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Steroid resistant in childhood Idiopathic Nephrotic Syndrome: Does epigenetic factors like HDAC2 may play role in steroid resistance via regulation of P-gp and MRP-1?

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Objectives: Glucocorticoids switch off activated inflammatory genes. The activated glucocorticoid receptors interact with co-repressor molecules to impair NFκB activity, reducing histone acetylation, Reduction in histone acetylation occurs via recruitment of histone deacetylase (HDAC) 2 to the activated inflammatory gene complex by activated GR, resulting in suppression of activated inflammatory genes.

To evaluate the effect of HDAC 2 on P-gp and MRP-1 expression and function.

Methods: 78 subjects were recruited 50 were steroid-sensitive nephrotic syndrome (SSNS), and 28 were steroid-resistant nephrotic syndrome (SRNS). Gene expression was analyzed on peripheral blood mononuclear cells (PBMCs) in SRNS patients (mean age 8.43±3.8 years), SSNS patients (mean age 7.54±3.5 years). PBMCs were treated with 1μM of Theophylline (HDAC2 stimulator) and 0.8μM of Trichostatin A (HDAC2 inhibitor) for 48 hours.

Results: P-gp (4.79±0.970 v/s 2.13±0.72, p<0.0001), MRP-1 (3.99 ±0.8 v/s 1.99 ±0.91, p<0.0001) expression was increased in SRNS v/s SSNS. HDAC2 expression was decreased in SRNS v/s SSNS (2.97 ± 0.95 v/s 6.02 ± 1.13, p<0.0001).

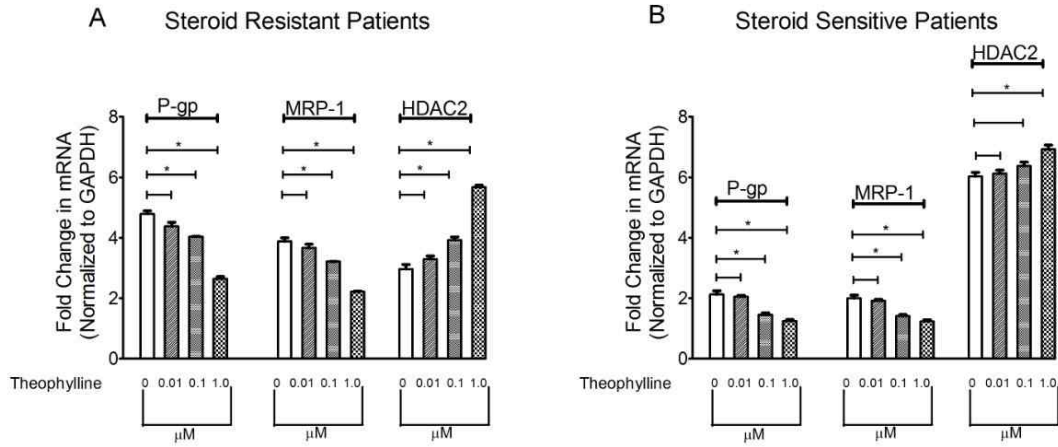
Theophylline decreased expression of P-gp and MRP-1 in SRNS with maximal induction at 1μM (fold change 2.65 and 2.21, *p<0.0001). HDAC2 expression increased (fold change 5.67, *p<0.0001). In SSNS P-gp and MRP-1 expression decreased at 1μM (fold change 1.25, 1.24, *p<0.0001). HDAC2 expression increased (fold change 6.93, *p<0.0001).

TSA increased expression of P-gp and MRP-1 in SRNS with maximal induction at 0.8μM (fold change 7.51, 7.31, *p<0.0001) and decreased expression of HDAC2 (fold change 1.50, *p<0.0001). In SSNS P-gp and MRP-1 expression increased at 0.8μM (fold change 3.49, 3.35, *p<0.0001) and HDAC2 decreased (fold change 2.53, *p<0.0001) at 0.8μM.

The functional activity of P-gp and MRP-1 was significantly higher in SRNS v/s SSNS (p<0.001), whereas the enzymatic activity of HDAC2 was increased in SSNS v/s SRNS (p<0.001)

Conclusions: HDAC2 regulates P-gp and MRP-1 expression, Inducer of HDAC2 may be a probable treatment strategy for patients of INS.

effect of Theophylline on P-gp and MRP-1



Effect of Tricostatin A on P-gp and MRP-1 expression

