A. Principles

I. Introduction

The opioid peptides were discovered during the early, explosive period of neuropeptide research. A great deal of excitement surrounded this research, in part because the path that led to the discovery of the opioids was, and remains, unique. Opioids have been the only neuropeptides isolated for their ability to bind to and act at an already well-characterized receptor. In addition, the function of these receptors was known in several neuronal systems, and the effects caused by either the alkaloid opiates or the newly characterized opioid peptides could be blocked by existing antagonists, such as naloxone. Thus, even at its birth, the field of opioid peptide research was more advanced than for any other neuropeptide.

The discovery of the endogenous opioids brought the long-distinguished field of opiate pharmacology into the new domain of the neurobiology of putative peptide transmitters. An important concept that emerged from this period of research was the idea that neuropeptides are produced by neurons which also produce classical transmitters, and that between the time of synthesis and release of neuropeptides, they coexist with classical transmitters within neurons. A functional consequence of this concept is that individual neurons can release a mixture of transmitters, consisting of one or more classical, low-molecular-weight neurotransmitters and one or more specific neuropeptides. The purpose of this review is to emphasize some of the findings that led to these concepts, the extent to which opioids are now known to coexist with other transmitters, and the implications of these cellular features for understanding the role that opioids and their receptors play in neurotransmission and neural communication.

By the late 1960s Pearse and colleagues (Pearse 1969) had presented arguments suggesting that many peptide-producing endocrine cells possess (at least transiently) uptake mechanisms for monoamine precursors (the amine precursor uptake and decarboxylation concept of Pearse; see also Owmam et al. 1973). In addition, studies of large, single neurons from invertebrates established that they produce more than one neurotransmitter (Brownstein et al. 1974). Soon after this, we discovered that somatostatin...
Fig. 1a–d.