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Additive Effect of Combined Treatment with the Small Peptide GH Receptor Antagonist, AZP-3813, and the Somatostatin Analog, Octreotide, in Decreasing IGF-1 Levels in the Rat.

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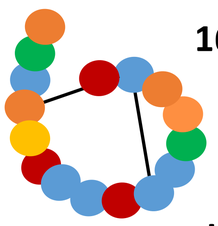
INTRODUCTION

The goal in treating acromegaly is to normalize insulin-like growth factor 1 (IGF-1) in order to alleviate the symptoms and manage potential medical complications caused by its excess. Three therapeutic approaches currently exist to treat acromegaly: surgery, medicinal therapy (with somatostatin analogs (SSAs), growth hormone receptor antagonist (GHRA) and dopamine agonists) and radiotherapy. While surgery is potentially curative, it fails in approximately 60% of patients. The majority of patients who fail surgery are currently medically treated with SSAs; however, normalization of IGF-1 is achieved in less than 40%.

AZP-3813 is a 16-amino acid, bicyclic peptide antagonist with high affinity for the GHR and an inherently long half-life in the blood stream. It was selected for clinical development as add-on therapy to SSAs in patients with acromegaly inadequately controlled by SSAs. Recently, we demonstrated that AZP-3813 is very effective in suppressing IGF-1 in juvenile and adult rats, normal Beagle dogs and in healthy individuals. Here, we examined the effect of subcutaneous administration of AZP-3813 on circulating IGF-1 levels in normal rats when administered in combination with the SSA, octreotide.

