemia, hypomagnesaemia, and metabolic alkalosis due to inactivating mutations of the distal convoluted tubule sodium chloride cotransporter. This entails reduced extracellular volume and consequent activation of counterbalancing systems such as the renin–angiotensin–aldosterone system. Although with high levels of angiotensin II, Gitelman's patients do not display hypertension or its cardiovascular and renal remodeling complications related to over activation of those systems. The study of renal tubular disorders, such as Gitelman's Syndrome (GS), is of paramount importance to understand the molecular mechanisms involved in the onset and progression of other diseases, in particular, hypertension and its correlated cardiovascular/renal remodeling. The kidneys play a pivotal role in the physiological fluid homeostasis, being the filtering system of the body and determining its chemical and hormonal equilibrium.

GS is a rare inherited salt-wasting tubulopathy first described as a familial disorder characterized by electrolytic alterations with concomitant hypomagnesaemia and hypokalemia. It is cataloged in the registry of the inherited rare Mendelian diseases. However, its estimated prevalence of 1:40000 makes it one of the most frequently inherited renal tubular disorders, and it is expected that a further portion of the population is affected by the syndrome without being aware. The clinical characteristics and the severity of biochemical abnormalities reflect a gene-specific pattern: the etiology of GS is determined, in fact, by mutations in a gene that encodes for a cotransporter involved in the trafficking of electrolytes in the Distal Convoluted Tubules (DCT) of the nephrons, the Sodium Chloride Cotransporter (NCC). GS typical clinical features are salt craving, muscle weakness, fatigue, and cramps with electrolyte imbalance associated with the side effects of treatment with thiazide diuretics that target the DCT specifically.

Calcium and magnesium imbalance is also associated with arthropathy with calcium pyrophosphate crystal deposition or chondrocalcinosis

in GS. Other clinical symptoms of GS are dizziness and prolongation of the QT interval on electrocardiogram (due to the depolarization and repolarization of the ventricles), which causes arrhythmia Hypertension-Mediated Organ Damage (HMOD). It is the result of the structural and functional alteration of vasculature and organs caused by elevated and uncontrolled BP, by hormonal or neurohumoral abnormalities and wrong life habits. In particular, the organs affected by HMOD are the brain where white matter lesions, silent micro infarcts, micro bleeds, and brain atrophy can be detected; the heart with left ventricular hypertrophy; the kidneys with impaired function, lower eGFR and albuminuria, and the eyes with retinal hemorrhage, micro aneurysm, papilledema, and hypertensive retinopathy. Nonetheless, hypertension impairs arteries' functionality by inducing atherosclerotic plaques and Intima to Media Thickness (IMT) and stiffening. Vascular beds are, in fact, extremely damaged by the continuous pressure of blood flow exerted against arteries which causes loss of elasticity, decreased blood flow, and consequent reduced oxygen supply to cell and to organs. The spreading of radical species causes damages to several macromolecules such as the Low-Density Lipoproteins (LDLs). This latter, once oxidized, has a critical role in the progression of atherosclerotic lesions. GS shows reduced susceptibility of LDL to oxidation, mainly due to an increase in the production of the antioxidant and protective factor NO, whose increased bioavailability is related to a reduced production of $O_2^{-\bullet}$.

Besides the pathways merely deputed to the production of oxidative species, the long-term Ang II signaling induced via oxidative stress occurs also through the activation of RhoA/ROCK pathway. The activation of this pathway alongside increased Ca^{2+} sensitization leads key processes in the progression of hypertension and cardiovascular/renal remodeling. ROCK, in fact, acts also on other targets such as Ezrin, Radixin, and Moesin (ERM) and LIM kinases, which are connected with actin filaments and cytoskeletal rearrangement. Oxidative stress-induced responses comprise also the activation of Extracellular Signal-Regulated Kinases (ERK) 1/2 and mitogen-activated protein kinases (MAPK). The activation of ERK induces integrated responses that involving nucleotide and protein synthesis and activates transcription factors and chromatin phosphorylation. The phosphorylation state of MYPT-1 and the phosphorylation of ERK 1/2 are reduced in GS further providing evidence for the association of these molecules with cardiovascular/renal remodeling pathways which is absent in GS.

The findings coming from experiments on GS compared to those on hypertensive subjects confirm the close link between Ang II signaling and cardiovascular/renal remodeling. GS patients provide insights for the intracellular pathways involved in the onset and of hypertension, through endothelial dysfunction, atherogenesis, and vascular remodeling. In particular, the protection and prevention of oxidative stress, which seems to be absent in GS, might be the key point to reduce the progression of cardiovascular-related negative outcomes.

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