The Therapeutic Potential of Neuropeptide Y: Analgesic, Anxiolytic and Antihypertensive

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Summary

Since its discovery in 1982, neuropeptide Y (NPY) has been shown to have numerous effects mediated by a growing number of NPY receptors in both the CNS and peripheral nervous system. Perhaps best appreciated is the role of NPY in the control of systemic blood pressure, together with its effects on feeding, anxiety and memory. However, recent evidence increasingly supports an important role for NPY in mediating analgesia and hyperalgesia by distinct central and peripheral mechanisms. In this review we concentrate on this important aspect of NPY pharmacology and consider mechanisms controlling the expression of NPY and its receptors. In addition, we also present the more recent data describing...
Neuropeptide Y (NPY) is a 36-amino-acid peptide of the pancreatic polypeptide family that includes pancreatic polypeptide (PP) and peptide YY (PYY). It is one of the most abundant peptides within the body and, since its isolation in 1982, NPY and NPY receptors have been implicated in many homeostatic functions. The abundance of NPY in the body is almost matched by the abundance of excellent articles devoted to the pharmacology of NPY and the therapeutic potential of drugs which act at NPY receptors. We refer to these earlier reviews where necessary, and intentionally focus upon newer data, with particular reference to pain and analgesia. We consider mechanisms of NPY expression, its release and its action at multiple receptor sites before outlining some of the potential roles of NPY modulating drugs.

1. Neuropeptide Y (NPY) Receptors

The field of NPY receptor pharmacology is expanding rapidly. Binding studies with NPY fragments or analogues and the related peptides PYY and PP identify 3 NPY receptor types classified as Y₁ to Y₃ receptors, and the existence of a further ‘atypical Y₁’ receptor has been proposed from functional studies of feeding behaviour. Of these, the Y₁[9,10] and more recently the Y₂ receptor[11] have been cloned and sequenced. Both are members of the 7 transmembrane protein superfamily of receptors. The status of the Y₃ receptor is less clear as a proposed clone for this receptor was subsequently shown not to encode an NPY receptor.[12,13] Using probes derived from the previously sequenced Y₁ receptor, a novel Y₄ receptor has very recently been identified and sequenced, although as yet this has only been reported in abstract form.[14] Preliminary data also suggest that subclasses of Y₂ receptors may exist.[15]

The N-terminal of the NPY molecule is critical for Y₁ effects whereas Y₂ effects require the presence of the C-terminal part of the peptide (see fig. 1). Therefore, substitution at the C-terminal of the NPY molecule produces preferential Y₁ agonists such as [Leu³¹.Pro³⁴]NPY, while C-terminal fragments such as NPY₁[8-36] are Y₂ selective agonists. The Y₃ receptor also binds C-terminal fragments of the NPY molecule (such as NPY₁8-36), but at this site they act as partial antagonists. Y₃ receptors are characterised by insensitivity to PYY (which is a potent agonist at both Y₁ and Y₂ receptor sites) while the Y₄ receptor appears to bind preferentially...