Secretion and Rescue Hypoglycemia in Neonatal Rat Models of Congenital Hyperinsulinism

Oral Administration of CRN04777, a Nonpeptide Selective SST5 Agonist, Suppresses Insulin Secretion and Rescue Hypoglycemia in Neonatal Rat Models of Congenital Hyperinsulinism

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CRN04777 is an orally administered nonpeptide that is a potent and selective agonist of somatostatin 5 (SST5) receptors and is currently under development for the treatment of congenital hyperinsulinism (HI), the most common cause of persistent hypoglycemia in newborns and infants. Congenital HI arises from mutations within the insulin secretion pathway and is characterized by excessive and/or inappropriate insulin secretion by pancreatic islet beta cells. This excess insulin can result in profound hypoglycemia which can lead to neurological impairment, coma, and even death if not treated promptly. The neuropeptide somatostatin is an important modulator of hormonal signaling in the pancreas, and SST5 activation has been shown to suppress insulin and raise blood glucose, thus providing a potential treatment mechanism for patients with congenital HI. We characterized the ability of CRN04777 to raise blood glucose and lower plasma insulin in preclinical models using neonatal (PND7-11) rats. Oral administration of CRN04777 in neonatal rats suppressed insulin secretion and dose-dependently increased blood glucose levels for up to 6 hours after a single dose. Furthermore, the CRN04777 mediated increase in blood glucose was sustained over 5 days of repeated oral administration.

The most common mutations underlying congenital HI are found in the genes encoding the ATP-sensitive potassium (KATP) channel, which controls the membrane potential of pancreatic beta cell, and children with KATP-dependent HI are typically unresponsive to diazoxide, the only FDA-approved drug for HI. Sulfonylurea drugs, such as glyburide, close KATP channels and can be used to induce hyperglycemic hyperinsulinemic states in rats that mimics some of the characteristics of KATP-HI. As expected, a single administration of glyburide in neonatal rats induced a pronounced increase in plasma insulin levels, with a concomitant decrease in blood glucose that persisted for several hours. Oral administration of CRN04777 rescued the glyburide-induced hyperinsulinemic hyperglycemia, lowering insulin levels and restoring blood glucose levels to >60 mg/dL. These findings provide evidence that CRN04777 is an efficacious nonpeptide SST5 agonist that suppresses insulin in neonatal rats, and, in addition, oral administration of CRN04777 rescued hypoglycemia in a neonatal rat model of congenital HI, demonstrating its potential as an oral therapeutic for children with congenital HI.

Conclusions

CRN04777 has been shown to be a potent and selective SST5 receptor agonist that suppresses insulin secretion and rescue hypoglycemia in neonatal rat models of congenital HI. The drug has been shown to be safe and effective in preclinical studies, and phase 1 clinical trials are currently ongoing. Therefore, CRN04777 has the potential to be a new oral therapeutic for children with congenital HI, demonstrating its potential as an oral therapeutic for children with congenital HI, demonstrating its potential as an oral therapeutic for children with congenital HI.