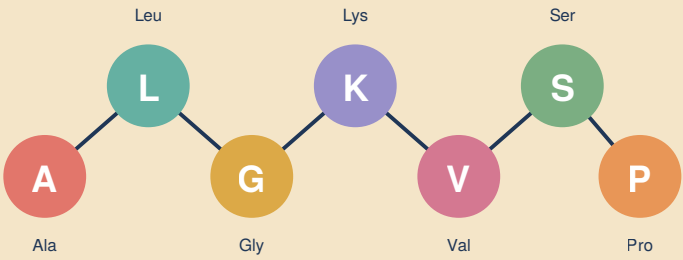
A MODERN INTRODUCTION

Peptides

Simplified



From insulin and GLP-1 agonists to the gray market — a clear-eyed guide to peptide medicine.

Fady Hannah-Shmouni, MD FRCPC

Clinical Endocrinologist & Geneticist

Founder & CEO, Hormonaly.ai

PHARMACOLOGY FOR THE CURIOUS

Peptides Simplified.

The information in this book is provided for general educational purposes only. It does not constitute medical advice and is not a substitute for the judgment of a licensed clinician. Specific products, doses, and protocols mentioned by name are described for reference, not recommended for use. The author and publisher disclaim any liability arising from the application of the information presented here. Where the evidence base is weak, contested, or commercially conflicted, the text says so.

Contents

How to read this book

This is a book about peptides. The first ten chapters explain what they are, what they do in the body, which ones have become drugs, and which ones are sold without having earned that status. The final two chapters add a practical layer for readers who have been prescribed an approved peptide medication: how to read a Certificate of Analysis, how to vet a prescriber and a source, how to inject a pen or a vial safely, and what to monitor on long-term therapy. None of it is a substitute for the clinical judgment of a licensed prescriber.

Peptide therapeutics are one of the most consequential areas of modern medicine. Insulin, the first peptide drug, has kept millions of people alive for a century. Glucagon-like peptide-1 receptor agonists — semaglutide, tirzepatide, and their relatives — are reshaping how diabetes and obesity are managed worldwide[1,2]. At the same time, a parallel market of unapproved peptides has emerged in fitness, sports, and wellness clinics, where compounds with no human clinical trial data are sold and injected on the basis of preclinical animal studies and word-of-mouth claims.

The two worlds get confused. Books written for general readers tend to either talk only about the prescription side (and ignore that gray-market peptides exist) or only about the gray-market side (and present unapproved compounds as if they were drugs). Neither version is honest. This book tries to cover both, with the same evidentiary standard applied to each.

Claims throughout the book are accompanied by inline numbered citations corresponding to the References section at the end. Where the published evidence is strong, the text says so. Where it is weak, conflicted, or generated by parties with commercial interests in the conclusion, the text says so too. Readers are encouraged to follow the primary literature rather than relying on this or any other secondary summary.

Nothing in this book is medical advice. Specific compounds are mentioned by name where useful for reference, including products that are not approved for human use anywhere in the world. Their inclusion is not a recommendation.

. . .

Preface

Peptide medicine is in the middle of its most consequential decade since insulin. Semaglutide and tirzepatide have moved a category that used to live in endocrinology textbooks into the public conversation, while a parallel market of unapproved compounds — BPC-157, TB-500, CJC-1295, and others — has built up alongside the approved drugs without ever passing through the trials that would justify the claims made for them. This book is an attempt to explain both worlds in language a careful general reader can follow.

The book reflects three commitments. The first is that every nontrivial claim should be sourced to a real reference, so that a reader who wants to verify it has somewhere to go. The second is that the peptide drug class most relevant to a general reader in 2026 — the GLP-1 receptor agonists, including semaglutide and tirzepatide — should be discussed in its own right, not buried in a generic chapter on hormones. The third is that the difference between an FDA-approved peptide and a research-chemical peptide should be made absolutely clear, in language a non-specialist can follow, and applied consistently throughout.

The book is organized in five parts. Part one introduces what peptides are chemically, how they function physiologically, and how peptide medicine got to where it is. Part two surveys the actual landscape of peptide therapeutics — first the FDA-approved drugs by class, then a focused chapter on the GLP-1 receptor agonists, and finally an honest assessment of the unapproved peptides sold in wellness and sports settings. Part three covers the practical pharmacology: how peptides are made, formulated, administered, regulated, and monitored. Part four adds two practical chapters for readers who have been prescribed an approved peptide medication: how to evaluate suppliers and prescribers, how to read a Certificate of Analysis, and how to self-administer a prescribed peptide drug safely. Part five steps back to the macroeconomic view — the cost of the diseases these drugs treat, the productivity effects of broad uptake, and what the published economic literature suggests the population-level value of these interventions could be.

