4.3: Treatments for Type I Diabetes

Type I diabetes patients may have genetic limitations in producing sufficient quantities of insulin, which means that they will not be able to respond to changes in blood glucose concentrations. One treatment strategy that has emerged is to supply exogenous insulin to the body (which can be prepared synthetically or obtained from biological sources). In this way, the insulin producing functions of β-cells are replaced. (Figure 4.7)

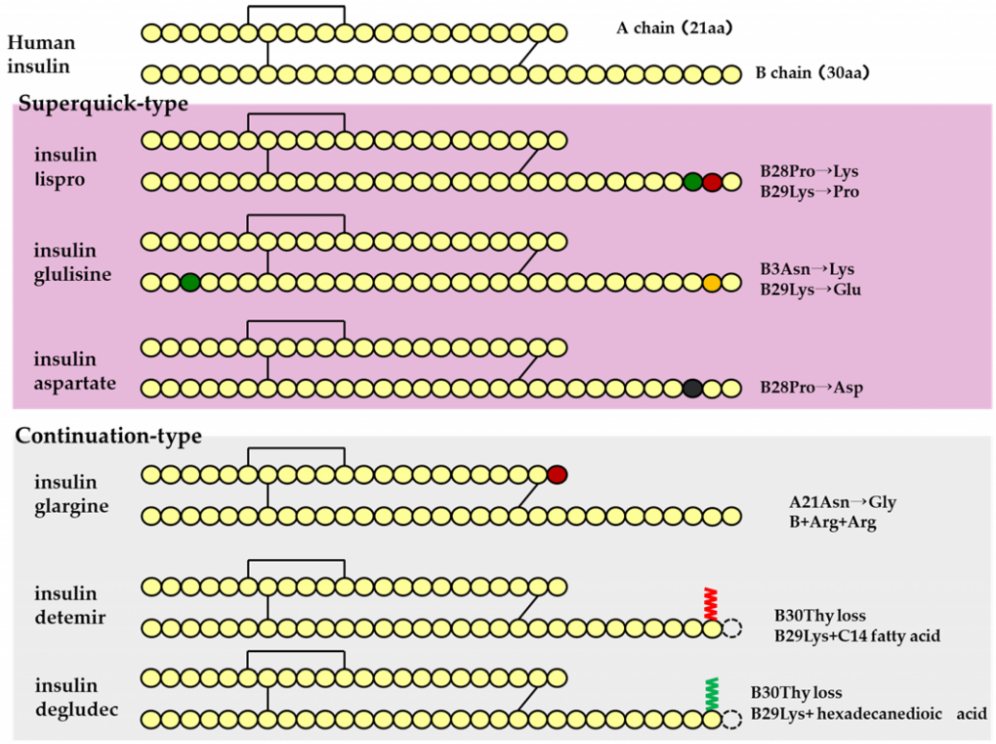

Figure 4.7 Schematic diagram of the different types of insulin-based pharmacological agents. Image Source: (Fig 4) by Takuo Ogihara, Kenta Mizoi and Akiko Ishii-Watabe is used under a CC-BY 4.0 license.

Short Acting Agents

The first strategy involves supplying insulin directly (in the form that it naturally exists in the body). This agent is called **Regular Insulin**. Regular Insulin has the exact same protein sequence as human insulin, and therefore also forms the same hexameric structure in the presence of Zn^{2+}. The main difference is that Regular Insulin is injected subcutaneously (unlike natural insulin which enters the blood stream directly from pancreatic β-cells). The direct release of natural insulin into the blood stream leads to near instantaneous dissociation of the hexamers. However, in subcutaneous injections, the hexamers need to dissociate into smaller monomers before they can find their way into the blood stream. This means that there is a delayed onset of action, as the insulin needs to dissociate into monomers before it can be effectively absorbed, which can take approximately 30 – 60 min. This can be inconvenient, because if a patient is consuming food, they would need to administer an injection and wait for ~30 min before eating.

Rapid Acting Agents

To help compensate for the delayed onset of action, different modifications were generated and evaluated in the peptide sequence of insulin. One modification that demonstrated improved efficacy involved switching Pro and Lys at positions B28 and B29 respectively. (Figure 4.7) This amino acid switch destabilized the hexadimerization interaction and resulted in rapid dissociation, which led to rapid absorption following injection. This resulting absorption profile is less than 15 min, and this version of insulin is called **Insulin Lispro**.

Another version that was generated is called **Insulin Aspart** where the Pro at position B28 was replaced with Asp. The newly introduced negative charge destabilizes the hexadimerizaiton interface, leading to a rapid absorption profile as seen with Insulin Lispro. Comparatively, Insulin Lispro has a slightly faster absorption rate and faster plasma peak time as well as rate of decline,

although Insulin Aspart demonstrates slightly better stability. However, these differences are minor, and the real-world use of these products is relatively indistinguishable.

