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Clinical Development of Avexitide for Hyperinsulinemic Hypoglycemia

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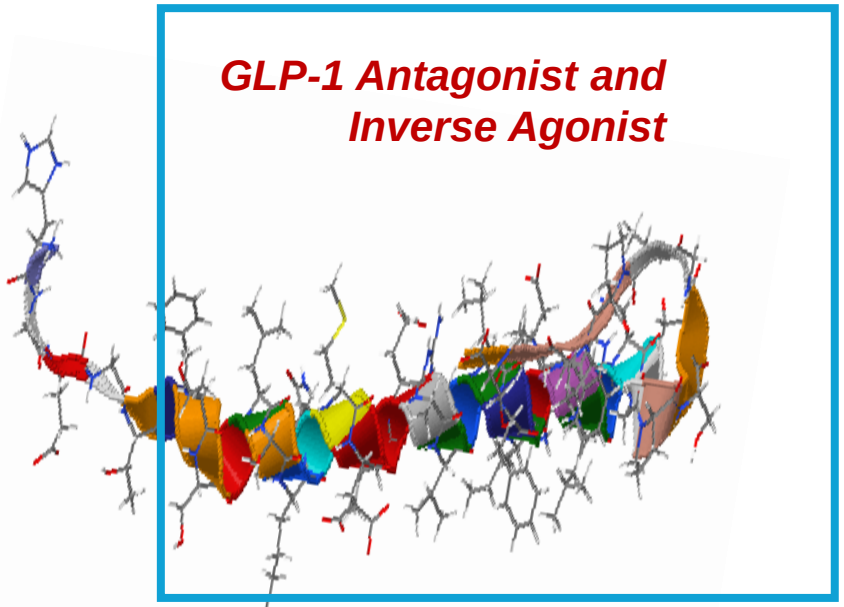
AVEXITIDE (EXENDIN 9-39)

First-in-class GLP-1 Receptor Antagonist with Inverse Agonist Properties

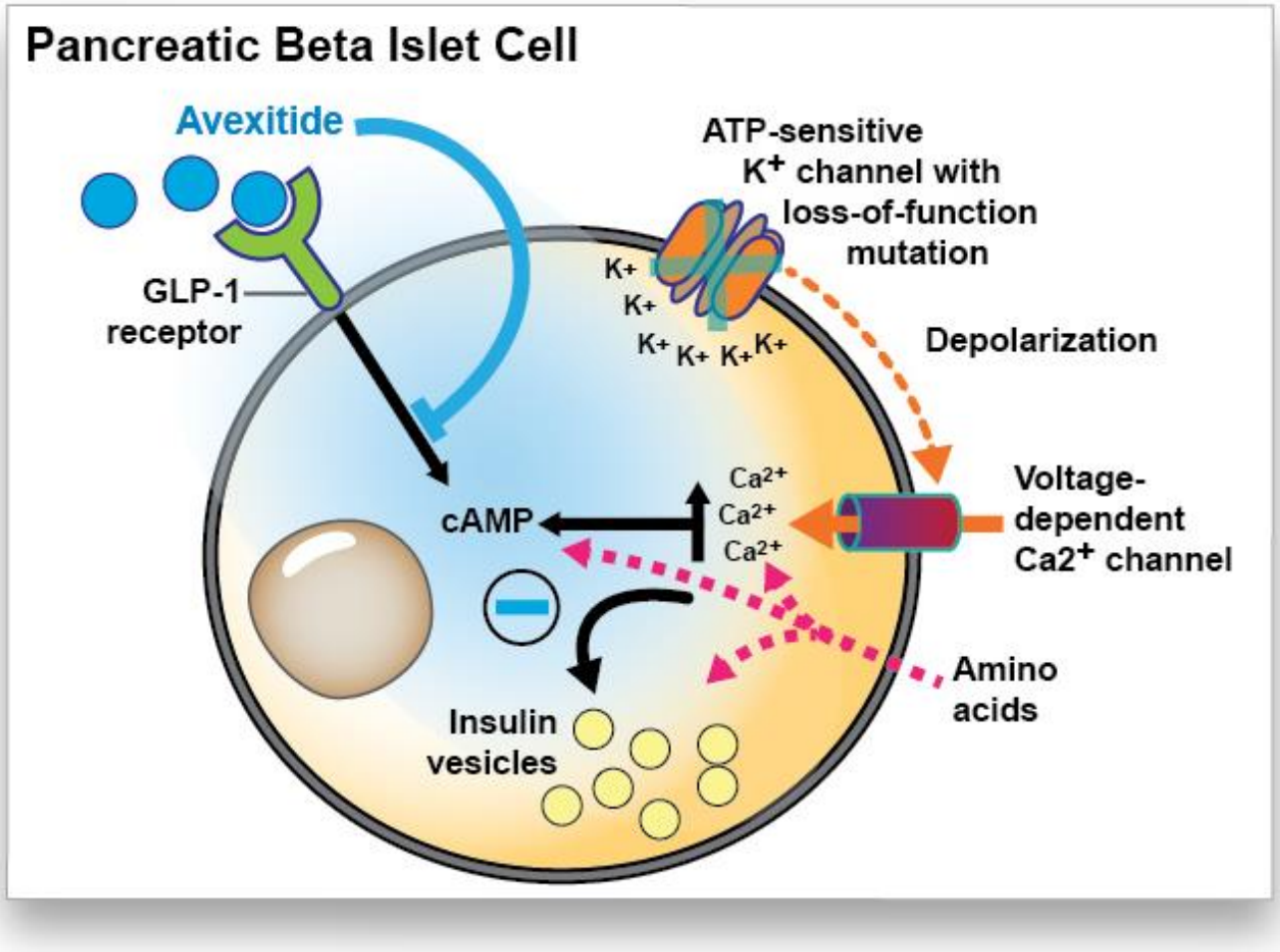
- N-terminus 31-amino-acid fragment of exendin-4, a 39 amino-acid naturally occurring peptide
- Investigational product in development by Eiger BioPharmaceuticals for the treatment of hyperinsulinemic hypoglycemia (HI)
- 39 patients with HI have received avexitide by continuous IV infusion under 3 proof-of-concept studies conducted at CHOP
- Eiger has developed a stable, sterile solution formulation for subcutaneous injection (SC avexitide injection).
- 63 adults have received avexitide SC injection to date
  - 40 healthy volunteers
  - 23 patients with post-bariatric hypoglycemia, of which 18 patients self-injected avexitide once or twice daily for 28 days



