Selective Nonpeptide Somatostatin Subtype 5 (sst5) Agonists Suppress Induced Insulin Secretion in Pancreatic Islets from both Rats and Healthy Human Donors.

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Hypoglycemia is a heterogeneous condition in which dangerously low blood sugar levels are caused by improperly regulated insulin secretion from pancreatic β-cells. The most severe form of hypoglycemia arises from congenital hyperinsulinemia (CHI), a set of genetic disorders in which the islet β-cells become unresponsive to glucose and continue to secrete large amounts of insulin, often resulting in severe hypoglycemia, especially in newborns and infants, and prompt recognition and treatment are essential to prevent long-term neurological complications, and even death. The neuropathy somatostatin is an important mediator of hormonal signaling from the paracrine mediated by different somatostatin receptor (sst) subtypes. Glucagon secretion is stimulated through sst5 and insulin secretion is inhibited by sst5. Therapeutic potential of sst5 agonists is high, as sst5 expression is more widespread than sst2a and sst3, and sst5 agonists are implicated in the control of insulin secretion from the β-cell.

We have developed several potent and selective sst5 agonists that inhibit glucose- and tolbutamide-stimulated insulin secretion from human and rat islets. This pharmacologic profile may be useful for the treatment of congenital hyperinsulinism.

• Glucostimulated insulin secretion is equally inhibited by peptide sst5 agonists (SS14, pasireotide, and octreotide) from human and rat islets (60% inhibition).
• Tolbutamide-induced insulin secretion from human islets is inhibited by peptides agonists: SS14 > pasireotide > octreotide, suggesting the participation of other sst receptors, in addition to sst2 and sst5.
• sst2-selective nonpeptide agonists (agonist 1-3) inhibit glucose- and tolbutamide-stimulated insulin secretion from human islets. Compounds 2 & 3 suppress insulin secretion to the same degree as a maximally effective concentration of diazoxide.
• A potent, sst2-selective nonpeptide agonist (agonist 4), has a limited effect (similar to octreotide) in glucose- and tolbutamide-stimulated insulin secretion from human islets.
• Agonist 4, however, demonstrates greater insulin suppression than agonist 1 in rat islets, suggesting that insulin secretion regulation by sst2 is more important in rat than in human islets.

Conclusions

Hypoglycemia is a heterogeneous condition in which dangerously low blood sugar levels are caused by improperly regulated insulin secretion from pancreatic β-cells. The most severe form of hypoglycemia arises from congenital hyperinsulinemia (CHI), a set of genetic disorders in which the islet β-cells become unresponsive to glucose and continue to secrete large amounts of insulin, often resulting in severe hypoglycemia, especially in newborns and infants, and prompt recognition and treatment are essential to prevent long-term neurological complications, and even death. The neuropathy somatostatin is an important mediator of hormonal signaling from the paracrine mediated by different somatostatin receptor (sst) subtypes. Glucagon secretion is stimulated through sst5 and insulin secretion is inhibited by sst5. Therapeutic potential of sst5 agonists is high, as sst5 expression is more widespread than sst2a and sst3, and sst5 agonists are implicated in the control of insulin secretion from the β-cell.

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