The audience is the curious general reader, the patient who has been prescribed (or is considering) a peptide drug, the clinician who wants a refresher, and the student who needs an entry point into the field. Mathematical and chemical detail is kept light; where a diagram conveys a concept more clearly than prose, the diagram is used.

One stylistic note. The English word "regulated" has two unrelated meanings in this field: legal regulation (FDA, EMA) and biological regulation (the body releasing a hormone). This book uses "FDA-approved" or "prescription" for the legal sense, and "endogenously controlled" or "physiologically regulated" for the biological sense. They are different concepts and they deserve different words.

A final note on methodology. This book was developed with the support of Hormonaly.ai, the author's clinical AI platform. Hormonaly uses a multi-agent evidence-grading system that systematically searches and assesses the peptide-therapeutics literature across PubMed, EMBASE, ClinicalTrials.gov, the FDA drug-approval records, WADA listings, and the major endocrine-society guidelines. Specialized agents handle separate stages of the appraisal — one searches and de-duplicates the literature, another applies modified GRADE criteria for risk of bias and study quality, another reconciles conflicts across replications, and a synthesis agent produces structured evidence summaries with explicit confidence levels for each clinical claim. Every factual statement in this book was checked against the platform's evidence map and every reference cited at the back was independently verified by the author. The framework the platform applies — what evidence is strong, what is weak, what is contested, and what is simply unknown — is the same framework this book applies to specific compounds and trials.

CHAPTER ONE

What peptides actually are

The word "peptide" has wandered a long way from its chemistry. In a laboratory it describes a chain of two or more amino acids joined by amide bonds. In a wellness shop it describes whatever the manufacturer wants it to describe — sometimes a real peptide, sometimes an herb extract, sometimes a small molecule given a peptide-sounding name. Before we can usefully separate good evidence from bad, we need to be clear on what a peptide actually is at the molecular level. That is the job of this chapter.

Amino acids, peptide bonds, and chains

A peptide is a chain of amino acids. Amino acids are small molecules with two reactive ends: an amino group on one side (the $-NH_2$) and a carboxylic acid group on the other (the $-COOH$). When the carboxylic acid of one amino acid meets the amino group of another in the right conditions, a chemical reaction joins them and releases a single molecule of water. The new bond formed between them is called a *peptide bond* — chemically, an amide linkage between a carbonyl carbon and a nitrogen. Figure 1.1 shows what is happening atom by atom.

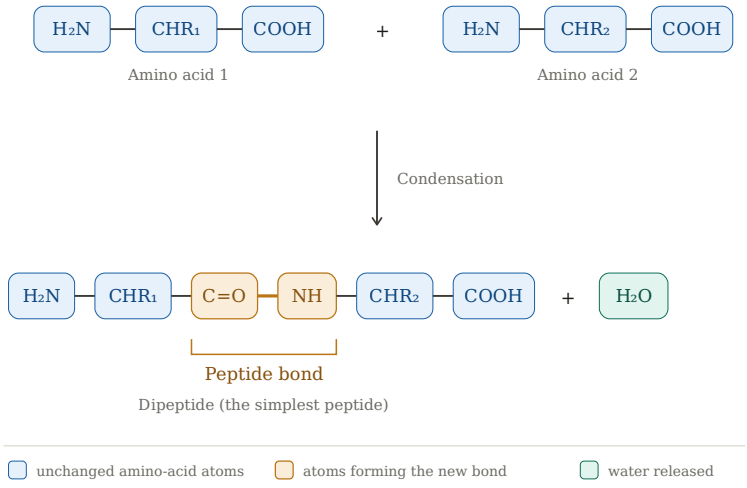


Figure 1.1. Peptide bond formation. Two amino acids react. The −OH from one carboxyl group combines with an −H from the next amino group to release a single water molecule, and a new C–N bond appears between them. That C–N bond is the peptide bond. The product of two joined amino acids is the simplest possible peptide, a dipeptide.

