

Successful synthesis of a new insulin analogue

August 8 2017

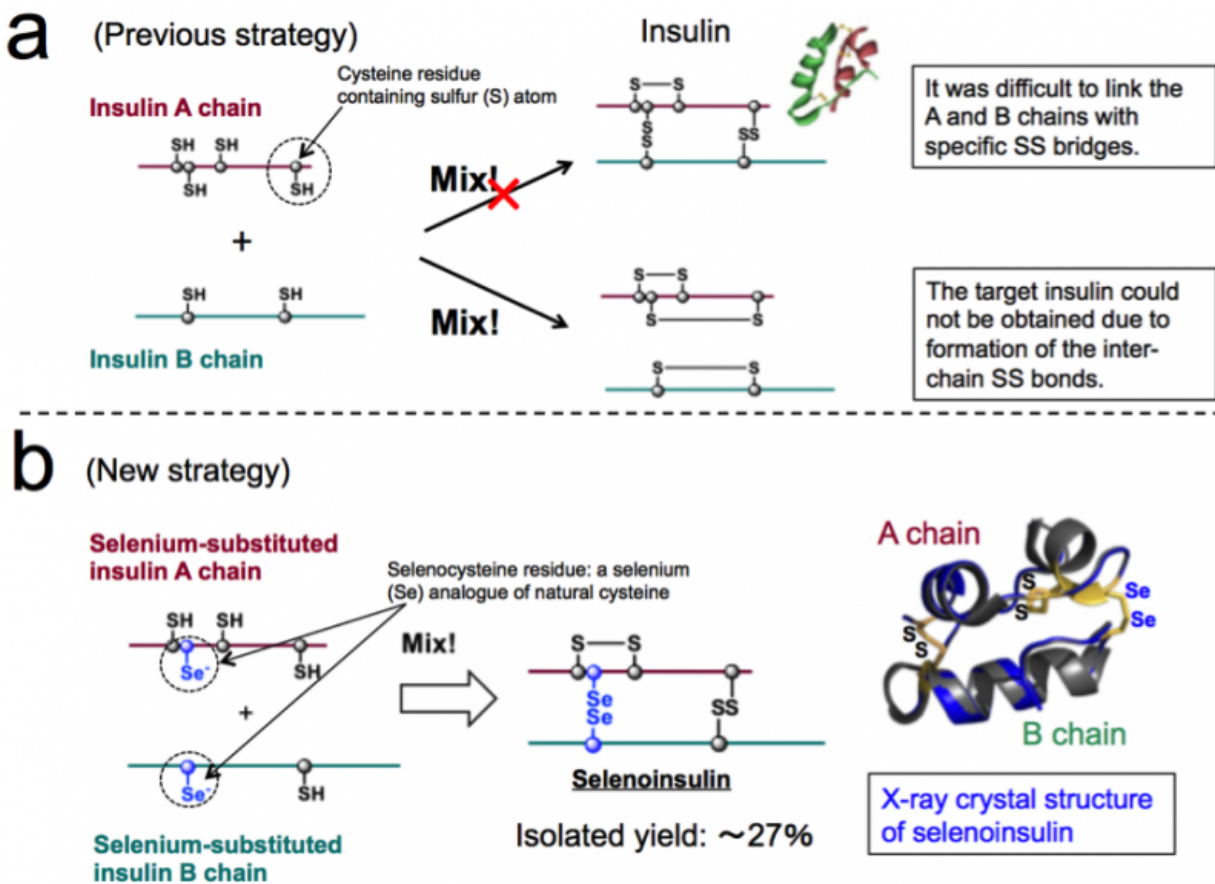


Figure 1. Chemical synthesis of insulin. (a) Previous strategy based on the coupling between native insulin A- and B-chains. (b) New strategy exploiting unique nature of selenocysteine and X-ray crystal structure of selenoinsulin. (These figures are quoted from the original article with modifications.). Credit: Osaka University

A group of researchers has developed synthetic insulin analogues selenoinsulin (Se-Ins) through the replacement of the interchain disulfide in bovine pancreatic insulin (BPIns) with a diselenide bridge.

This group demonstrated that Se-Ins had a nearly identical structure and bioactivity comparable to those of BPIns, and that it had enhanced resistance to IDE degradation. This holds promise for application of Se-Ins to a long-lasting insulin preparation in diabetes therapy.

After circulating in the blood stream, insulin is degraded by an insulin degrading enzyme (IDE) in the kidney and excreted in the urine. This group thought that the production of insulin with high resistance to degradation by IDE would lead to the development of a new type of long-lasting insulin preparations that could circulate in the body for a long time.

