The effects of 9-cis retinoic acid on 1,25-dihydroxyvitamin-mediated transcriptional activation in Atlantic bottlenose dolphin (*Tursiops truncatus*) skin cells

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The vitamin D pathway, mediated by the bioactive form of vitamin D3, has been well characterized in terrestrial animals. Vitamin D intake via diet or exposure to UVB radiation triggers the synthesis of 1,25-dihydroxyvitamin (1,25D3), the biologically active metabolite of vitamin D3, within the skin. 1,25D3 binds to the nuclear vitamin D receptor (VDR), which is a ligand-activated transcription factor regulating a large suite of genes. VDR's activation requires heterodimerization with another nuclear receptor: the retinoid X receptor (RXR). The RXR/VDR formation identifies and binds to vitamin D response elements (VDRE) within the promoters of certain genes to induce their expression. We are interested in whether 9-cis retinoic acid (9-cis RA), RXR's ligand, acts negatively or synergistically with 1,25D3 to induce the vitamin D pathway. The effect that 9-cis RA has on the vitamin D pathway is controversial and not well studied. We are using dolphin skin cells as our model because neither vitamin A nor vitamin D pathways have been well-studied in marine mammals, and each may serve as a potential innate immune mechanism within dolphin skin. Preliminary results show that 9-cis RA moderately activates transcription of a vitamin D sensitive promoter, albeit not nearly as strongly as that by 1,25D3. Combined exposure to 1,25D3 and 9-cis RA produces similar transactivity of this promoter as 1,25D3 alone, suggesting that 9-cis RA, if anything, exerts a positive effect on 1,25D3-mediated transcription. We propose to further test the differential effects of the two ligands on VDR and RXR protein levels and on the expression of dolphin-specific vitamin target genes using Western blot analysis and real-time PCR. Because dolphins may be appropriate models for humans, elucidating the effects that 9-cis RA has on the vitamin D pathway in dolphin skin cells provides information for crosstalk between the two pathways and for the appropriate vitamin A supplementary intake with respect to vitamin D in humans.

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