AZP-3813



16 Amino Acid, Bi-Cyclic Peptide

MW = 2479.9 Da

Human GHR affinity (K_D) = 1.9nM

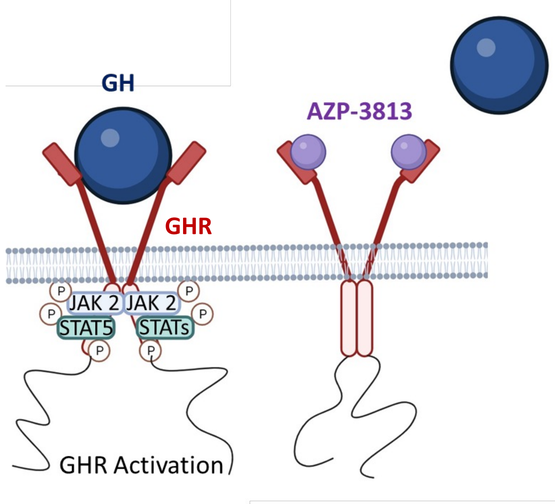
Human GHR antagonism (IC_{50}) = 29nM

Half-Life in Rat

$T^1/_2$ = 11.2 hours

Half-Life in Dog

$T^1/_2$ = 14.2 hours



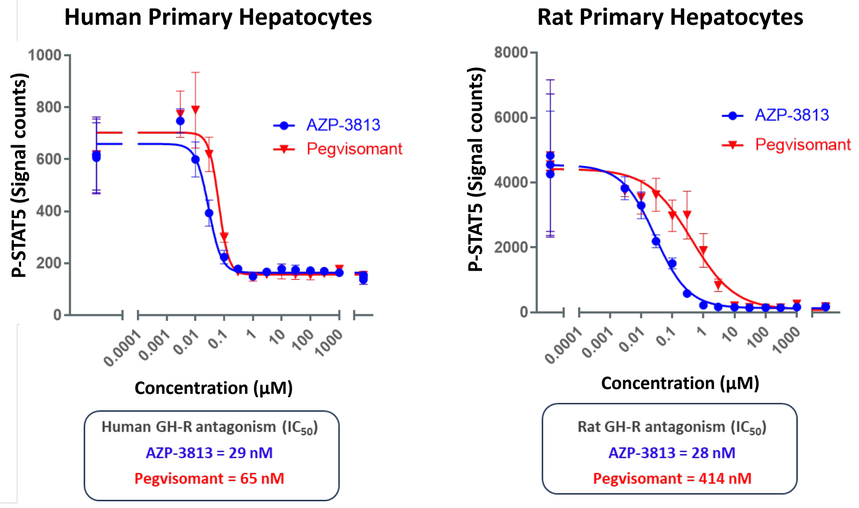


FIG 1: AZP-3813 inhibits the activation/phosphorylation of STAT5 by GH in a dose-dependent manner in hepatocytes. Human primary hepatocytes were treated with 10 nM (ED80) of human recombinant GH and rat primary hepatocytes were treated with 31 nM (ED80) of rat recombinant GH followed by treatment with either AZP-3813 or pegvisomant at concentrations 0.003 µM to 1 mM. Graphs represent mean signal +/- s.d. (n=9 replicates).

