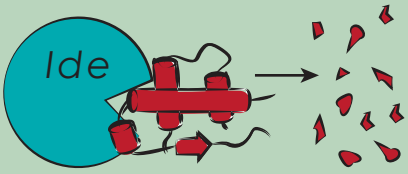
THE SHORT ANSWER

ISSUE 4, JUNE 2014

Anti-diabetic activity of insulin-degrading enzyme inhibitors mediated by multiple hormones.

Maianti J.P., McFedries A., Foda Z.H., Kleiner R.E., Du X.Q., Leissring M.A., Tang W.J., Charron M.J., Seeliger M.A., Saghatelian A., Liu D.R. *Nature*. 2014 May 21. doi: 10.1038/nature13297. [Epub ahead of print]

BACKGROUND:



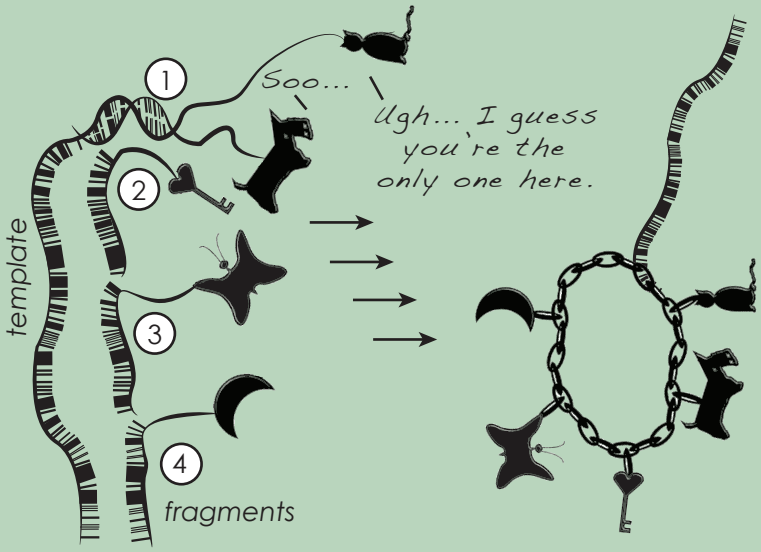
Inhibition of Insulin-degrading enzyme (Ide) should make a nice alternative to treating diabetes patients with insulin, but Ide$^{-/-}$ mice counterintuitively have higher blood sugar than wild type mice after being given a bunch of sugar.

HYPOTHESIS:

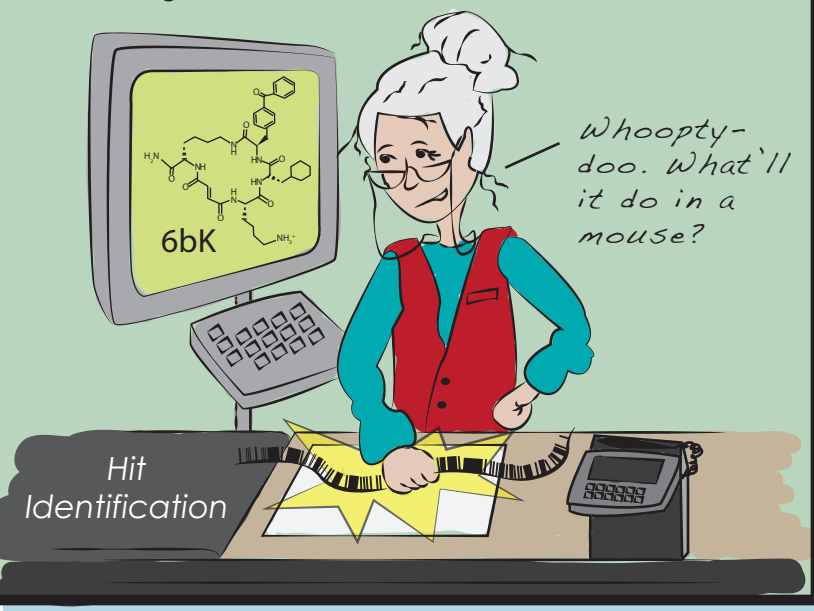
A potent and specific Ide inhibitor could help to solve this mystery and establish whether or not Ide is a good drug target, by allowing control over when Ide is active or turned off.

APPROACH:

Use DNA-templated synthesis to make a >13,000-member library of macrocycles and screen for tight Ide binders.



>13,000 templates + boatloads of fragments made >13,000 macrocycle candidates that were screened for binding to immobilized Ide.



EVIDENCE:

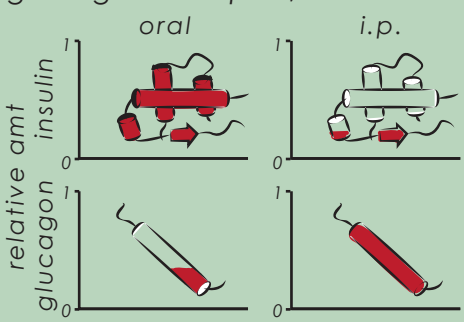
(Doesn't bind in active site.)

6bK was identified as a potent (IC_{50} = 50 nM) and specific (>1,000-fold selectivity over all other metallo-proteases tested) inhibitor of Ide, so mice were dosed with it before being administered glucose.

Oral glucose tolerance test

Intraperitoneal (i.p.) glucose tolerance test

Turns out, Ide degrades glucagon and amylin in vivo in addition to insulin. Mice given i.p. glucose secrete less insulin and more glucagon than those given oral glucose. Glucagon triggers release of glucose, explaining the increased blood sugar. When the i.p. glucose tolerance test is done in mice lacking the glucagon receptor, 6bK has no effect. Therefore, chronic Ide inhibition could lead to more glucagon being left around, meaning more glucose released. Remember the Ide$^{-/-}$ mice? There you go.



@O'Reilly Science Art

CONCLUSIONS:

The discovery and in vivo analysis of the Ide inhibitor 6bK has shown Ide inhibition to be a promising therapeutic strategy for the treatment of diabetes, but they have also very importantly revealed that the hormones glucagon and amylin are also affected, and the timing of patient dosing will be crucial to its therapeutic benefit. 6bK also provides a starting point from which to develop a drug that could ultimately be used in humans.