Pediatr Nephrol. 2016 Jun;31(6):965-74. doi: 10.1007/s00467-015-3289-x.

Impaired phosphorylation of JAK2-STAT5b signaling in fibroblasts from uremic children.

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Abstract

BACKGROUND:

Chronic kidney disease (CKD) in children is characterized by severe growth failure. The growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis in uremic animals shows a post-receptor impaired phosphorylation of Janus kinase 2/signal transducer and activator of transcription (JAK-STAT) proteins. The objective of our study was to characterize the intracellular phosphorylation of JAK-STAT signaling in fibroblasts from children with CKD on chronic peritoneal dialysis (PD).

METHODS:

Serum GH-binding protein (GHBP), IGF-1 and IGFBP3 were measured in 15 prepubertal CKD stage-5 children on PD. Cytoplasmic JAK2, cytoplasmic/nuclear STAT5b and nuclear IGFBP3, acid-labile subunit (ALS) and IGF-1 mRNA expression were quantified in fibroblasts obtained from skin biopsies before and after stimulation with 200 ng/ml recombinant human growth hormone (rhGH). Phosphorylation activity at both the cytoplasmic and nuclear level was expressed as the ratio phosphorylated (p)/total (t) abundance of the product (p/t) at 30 and 60 min. Fifteen healthy children were recruited as the control group. Values were expressed in arbitrary units (AU) and normalized for comparison. Significance was defined as $p < 0.05$.

RESULTS:

Thirty minutes after rhGH stimulus, the cytoplasmic (p/t) JAK2 ratio was significantly lower in patients than in controls [median and interquartile range (IQR): 7.4 (4.56) vs. 20.5 (50.06) AU]. At 60 min after rhGH stimulation, median JAK2 phosphorylation activity was still significantly lower in the patients [7.14 (IQR 3.8) vs. 10.2 (IQR 29.8) AU; $p < 0.05$]. The increase in the cytoplasmic (p/t) STAT5b/β-actin ratio was lower at both measurement points in the patients compared to the controls, without reaching statistical significance between groups. Median IGFBP3 mRNA abundance was significantly decreased in fibroblasts from uremic patients 24 h after rhGH stimulation compared to the healthy controls [1.27 (IQR 0.83) vs. 2.37 (IQR 0.80) AU]. Median ALS and IGF-1 mRNA expression changed in response to rhGH stimuli at 24 and 48 h.

CONCLUSION:

In this study, children with CKD undergoing PD therapy showed an impaired phosphorylation of JAK2/STAT5b signaling in fibroblasts after GH stimulation, as well as impaired IGFBP3 mRNA abundance. Both impairments may be partially responsible for the observed resistance to the growth-promoting actions of GH in chronic kidney failure.

KEYWORDS:

Chronic kidney disease; Growth hormone; IGF-1; IGFBP3; JAK2; Peritoneal dialysis; STAT5b