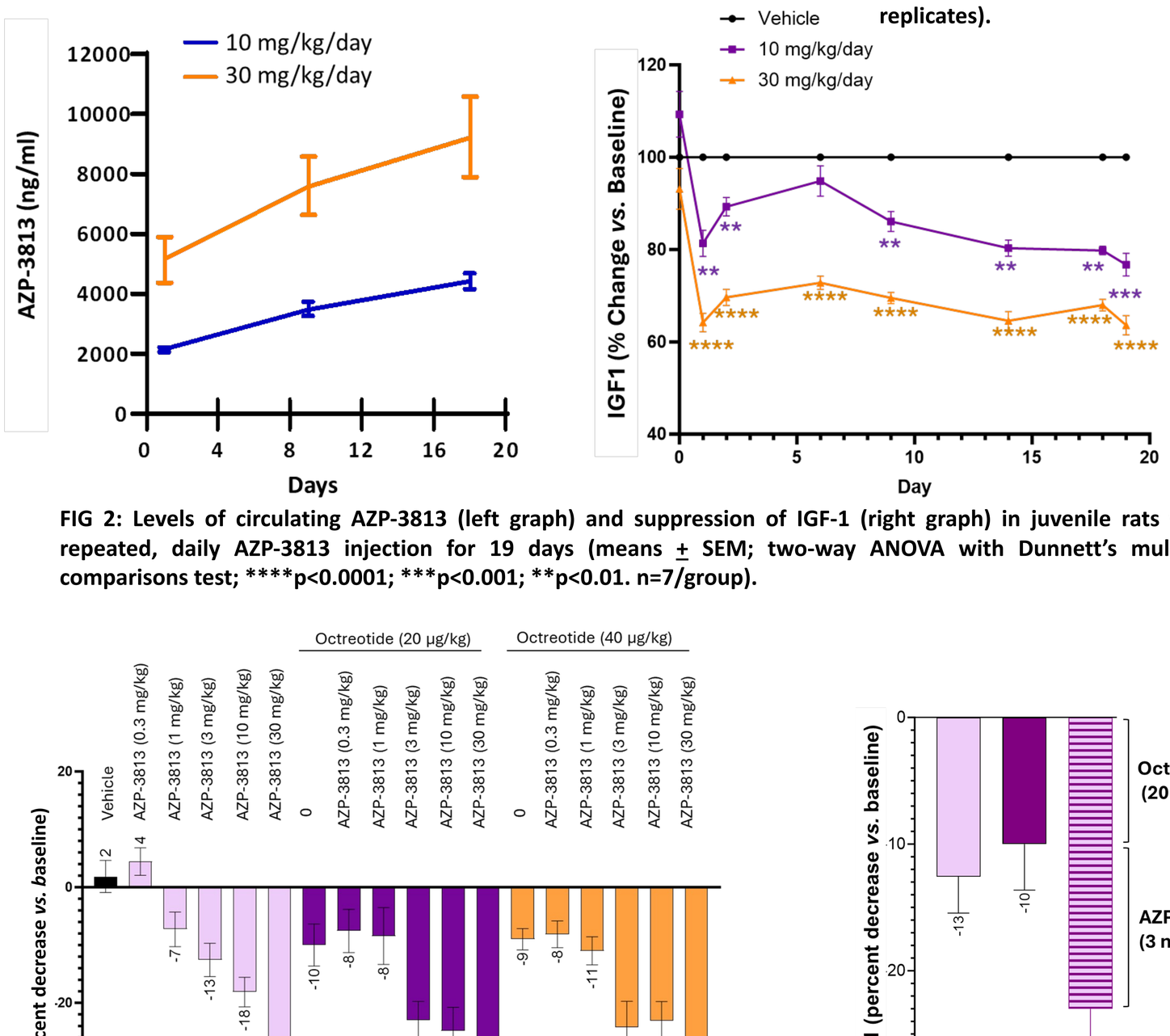


FIG 2: Levels of circulating AZP-3813 (left graph) and suppression of IGF-1 (right graph) in juvenile rats with repeated, daily AZP-3813 injection for 19 days (means ± SEM; two-way ANOVA with Dunnett's multiple comparisons test; ****p<0.0001; ***p<0.001; **p<0.01. n=7/group).