CHOP = Children's Hospital of Philadelphia

AVEXITIDE TARGETS THE GLP-1 RECEPTOR

Inhibition of GLP-1 Receptor Signaling Reduces Fasting and Postprandial Hyperinsulinemia



Preclinical studies in a mouse model of K_{ATP}HI[1] and in pancreatic islets from patients with HI[2] have demonstrated critical role of GLP-1r in K_{ATP}HI and elucidated Avexitide's mechanism of action:

- Avexitide binds to the GLP-1r
- Competes with endogenous GLP-1 at the receptor (antagonist)
- Prevents basal GLP-1r signaling (inverse agonist)
- Reduces cAMP-mediated insulin release
- Reduces fasting and postprandial hyperinsulinemia
- Represents a targeted therapeutic approach

1. De Leon et al. *J Biol Chem.* 2008;283(38):25786–25793; 2. Calabria et al. Diabetes. 2012;61(10):2585–2591

PROOF OF CONCEPT DEMONSTRATED IN MULTIPLE CLINICAL TRIALS

Intravenous and Subcutaneous Administration in Patients with Hyperinsulinemic

Route of Administration		Formulation*	Dosing Duration	Patient Number and Age Cohort	Hyperinsulinemic Hypoglycemia Indication
IV Infusion	Children's Hospital of Philadelphia	Lyophilized Formulation	Single Dose	10 adolescent & adult	Congenital Hyperinsulinism
		Lyophilized Formulation	Single Dose	16 children	Congenital Hyperinsulinism
		Lyophilized Formulation	Single Dose	13 neonates & infants	Congenital Hyperinsulinism
	EIGER BIOPHARMACEUTICALS	Lyophilized Formulation	Single Ascending Dose	8 adults	Post-bariatric Hypoglycemia
SC Injection		Lyophilized Formulation	Single Ascending Dose	8 adults	Post-bariatric Hypoglycemia
		Lyophilized Formulation: 15 patients Solution Formulation: 5 patients	Multiple Ascending Dose Up to 3 Days Twice Daily Injection	20 adults	Post-bariatric Hypoglycemia
		Solution Formulation	Single Ascending Dose; Multiple Ascending Dose 3 Days Twice Daily Injection	40 adults	Healthy Volunteers
		Solution Formulation	28 Days Outpatient Administration Once and Twice Daily Injection	18 adults	Post-bariatric Hypoglycemia

**Lyophilized Formulation = lyophilized avexitide reconstituted prior to intravenous or subcutaneous administration; Solution Formulation = stable, sterile solution formulation of avexitide for subcutaneous injection.*

CONCLUSIONS

- Avexitide is a first-in-class GLP-1 receptor antagonist with inverse agonist properties
- The GLP-1 receptor plays an important role in the mechanisms mediating K_{ATP}HI
- Three Proof of Concept studies of Avexitide in K_{ATP}HI at CHOP (IV infusion; n=39)
  - Demonstrated reduction in fasting and postprandial hyperinsulinemic hypoglycemia
- Eiger has developed a stable, solution formulation of avexitide for subcutaneous injection (SC avexitide injection) and has evaluated this formulation in 63 adults
- SC avexitide injection has been well-tolerated with no treatment-related SAEs or withdrawals
- Future investigations in patients with K_{ATP} HI may employ SC avexitide injection

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