



Protein-Based Drugs: A Look Through The Crystal Ball

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Traditionally, medications come from any of several classes of small molecules, like amino acids, steroids, or small lipids. Such agents are relatively easy to put into tablets, and generally they are not destroyed by acid in the stomach before they can be absorbed. Proteins, on the other hand, present a difficult challenge for pharmacologists. They are large and bulky, which can prevent them from gaining access to the sites where they are needed. They are also very sensitive to the acid and digestive enzymes of the gut, which prevents them from being administered orally. This means that protein-based drugs, such as insulin, have to be injected to be useful. There may come a day when some proteins can be delivered orally or via other routes, such as inhalation, but for the time being, patients are (quite literally) stuck with the needle.

The difficulties faced by protein drug developers are more deep-seated than this, however. Proteins are often unstable, thus preventing long-term storage, and once injected, proteins often degrade rapidly. This problem has been dealt with most effectively in the case of insulin, the granddaddy of them all when it comes to protein-based therapy. As early as the 1930s, it was recognized that the absorption of insulin from an injection site could be delayed by complexing it with zinc (in the case of lente insulin) or zinc plus protamine, a protein derived from the sperm of herring or salmon (in the case of NPH insulin). These alterations reduce the solubility of insulin in the fluids beneath the skin, allowing them to enter the bloodstream over a longer period of time. Moreover, by changing the amount of zinc, you can exert some control over the timeframe that absorption will occur. Nonetheless, it has been difficult to obtain the full range of desired insulin activity with these methods. For example, extremely quick-acting and very long-acting forms of insulin remained elusive targets for decades.

That all changed when it was discovered that flip-flopping some of the amino acids in the insulin chain would be just what the doctor ordered. Insulin molecules have a natural tendency to clump into aggregates of six; these hexamers must then dissolve before the hormone can be taken up into the bloodstream. This natural tendency to clump can be exaggerated or reduced by simply altering the amino acid sequence ever so slightly, a fairly simple task in today's world of genetic

engineering. For example, switching two amino acids, a lysine and a proline, gives you "lispro" insulin, or Humalog™. Lispro insulin hardly clumps at all, and so is rapidly taken up by the body. By switching an asparagine residue to glycine, and adding a few extra arginines, you get insulin glargine (Lantus™), which clumps tenaciously, and is thus absorbed by the body very slowly.

Now, a research group has reported that they have come up with a new way to make a long-acting insulin (1). Essentially, they took human insulin and modified it slightly by sticking a small fatty molecule onto it. This chemical change does not affect the performance of the insulin. By crystallizing mixtures of the modified insulin with normal insulin, the scientists showed that they could affect the absorption of the hormone. Putting more of the modified insulin into the crystals prolonged the absorption, and they were able to show that this mixture would provide day-long activity in diabetic dogs.

Why does this represent an advance, given that we already have Lantus™ on the market? Well, for one thing, Lantus™ represents an improvement on NPH or lente as a "basal" insulin replacement, but it's not perfect. Until it's compared head-to-head with these new crystallized insulin mixtures, we won't know which will be more useful.

More important, I think, is the potential that this new technology will enable us to deliver proteins other than insulin in a sophisticated way. The fat cell-derived hormones leptin and adiponectin, for example, are both under intense investigation for possible use in treating obesity and diabetes, yet it is unclear that simple injections will have the desired effects. By allowing greater flexibility in absorption times, this new crystallization strategy may be the difference between a drug of mere scientific interest and a terrific new therapy. Other technologies for long-term protein delivery are being studied, such as encapsulation within tiny microspheres, but it is far from clear that these approaches will work. In the brave new world of protein-based drug therapy, we need all the good ideas we can get.

References

1. Brader ML, Sukumar M, Pekar AH, McClellan DS, Chance RE, Flora DB, Cox AL, Irwin L, Myers SR. Hybrid insulin cocrystals for controlled release delivery. *Nature Biotechnology*. 2002 20: 800-4.