Anthony Norman, Endocrinol Metab Synd 2014, 3:2
http://dx.doi.org/10.4172/2161-1017.S1.004

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Endocrinology
October 20-22, 2014 DoubleTree by Hilton Hotel Chicago-North Shore, USA

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Vitamin D Receptor (VDR) regulation of voltage-gated chloride channels by ligands preferring the VDR-Alternative Pocket (VDR-AP)

Based on molecular modeling and ligand binding studies, it has been postulated that the vitamin D receptor (VDR) contains two overlapping ligand binding sites, a genomic pocket (VDR-GP) and an alternative pocket (VDR-AP), that mediate rapid responses and regulation of gene transcription, respectively. Our data obtained from molecular mechanics docking studies predict that the major blood metabolite, 25(OH)-vitamin D_3 (25D3), selectively bind to the VDR-AP while the steroid hormone 1α,25$(OH)_2$-vitamin D3 (1,25D3) binds equally well to both pockets, however analog JN prefers the alternative pocket and analog HL is an inhibitor of genomic responses. 1,25D3, 25D3, and JN each rapidly stimulated voltage-gated outwardly rectifying chloride channels (ORCC) in TM4 sertoli cells. In a dose response study, 25D3 and 1,25D3 were equipotent in stimulating ORCC rapid response while 1 nM 1,25D3 was 1000x more potent than 25D3 in stimulating gene expression. These results are consistent with the concept that whereas ligand occupancy of the VDR-GP initiates genomic actions, occupancy of the VDR-AP is essential to initiate signaling required for rapid opening of ORCC. The VDR-AP agonist effects of 1,25D3, 25D3 and JN are absent following pretreatment of TM4 cells with VDR siRNA. In COS-1 cells transfected with VDRwt or a mutant construct lacking the DNA binding domain, 1,25D3 and 25D3 potentiate the opening of ORCC. Cells transfected with VDR mutants lacking either the ligand binding domain or the hinge/loop region lost this response to the ligands. The fact that 25D3 is equipotent to 1,25D3 in mediating rapid responses possibly suggests a paradigm shift in thinking about the ability of 25D3 *in vivo* to generate biological responses.

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