Hot Topics in Pharmacognosy: Antidiabetic Drugs from a Surprising Source

By Dr. David Newman

There have been some relatively recent examples of toxins as sources of drugs and leads for pain control, such as the cone-snail ziconotide (approved in late 2004 and launched in 2005), and the very well-known puffer fish (Fugu) toxin tetrodotoxin, probably from an endogenous microbe, currently in phase III trials for severe pain; another example is the non-opioid analgesic peptidic toxin, reported by the King laboratory at the University of Queensland in late 2013, from the venom of the Chinese red-headed centipede.1,2

However, even though it appears to be counterintuitive that a toxin that causes pain and death would be a good agent against some forms of pain, what about toxins from animals that may have a much more benign effect, even though they come from toxic venoms/saliva?

In the last 30 years, physicians dealing with diabetes have been interested in two particular aspects of the gut in mammals. The first was the “incretin effect” (the amplification of insulin secretion by hormones from the gut), and the second was the “occurrence of glucagon-producing L-cells in the gut.” It turned out that “gut-glucagon” was not the same peptide as glucagon when the peptides were finally sequenced, but the major peptide was glicentin (69 amino acids), containing the full sequence of glucagon as residues 33-61 and a truncated form (33-69 amino acids) known as oxyntomodulin.

Further work demonstrated that the existence of multiple “glucagon-like peptides,” including the peptide now known as GLP-1,3 Direct administration of GLP-1 normalized blood glucose levels in type 2 diabetic patients. However, the peptide was very rapidly broken down by the enzyme DPP-IV (dipeptidyl peptidase IV), with a half-life of less than 2 minutes in plasma. Then, a peptide was found known as “exendin-4” that turned out to be a full agonist of the GLP-1 receptor, was resistant to the effects of DPP-IV and was cleared by the kidneys via glomerular filtration.4

Where did this peptide come from and how was it found?

In the 1970s, the work of the Italian pharmacologists, Erspamer and Melchiorri, who investigated the bioactive peptides in the skin secretions of amphibians,5 led to the work by Tatemoto and Mutt;6 they realized that many biologically active peptides had C-terminal amides and developed an assay for such substitutions. Subtly turning this around, Raufman and Eng7 noted that the N-terminal histidine was of prime importance in peptides that “worked” in the secretin-glucagon locus and developed a method to identify such peptides in the venomous saliva of two species of Gila monsters (Heloderma suspectum). They identified exendin-4 from the saliva of these animals and were looking for a mammalian analogue when they noted that GLP-1 had similar biological activities and was an apparent competitor for binding to acini (functional components of the pancreas).8 Later work confirmed that exendin-4 was a high potency agonist, and the truncated version with a C-terminal amide was an antagonist of acini, thus demonstrating that a subtle change in the structure of the peptide gave diametrically opposite results.

The rest is effectively history as the same molecule (now made synthetically), was approved as Byetta™ in 2005 and is in current clinical use. Recently, the story was brought up to date by Levy et al.10 Thus, venom from one of the two venomous lizards in North America has led to a new treatment for type 2 diabetes, not a source that one would normally consider as anti-diabetic therapy. A few famous sayings come to mind: “One never knows what is going to be of import in basic biochemical studies,” and “fortune favors the prepared mind.”

REFERENCES


