POTENTIAL APPLICATION OF TESTOSTERONE METABOLITES IN THE TREATMENT OF ADRENOLEUKODYSTROPHY

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X-linked adrenoleukodystrophy (X-ALD) is a demyelinated disorder. Due to defective peroxisomal beta-oxidation, Very long chain fatty acids (VLCFA), the biochemical markers of the disease, accumulate in plasma, fibroblasts and different tissues.
The mutated gene (ABCD1, Xq28), encodes for the peroxisomal ABC half-transporter ALDP. It has been shown that gene ABCD2, which presents the closest relation to ABCD1, and the other related genes ABCD3 and ABCD4 can compensate the impaired function of ALDP and that different agonists are able to induce their expression, partially compensating the pathological abnormalities of the disease such as enhancing VLCFA beta-oxidation.
We have evaluated the effect of the androgen dihydrotestosterone (DHT) and 5α-androstan-3α,17β-diol (3α-diol), as a promising therapeutic approach, on the expression of the ABC half-transporters encoded by ABCD2 and ABCD3 genes, in fibroblasts drawn from controls and from two affected brothers. The two patients presented the same mutation in exon 9 but had different clinical manifestations, one patient being asymptomatic and the second one severely affected.
When the cells were stimulated with the testosterone metabolites only the patient with the severe form showed a significant increase in ABCD2 mRNA levels, whereas ABCD3 expression remained unchanged in both cases.