Substance P and the Neurokinins: Novel Peptide Neurotransmitters in Psychopharmacology

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Issue: *A new neurotransmitter system is a family of 3 related peptides known as neurokinins. The best known of these is substance P. The others are known simply as neurokinin A and neurokinin B. The specific receptor subtypes that correspond to these 3 neurokinins are neurokinin 1 receptors for substance P, neurokinin 2 receptors for neurokinin A, and neurokinin 3 receptors for neurokinin B. These neurotransmitters appear to play a key role in the regulation of emotions, and antagonists of their receptors may be novel psychotropic drugs of the future.*

This month's feature is the second of a 3-part series on peptides and psychiatry. Part 1 appeared last month as a visual lesson on neuropeptide neurotransmitter synthesis, storage, and release in the central nervous system.[1] Part 2 is presented here and explores a specific family of neuropeptides and their receptors, known as neurokinins, of which substance P is the best known example.[2–4] Part 3 will appear in the March 1999 BRAINSTORMS and will review interesting developments with substance P antagonists as novel antidepressants in a feature entitled "Substance P and Serendipity: Novel Psychotropics Are a Possibility."

Take-Home Points

- Substance P is a member of a family of related peptides originally known as tachykinins because they are rapid-acting, but are now called neurokinins (NKs)
- The names for the precursors, neurotransmitters, and receptors within the same family are confusing. For the clinician, it is worth knowing 3 neurotransmitters and 3 receptors for the tachykinin family: Substance P is the neurokinin neurotransmitter that selectively binds to NK-1 receptors; NK-A selectively binds to NK-2 receptors; and NK-B selectively binds to NK-3 receptors

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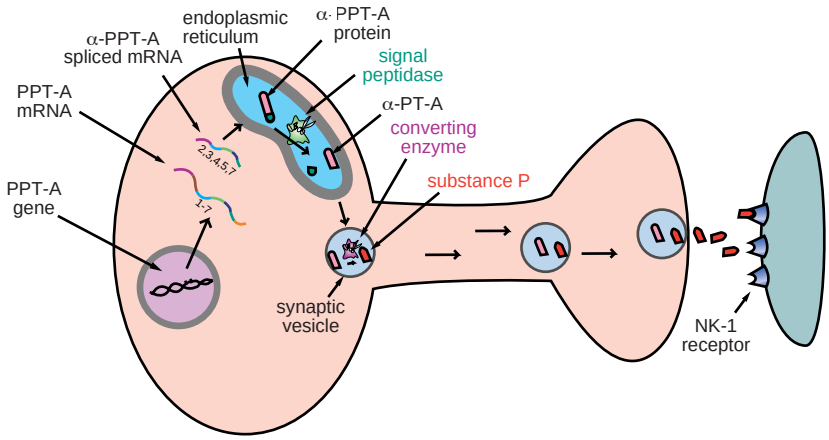
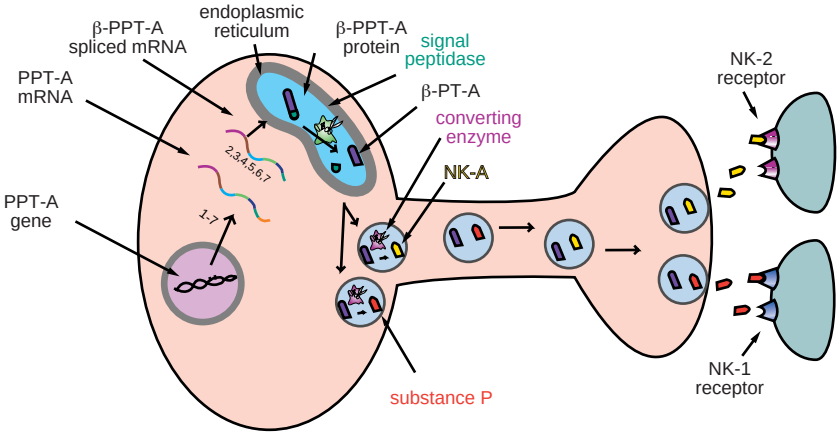
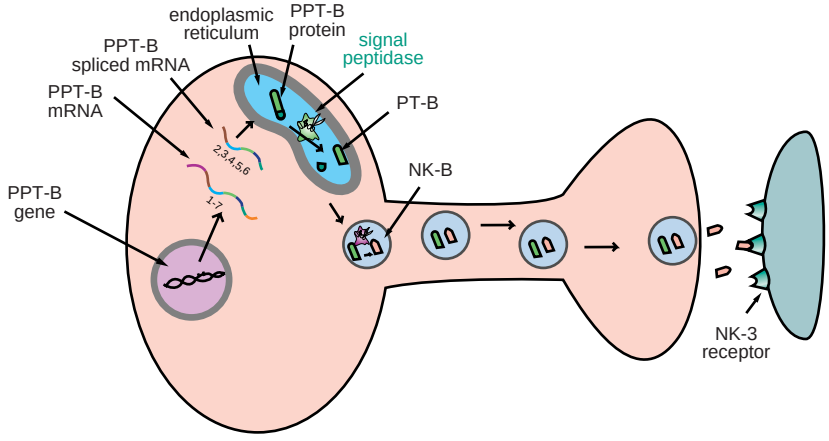


Substance P can be synthesized from only 1 gene, but from 3 different forms of alternatively spliced mRNA: alpha, beta, and gamma.[2–4] The gene is called PPT-A for preprotachykinin A. Here, substance P is being synthesized from the α-PPT-A form of mRNA. Substance P is eventually formed when α-PPT-A protein is cleaved twice: first to α-PT-A (protachykinin) by a signal peptidase enzyme and then further to substance P itself by a converting enzyme. Once substance P is released, it interacts selectively with neurokinin 1 (NK-1) receptors.



Both substance P and NK-A can be synthesized from 2 types of mRNA derived from the PPT-A gene, namely the beta and gamma forms of PPT-A mRNA.[2–4] Figure 2 shows the creation of substance P and NK-A from the β-PPT-A type of mRNA. Not shown is the analogous process for creating these same 2 peptides from the γ-PPT-A type of mRNA. The conversion of these 2 forms of mRNA into substance P or NK-A occurs by the same processes outlined in Figure 1. Once released, substance P will interact with NK-1 receptors, but NK-A will interact with NK-2 receptors.



Finally, NK-B is formed from a different gene called PPT-B, which is transcribed to PPT-B mRNA, translated to PPT-B protein, and eventually cleaved into NK-B, which can interact with NK-3 receptors.[2–4]