Inhibitors of GOAT: Ghrelin O-Acyltransferase

New Mechanism for Inhibition of Ghrelin

Ghrelin is activated by the addition of an octanoyl group to its Ser-3 by an enzyme known as GOAT, or ghrelin O-acyltransferase. Ghrelin's stimulation of appetite depends on this octanoyl group. Blocking this enzyme would presumably block the hunger effect of Ghrelin.

Findings have been published suggesting that by adding peptides with the same sequence as the first five amino acids of Ghrelin, it is possible to inhibit the activity of GOAT, and therefore Ghrelin.

Phoenix synthesized an octanoylated Ghrelin pentapeptide over four years ago, along with related analogs (des-octanoylated, biotin-labeled, I-125 labeled, 4 and 5 amino acid length fragments…) and a peptide with a diaminopropionic acid (DAP) in the third position, which research suggests is 45 times more potent as an inhibitor of GOAT.

Phoenix Pharmaceuticals, Inc.

Amino acid sequence of human Ghrelin O-acyltransferase (GOAT)

```
MEWLWLFFLH PISFYQGAAF PFALLFNYLC  30
IMDSFSTRAR YLFLLTGGGA LAVAAMGSYA  60
VLVFTPAVCA VALLCSLAPQ QVHRWTFCFQ  90
MSWQTLCHLG LHYTEYYLHE PPSVRFCITL 120
SSLMLLTQRV TSLSLDICEG KVKAASGGFR 150
SRSSLSEHVC KALPYFSYLL FFPALLGGSL 180
CSFQRFQARV QGSSALHPRH SFWALSWRGL 210
QILGLECLNV AVSRVVDAGA GLTDCQQFEC 240
IYVVWTTAGL FKLTYYSHWI LDDSLLHAAG 270
FGPELGQSPG EEGYVPDADI WTLERTHRIS 300
VFSRKWNQST ARWLRRLVFQ HSRAWPLLQT 330
FAFSAWWHGL HPGQVFGFVC WAVMVEADYL 360
IHSFANEFIR SWPMRLFYRT LTWAHTQLII 390
AYIMLAVEVR SLSSLWLLCN SYNSVFPMVY 420
CILLLLAKR KHKCN 435
```

transmembrane

Inhibition of ghrelin O-acyltransferase (GOAT) by octanoylated pentapeptides

The discovery of ghrelin O-acyltransferase (GOAT) opens the way to the design of drugs that block the attachment of an octanoyl group to the appetite-stimulating peptide hormone ghrelin, potentially preventing obesity. Here, we develop a biochemical assay that uses membranes from insect cells infected with baculovirus encoding mouse GOAT. The GOAT-containing membranes transferred the [3H] octanoyl group from [3H]octanoyl CoA to recombinant proghrelin in vitro. Transfer depended on the serine at residue 3 of proghrelin, which is the known site of acylation. GOAT also transferred [3H]octanoyl to a pentapeptide containing only the N-terminal five amino acids of proghrelin. GOAT activity could be inhibited by an octanoylated ghrelin pentapeptide, and its potency was enhanced 45-fold when the octanoylated serine-3 was replaced by octanoylated diaminopropionic acid. The data suggest that GOAT is subjected to end-product inhibition and this inhibition is better achieved with substrates having the octanoyl group attached through an amide linkage rather than the corresponding ester. These insights may facilitate the future design of useful inhibitors of GOAT.

Yang J., et al. PNAS. 2008, July 31

Available Products

B-032-21	Ghrelin (1-5) (Ser3-Octanoyl) Amide, Biotin-labeled	100ug
T-032-15	Ghrelin (1-5) Amide, (Ser3-Octanoyl), [Tyr0]-I-125 labeled	10 µCi
T-032-17	Ghrelin (1-5) Amide, (Ser3-Octanoyl), [Tyr4]-I-125 labeled	10 µCi
032-14	Ghrelin (1-5) Amide, [Dap3]-Octanoyl (Human, Rat, Mouse)	200 µg
031-42	Ghrelin (1-5) Amide, [Ser3-(Des-Octanoyl)] (Human, Rat, Mouse, Bovine, Canine)	200 µg
B-032-22	Ghrelin (1-5) Amide, [Ser3-Des-Octanoyl], Biotin-labeled	100ug
T-032-16	Ghrelin (1-5) Amide, [Ser3-Des-Octanoyl], [Tyr0]-I-125-labeled	10uCi
T-032-18	Ghrelin (1-5) Amide, [Ser3-Des-Octanoyl], [Tyr4]-I-125-labeled	10uCi
031-41	Ghrelin (1-5)-Amide, [Ser3-Octanoyl], (Human, Rat)	100 µg
T-032-19	Ghrelin (1-6) Amide, (Ser3-Octanoyl) [Tyr6]-I-125 labeled	10 µCi
B-032-24	Ghrelin (1-6) Amide, [Ser3-Des Octanoyl] [Lys6]-Biotin-labeled	100ug
T-032-20	Ghrelin (1-6) Amide, [Ser3-Des Octanoyl] [Tyr6]-I-125-labeled	10 µCi
B-032-23	Ghrelin (1-6) Amide, [Ser3]-Octanoyl, [Lys6]-Biotinyl	100µg
032-11	Ghrelin O-acyltransferase (GOAT) (181-199) (Human)	100 ug
032-12	Ghrelin O-acyltransferase (GOAT) (356-375) (Human)	100 ug