Insulin Glulisine is another version of insulin where Gly at B3 and Pro at B28 are replaced with Lys and Glu respectively. In addition to these modifications, the formulation contains polysorbate 20 instead of Zn^{2+}. This becomes important because Zn^{2+} is required to maintain the insulin as hexamers. Without the hexamer formation, there is a significantly faster rate of absorption than Insulin Lispro or Insulin Aspart.

Intermediate Acting Agents

There are also relatively slower acting agents as well, with the most common version as **Neutral Protamine Hagedorn (NHP) Insulin**. In this case, the insulin molecule has the exact same sequence as naturally occurring insulin, but protamine is also included in the formulation. Protamine is a highly positively peptide and the introduction of this cation species creates a large, aggregated network of insulin hexamers. Once injected, insulin monomers need to be released from the hexameric structure, but also need to snake their way out of the mesh-like formulation. This leads a slow release of insulin over a period of hours, and NHP Insulin has a more delayed onset of action. NHP Insulin helps provides a steady low supply of insulin to the bloodstream, without repeated or continuous injections.

Long-Acting Agents

There are also agents that lead to significantly longer periods for onset of action, where the release of insulin is further delayed. These long-acting agents have similar pharmacokinetic profiles that lead to insulin release over 12-24 h. **Insulin Glargine** is the most prescribed long-acting agent (where A21 has Gly that replaces an Asn, and two Arg residues are added to the C-terminus of the B-chain). These changes lower the pI of the protein to 6.7, which results in precipitation at neutral pH as well as at the site of injection. Over time, Insulin Glargine will slowly re-enter solution and dissociate into monomers that can enter the blood stream.

There are other versions as well such as **Insulin Determir** (where a Thr at B30 is removed and a 14-C myristoyl fatty acid group is added) which creates additional binding to albumin proteins, and **Insulin Degludec** (where a Thr at B30 is removed and a 16-C fatty acid with Glu-spacer is added) which forms multi-hexamers and also binds albumin. In all cases, these versions add additional interactions that extend the timeframe required for insulin to dissociate into active monomers.

The different dissociation patterns of each type of insulin agent are shown in Figure 4.8.

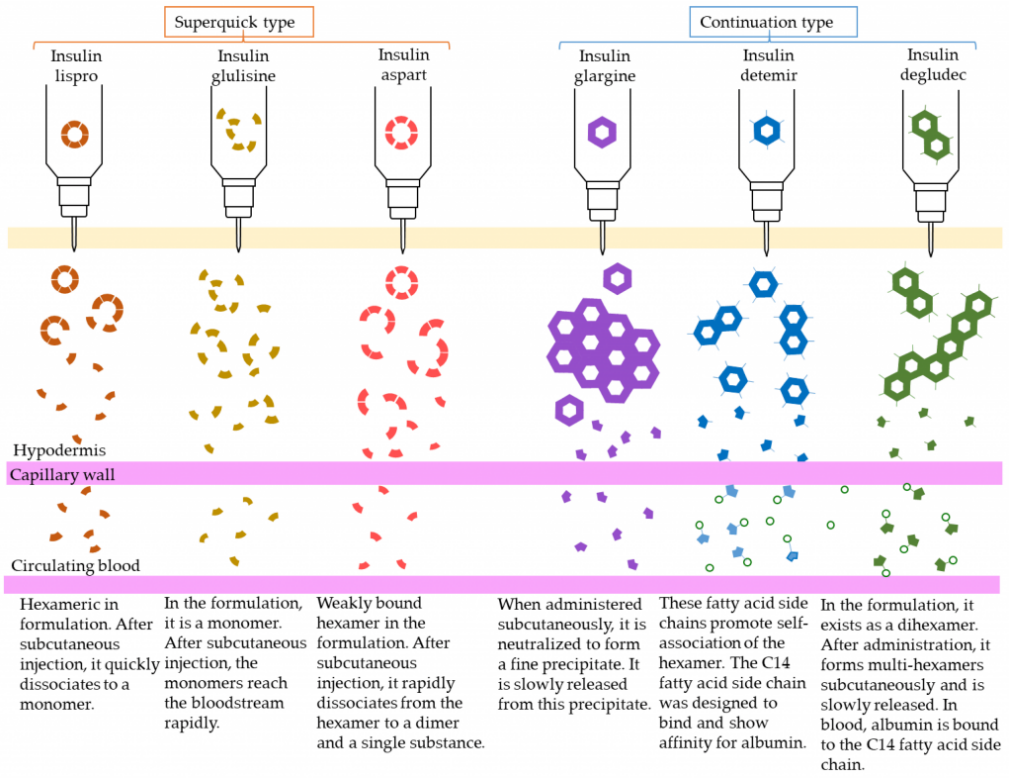

Figure 4.8 Dissociation processes for different types of insulin molecules for the treatment of Type I diabetes. Image Source: (Fig 5) by Takuo Ogihara, Kenta Mizoi and Akiko Ishii-Watabe is used under a CC-BY 4.0 license.