Insulin consists of two polypeptide chains: A [chain](#) and B chain, connected by a disulfide [bond](#) (Se–Se bond), so it's difficult to take insulin only from these chains because of Se–Se bonds. Thus, this group thought that if insulin A-chains and B-chains containing selenium (Se) instead of sulfur (S), were used, the diselenide bond (Se–Se bond) would be formed quickly and then the chain-assembly reaction could be carried out efficiently, as Se is more reactive than S.

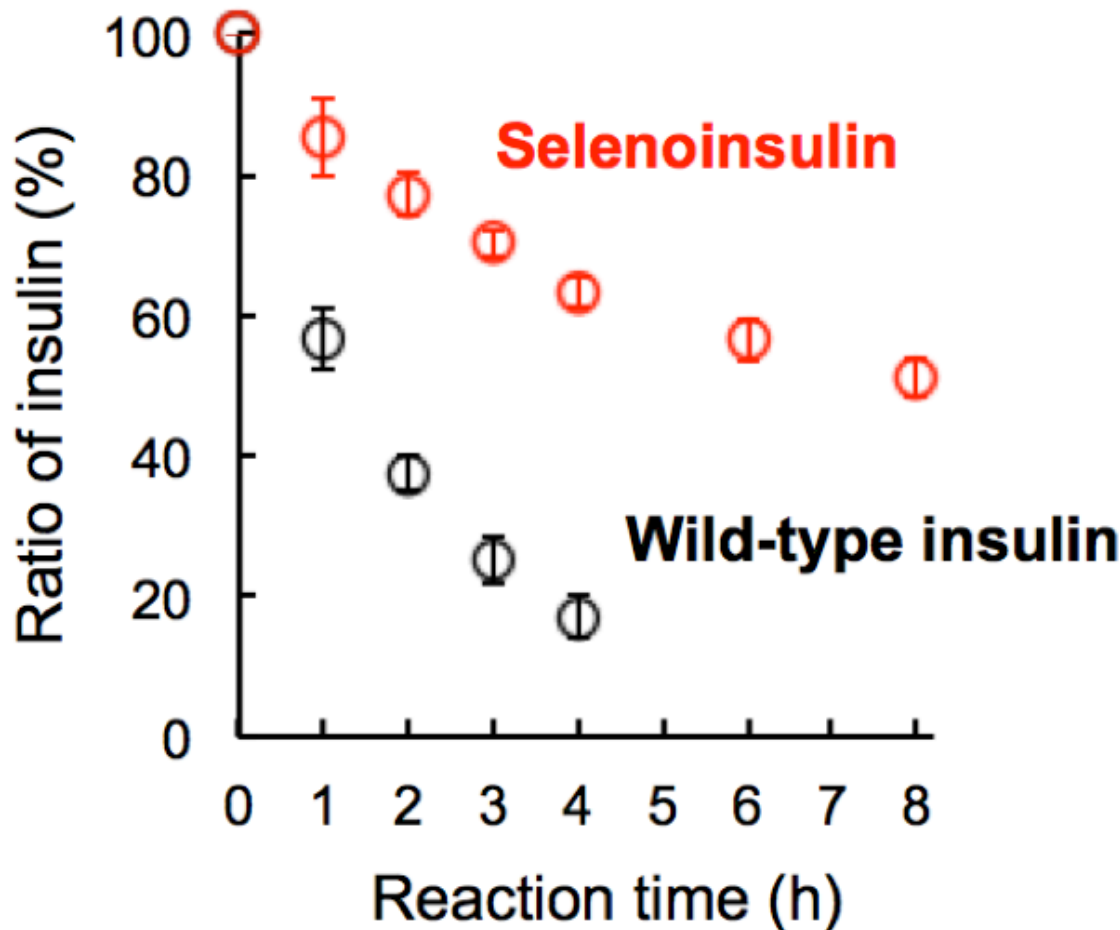


Figure 2. Degradation of selenoinsulin (red) and wild-type insulin (black) by insulin-degrading enzyme (IDE). (This figure was quoted from the original article with slight modifications.). Credit: Osaka University

In addition, Se-Se bonds are more stable than S-S bonds, so this group anticipated that Se-Se bonds would give extra structural robustness on the insulin fold, thus resulting in the enhanced resistance to IDE degradation due to its intrinsic stability. Based on this concept, this

group succeeded in the synthesis of Se-containing insulin A and B chains, as well as obtaining Se-Ins at the isolation yield of up to 27% by reacting peptide chains under optimal conditions.