Repeating this reaction many times produces a chain. Three amino acids joined make a tripeptide, four make a tetrapeptide, and so on. The chemistry is the same at every step; the only thing that changes is the side chain identity at each position. Twenty different amino acids appear in the proteins built by ribosomes from the genetic code, and an essentially unlimited number of synthetic side chains can be incorporated when a chemist builds a peptide in the laboratory[3].

The sequence of amino acids matters. Two peptides with the same amino acid composition but in a different order are different molecules with different shapes and different biological effects. This is why peptides are described by their one-letter sequence — for example, BPC-157 is GEPPP-GKPADDAGLV — and not just by their amino acid count.

So where does "peptide" end and "protein" begin?

Textbooks usually say peptides have somewhere between two and fifty amino acids, with anything longer counted as a protein. This is a convention, not a law of chemistry. Insulin, with fifty-one amino acids in two chains, is called both a "peptide hormone" and a "small protein" in the biochemistry literature, depending on who is writing. Glucagon, at twenty-nine residues, is unambiguously called a peptide hormone but is also referred to as a polypeptide. The transition is gradual.

A more useful frame: the smaller the chain, the more its three-dimensional behavior is driven by sequence and individual amino acid properties. The larger the chain, the more it folds into stable secondary structures (alpha helices, beta sheets) and the more its function depends on overall shape. Big proteins are typically enzymes, structural components, or receptors. Peptides are typically signals — hormones, growth factors, neurotransmitters — that bind to those bigger receptors and tell the cell to do something[4].

Figure 1.2 places some well-known molecules along the size axis so the spectrum is visible.

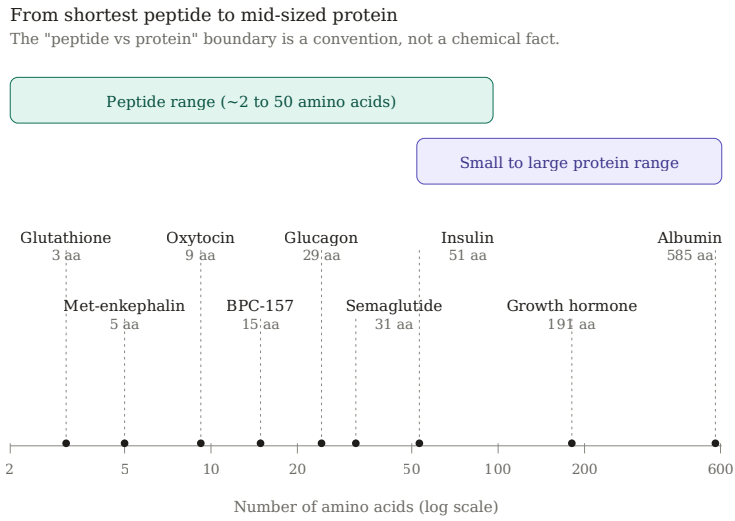


Figure 1.2. The conventional "fifty amino acid" cutoff between peptide and protein, with several familiar molecules placed along a logarithmic axis. Glutathione (3) is the body's main intracellular antioxidant. Oxytocin (9) is the labor and bonding hormone. BPC-157 (15) is the experimental tissue-repair peptide. Glucagon (29) and semaglutide (31) sit right at the conventional boundary. Insulin (51) is on the protein side of the line but is universally called a peptide hormone. Growth hormone (191) is a small protein. Serum albumin (585) is a mid-sized protein.

Physical properties that matter for drugs

Three properties of peptides have outsized consequences for whether a given peptide can become a useful medicine.

Stability in stomach acid and digestive enzymes. The default fate of a peptide you swallow is that it gets broken down. The stomach secretes hydrochloric acid (lowering pH to about 1.5–3.5) and a protease called pepsin, which cleaves peptide bonds preferentially next to aromatic and large hydrophobic residues. The small intestine adds trypsin (cleaves after

lysine and arginine), chymotrypsin (cleaves after aromatic residues), and elastase (cleaves after small uncharged residues), all secreted as zymogens by the pancreas and activated in the duodenum. Carboxypeptidases A and B chew residues off the C-terminus; aminopeptidases lined along the brush border of the small intestine chew them off the N-terminus. The combined effect is that an ordinary peptide swallowed as a pill is reduced to free amino acids within an hour or two of ingestion. This is why insulin and most other peptide drugs cannot simply be put in a pill the way aspirin can — the molecule never reaches the bloodstream intact[5]. Exceptions exist (oral semaglutide, approved as Rybelsus, uses a special absorption enhancer to get a small but useful fraction across the gut wall[6]) but they are exceptions, and a great deal of drug-development effort goes into engineering them.

