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Post-Translational Nuclear Protein Modification and High Vitamin-D Receptor Levels in Genetic Hypercalciuric Stone-Forming Rats

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ABSTRACT

Studies conducted on Genetic Hypercalciuric-Stone Forming (GHS) rats have shown that their excess calcium urine excretion might be caused by significantly high vitamin D receptor (VDR) levels found in key calcium-transporting tissues, since high VDR raises physiological response to $1,25(OH)_2D_3$, the hormonally active metabolite of vitamin D that regulates calcium levels in the body. We suggest that the high VDR levels in GHS tissue are a result of altered post-translational modification by ubiquitin and Small Ubiquitin-like Modifier (SUMO), which regulate the degradation of nuclear proteins substrates such as VDR.

Our inquiry begins by overexpressing ubiquitin, SUMO-1, SUMO-2, and SUMO-3 in rat tissue to perform targeted gene expression of VDR. Western blot will be used to analyze resulting changes in the VDR signaling pathway and the degree to which the GHS rat phenotype is emulated with the added ubiquitin or SUMO. Our proceeding step will be to measure changes in VDR levels after performing an siRNA-facilitated knockdown of the E1, E2, and E3 enzymes that facilitate ubiquitination of nuclear proteins. Our final experiment will consist of isolating proteins from GHS bone marrow, intestinal, and renal cells and recording ubiquitin levels to compare with control tissue.

If there is a consistent trend in the ubiquitin levels of GHS cells compared to control cells, and the western blot and enzyme knockdown procedures reveal that altered ubiquitin/SUMO presence affects VDR levels, then there will be evidence to show that the general hypercalciuiric phenotype could be an eventual result of insufficient VDR degradation due to abnormal post-translational protein modification.

Key Words: SUMO, Ubiquitin, Hypercalciuria, Protein Degradation

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