This [group](#) demonstrated that Se-Ins had a nearly identical structure to that of BPIIns, suggesting that Se-Ins has a bioactivity comparable to that of BPIIns. Experiments of degradation of BPIIns and Se-Ins by using IDE showed that the [degradation](#) rate of Se-Ins was much slower than that of BPIIns. From this, it is thought that Se-Ins has a long-lasting nature and could be a new class of long-acting [insulin](#) analogues for diabetes therapy.

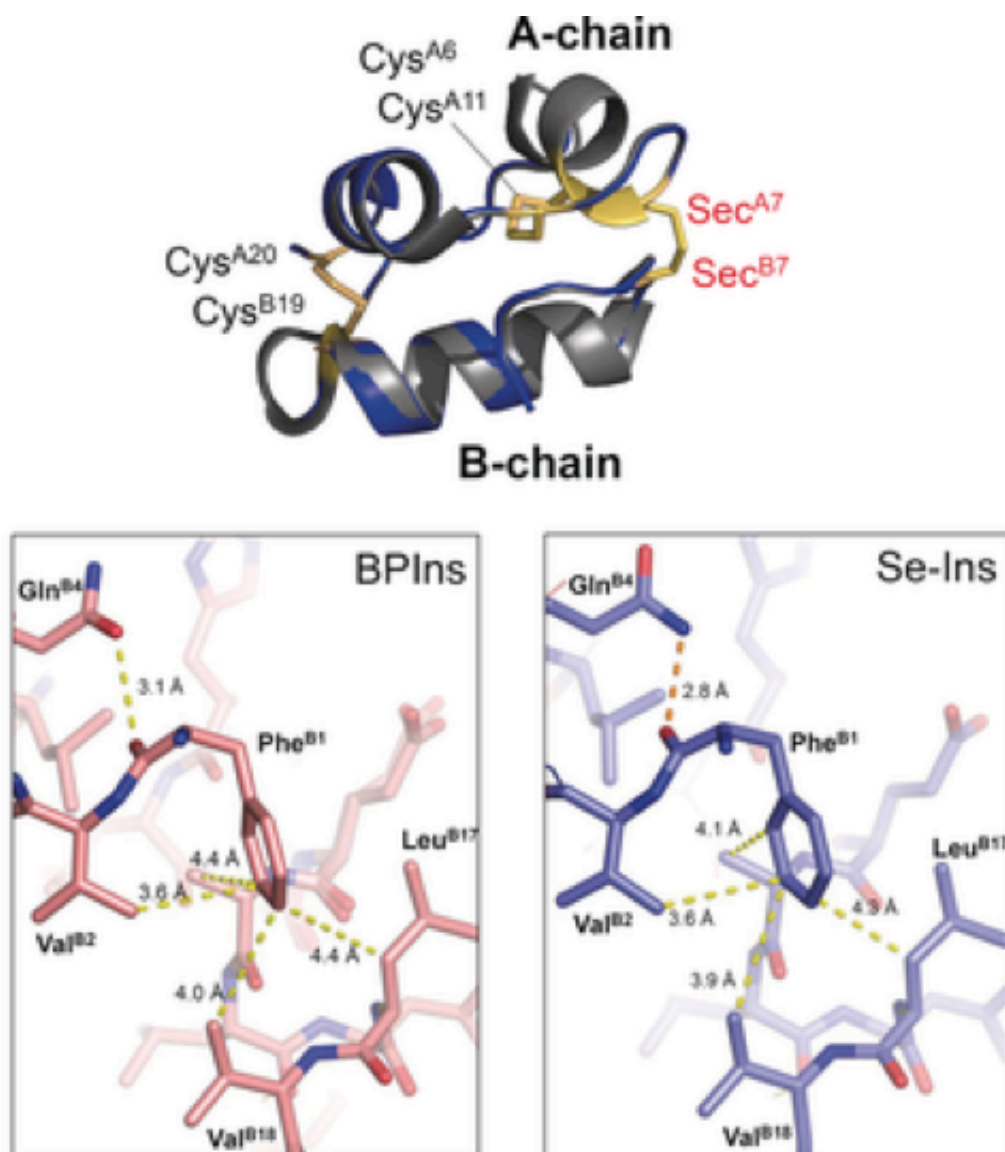


Figure 3. Preparation of Selenoinsulin as a Long-Lasting Insulin Analogue.
Credit: Osaka University

More information: Kenta Arai et al. Preparation of Selenoinsulin as a Long-Lasting Insulin Analogue, *Angewandte Chemie International Edition* (2017). DOI: [10.1002/anie.201701654](https://doi.org/10.1002/anie.201701654)

Provided by Osaka University

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