Half-life in the bloodstream. Even when a peptide is injected, it usually does not stay around long. The bloodstream is patrolled by another set of peptide-cutting enzymes: dipeptidyl peptidase-4 (DPP-4) clips two amino acids off the N-terminus of GLP-1, GIP, and many other peptides; neprilysin cleaves natriuretic peptides and several others; and insulin-degrading enzyme (IDE, sometimes still called insulinase) is the principal route of insulin breakdown in the liver and kidneys. The kidneys add another layer of clearance, filtering smaller peptides at the glomerulus and then chewing them apart in the proximal tubule. The net effect is that native insulin has a circulating half-life of about five minutes, native GLP-1 lasts roughly one to two minutes before DPP-4 destroys it[7], and many other native peptides have half-lives measured in single-digit minutes. For something a patient needs to take daily or weekly, that is far too short. The single most important advance in modern peptide drug design has been figuring out how to engineer longer half-lives — typically by adding fatty acid chains that bind albumin, by modifying the residues DPP-4 targets, or by attaching polyethylene glycol — without losing receptor binding. We return to those techniques in Chapter 7.

Size and charge. Peptides are much bigger than typical small-molecule drugs (an aspirin tablet contains a molecule with a molecular weight of 180 daltons; semaglutide is 4114 daltons; insulin is 5808 daltons). They carry electrical charge from their amino and carboxyl groups and from charged side chains. Big and charged molecules cross cell membranes poorly, which limits where they can act and how they can be delivered. Most peptide drugs exert their primary pharmacologic effects through cell-surface receptors — they bind on the outside of the cell and trigger intracellular signaling cascades, rather than entering the cell themselves. (Many peptides then undergo receptor-mediated internalization, and several peptide drug classes ultimately modulate intracellular pathways downstream of that binding — the distinction is about the initial site of action, not the eventual reach of the signal.)

How peptides differ from small-molecule drugs

Most medicines prescribed today are small molecules — aspirin, ibuprofen, atorvastatin, sertraline. They are made by synthetic organic chemistry, weigh a few hundred daltons each, and are usually taken by mouth. Peptide drugs occupy a different niche.

The advantages of peptides are that they are typically much more selective for their intended target than small molecules. A peptide drug that mimics an endogenous hormone slots into the receptor that hormone evolved to bind, with high specificity and high potency. Side effects from off-target binding are usually smaller than for small molecules of similar efficacy. Toxicity from breakdown products is usually low, because the breakdown products are amino acids the body already handles[8].

The disadvantages are that peptides are more expensive to manufacture, harder to get into the body (usually requiring injection), and shorter-lived in the bloodstream than a typical pill. They can also provoke an immune response in some patients, leading to antibodies that reduce the drug's effect

over time — a phenomenon called immunogenicity, which limited the early use of bovine insulin in human patients before recombinant human insulin became available[9].

The "peptide" label in the marketplace

A practical warning before we proceed. The word "peptide" is sometimes attached to products that are not peptides. Examples encountered in actual commerce include herbal extracts marketed as "plant peptides" (most are not), small synthetic molecules with peptide-sounding names that activate peptide receptors but are not themselves peptides (ibutamoren / MK-677 is a small molecule, not a peptide, despite often being grouped with growth-hormone-releasing peptides), and peptide *receptors* sold or discussed as if they were the peptide itself.

Creatine deserves a particular mention because it is so often described as a "tripeptide" or "peptide-like" molecule in supplement marketing. It is neither. Creatine (chemically, N-methylguanidinoacetic acid) is biosynthesized in the human body from arginine, glycine, and a methyl group donated by methionine — it shares the same amino-acid raw materials as peptides — but the resulting molecule contains no peptide bonds. It is a small nitrogen-containing organic compound, not a chain of amino acids, and its pharmacology (cellular energy storage as phosphocreatine in muscle) is unrelated to anything covered in this book. The same caveat applies to several other amino-acid-derived supplements (taurine, β-alanine, carnitine): related to peptide chemistry by origin, but not peptides.

For the rest of this book, "peptide" means the chemical thing — a chain of amino acids linked by peptide bonds — and we will be explicit when the label has been used otherwise.

