Selective somatostatin 5 (SST5) and somatostatin 2 (SST2) nonpeptide agonists potently suppress glucose- and tolbutamide-stimulated dynamic insulin secretion from isolated human islets

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Conclusions

We have developed several potent and selective nonpeptide SST5 and SST2 agonists that inhibit glucose- and tolbutamide-stimulated insulin secretion from human islets more potently than diazoxide, a well-known inhibitor of insulin secretion.

- Stimulation of pancreatic β-cells with high glucose and tolbutamide results in dynamic insulin secretion in a biphasic manner. The magnitude of the response varies among donors, as expected.
- Diazoxide at 100 µM inhibits glucose-stimulated insulin secretion but has a small effect on tolbutamide-stimulated insulin secretion.
- SST5, a potent agonist of all SST receptors, inhibits insulin secretion by >75% in both conditions, glucose- and tolbutamide-stimulated secretion.
- The SST5-selective nonpeptide agonists 5a and 5b (100 nM) suppress 35 and 75% insulin secretion, respectively. These results agree with the established in vitro pharmacology, showing that agonist 5b is 8-10 fold more potent than agonist 5a and more importantly it is as effective as SST4 on insulin secretion suppression.
- The SST3-selective nonpeptide suppresses <50% insulin secretion at 0.1 µM, while the SST3 and SST4-selective antagonists have no effect on insulin secretion.

Somatostatin 14 (SS14) and nonpeptide SST5 and SST2 specific agonists suppress dynamic glucose- and tolbutamide-stimulated insulin secretion from human islets

- SS14, a potent agonist of all SST receptors, inhibits insulin secretion by 50% at 100 nM and has a small effect on tolbutamide-stimulated insulin secretion.
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Glucose and tolbutamide stimulate insulin secretion in a biphasic manner in islets from healthy donors

- Insulin secretion is initiated by closing the KATP channel in β-cells (red dotted line) in response to glucose, and stimulation of insulin secretion that is not concentration-dependent.

Diazoxide inhibits glucose- but not tolbutamide-stimulated insulin secretion from human islets

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