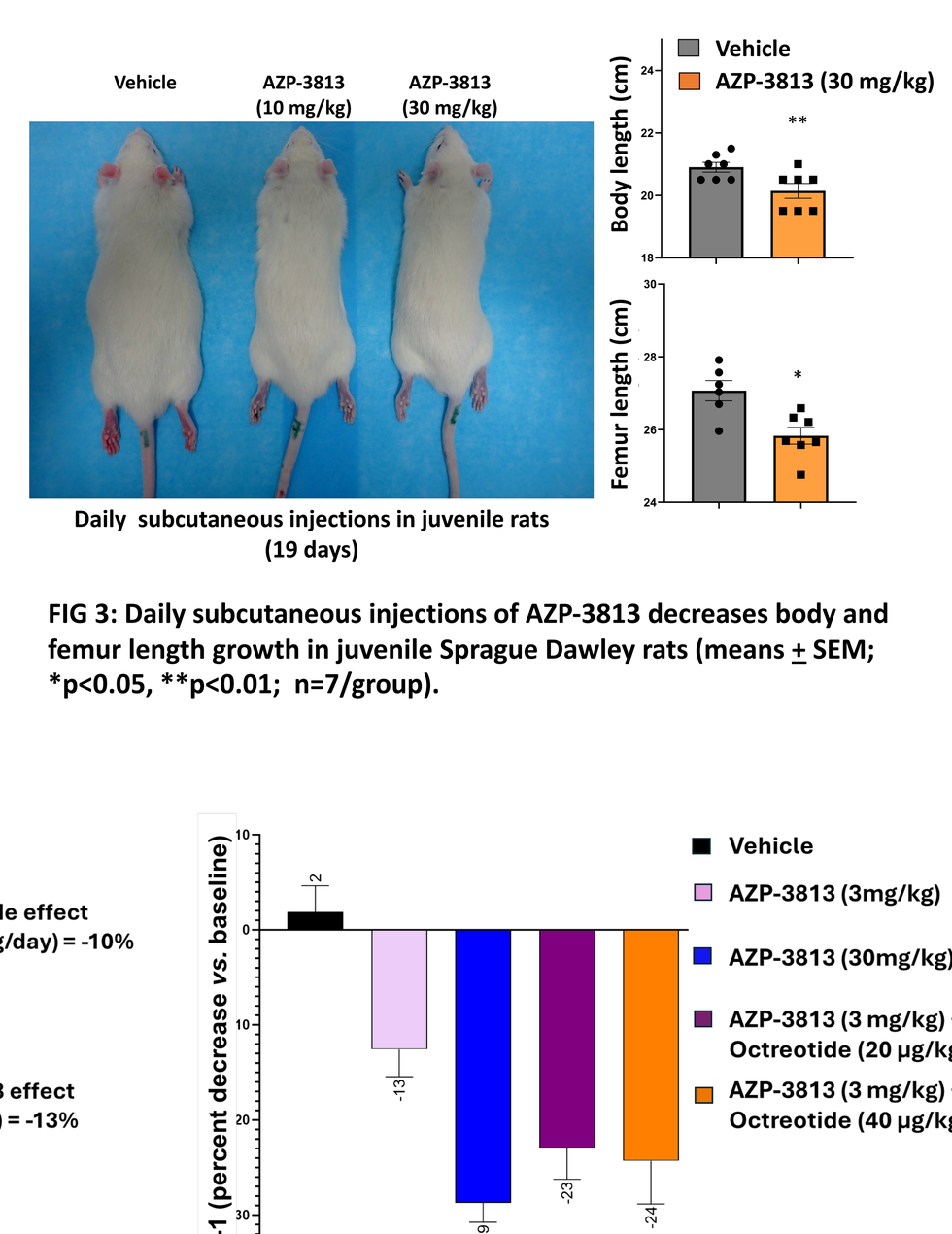


FIG 3: Daily subcutaneous injections of AZP-3813 decreases body and femur length growth in juvenile Sprague Dawley rats (means ± SEM; *p<0.05, **p<0.01; n=7/group).

FIG 4: Dose-dependent suppression of IGF-1 24 hours after a single sc injection of AZP-3813, administered either alone or in combination with infused octreotide in adult rats. AZP-3813 was administered 72 hours after initiating octreotide infusion (means ± SEM; one-way ANOVA followed by Tukey's multiple comparison test; **p<0.01; ***p<0.001; ****p<0.0001 in AZP-3813 +/- octreotide vs. control vehicle treated groups (n=7/group).

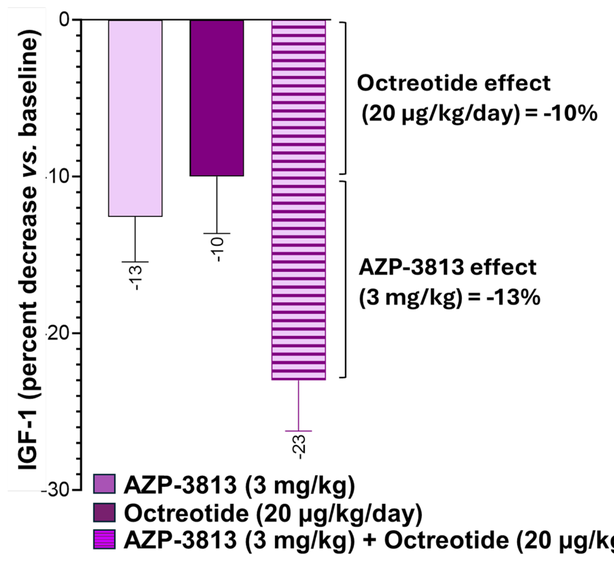


FIG 5: Additive effect of octreotide and AZP-3813 in suppressing serum IGF-1 levels in adult rats exemplified by the AZP-3813 3mg/kg dose (mean of IGF-1 compared to baseline ± SEM. n=7/group).

FIG 6: Octreotide administration reduces the dose of AZP-3813 required for maximum reduction of circulating IGF-1 levels in adult rats (means ± SEM; one-way ANOVA followed by Tukey's multiple comparison test; ns: not significant; *p<0.05 in IGF-1 compared to baseline. n=7/group).

SUMMARY AND CONCLUSION

The results presented here demonstrate that AZP-3813 binds to the GHR with high affinity and, consequently, inhibits GH-stimulated activation of STAT5 *in vitro*. The antagonistic effect of AZP-3813 on the GHR leads to a dose-dependent decrease of circulating IGF-1 levels *in vivo*. In juvenile rats, prolonged AZP-3813 treatment decreased body size and femur length growth, demonstrating that AZP-3813 inhibits GH and IGF-1 action on their target tissues. Co-administration of AZP-3813 with the SSA, octreotide, revealed an additive effect in suppressing circulating IGF-1 levels in rats, and reduced by ten-fold the AZP-3813 dose needed to induce a maximum decrease in IGF-1. These results illustrate the enhanced efficacy of AZP-3813 in suppressing IGF-1 when combined with the SSA, octreotide, and support the use of AZP-3813 as add-on therapy in patients inadequately controlled with SSA treatment.