. . .

Now that the chemistry is in place, the next chapter turns to what peptides do in living bodies. Most of the drugs we will discuss later are based on peptides that the body itself makes for its own purposes; understanding those purposes is the bridge from the chemistry to the pharmacology.

CHAPTER TWO

How peptides work in the body

A small molecule with the right shape can switch a whole organ system on or off. That is the trick the body discovered long before we did, and it is the reason peptides matter clinically — every peptide drug we will discuss in this book is either a direct copy of, or a deliberate modification of, a peptide the body already uses for signaling. This chapter walks through the main jobs peptides do in human physiology and introduces the receptors they bind, because the same receptors are the targets of the drugs that come later.

Hormones, neurotransmitters, growth factors, antimicrobials

Endogenous peptides — those made by the body — divide loosely into four functional groups. The lines between groups blur, and some peptides span more than one.

Hormones. Insulin and glucagon control blood glucose. The glucagon-like peptide-1 (GLP-1) family, secreted by the gut after a meal, amplifies insulin release and slows gastric emptying[10]. Oxytocin and vasopressin, made in the hypothalamus and released by the posterior pituitary, regulate

uterine contraction, milk letdown, water retention, and social bonding behaviors[11]. The hypothalamic-pituitary axis is essentially a network of small peptide hormones — gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and growth hormone-releasing hormone (GHRH) — each of which tells the pituitary to release a larger pituitary hormone. Calcitonin from the thyroid and parathyroid hormone (PTH) from the parathyroid glands together regulate calcium balance.

Neurotransmitters and neuromodulators. The brain uses peptides as signaling molecules between neurons, often in parallel with classical small-molecule transmitters like glutamate or dopamine. The endogenous opioids — enkephalins, endorphins, and dynorphins — are short peptides that activate opioid receptors and produce analgesia and reward signaling[12]. Substance P, neuropeptide Y, vasoactive intestinal peptide (VIP), and dozens of other neuropeptides participate in pain, appetite, sleep, and circadian regulation.

Growth factors and tissue-repair signals. Some growth factors are large proteins, but many of the most important — including epidermal growth factor (EGF, 53 residues), insulin-like growth factor 1 (IGF-1, 70 residues), and various small fragments of larger proteins — are peptide-sized. They coordinate cell proliferation, migration, and differentiation during development and during wound healing[13].

Antimicrobial peptides. The skin, mucous membranes, and white blood cells produce short peptides that physically disrupt bacterial and fungal membranes. Defensins (about 30 residues), cathelicidins (LL-37 in humans is 37 residues), and dozens of other antimicrobial peptides form part of the innate immune system[14]. Their importance has become more visible as resistance to small-molecule antibiotics has worsened: several antimicrobial peptide-based drugs are in clinical development for hard-to-treat infections.

Where peptides come from physically

A naturally occurring peptide is almost always built the way any protein is built: ribosomes inside a cell read messenger RNA from a gene and assemble amino acids in the encoded order. The fresh chain often emerges in a longer "preproprotein" form and then gets cut down to the active sequence by specialized enzymes called proprotein convertases. Insulin is the canonical example: the gene encodes a 110-amino-acid preproinsulin, which is processed inside pancreatic beta cells through proinsulin to mature insulin (the 51-residue heterodimer we recognize as the drug)[15].

A few endogenous peptides — most notably antimicrobial peptides like LL-37 — are stored in granules inside immune cells and released by exocytosis when needed. Others, like beta-endorphin, are processed from the same precursor as completely unrelated peptides (proopiomelanocortin is the source of ACTH, alpha-MSH, beta-endorphin, and several other signals). The biology is intricate, and the practical consequence for drug development is that mimicking a particular peptide signal in a useful way usually requires reproducing the mature, active form rather than the precursor.

Receptors: where the message lands

A peptide signal does nothing on its own. It needs a receptor to interpret it. Most peptide receptors fall into two structural families.

The first and most numerous family is the G-protein-coupled receptors (GPCRs), so called because they signal through guanine-nucleotide-binding proteins inside the cell. GPCRs are sometimes described as "seven-trans-membrane" receptors because their polypeptide chain threads through the cell membrane seven times. They sit at the cell surface like little letterboxes; when a peptide binds the outside, the receptor changes shape, and the change is transmitted to the interior of the cell, where a G-protein is activated and