ABSTRACT

CALCITONIN GENE-RELATED PEPTIDE: ISOLATION, DISTRIBUTION AND RECEPTOR BINDING.

Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide with a potent vasodilatory activity, predicted to result from alternative processing of the primary RNA transcript of calcitonin (CT) gene. The work described in this thesis includes; assay development and validation, isolation and purification of CGRP, and the characterisation of the CGRP receptor from man and four other species.

Following an introduction and literature survey of the CT/CGRP gene and its products, the methods used to isolate and purify CGRP, and to study the distribution of this peptide and its receptors are described. These methods were then validated, and the distribution of CGRP, CT and katacalcin in man (and the carboxy-terminal adjacent peptide in rat) were studied to understand the basic physiology of CGRP. I have demonstrated the presence of both α-CGRP and β-CGRP in tissues, plasma and in cerebrospinal fluid (CSF) in man. Messenger RNAs for α-CGRP and β-CGRP were identified, and the expressed α- and β-CGRP peptides isolated and purified from normal human tissues, and fully characterised. To further understand the patho-physiology of CGRP, the receptor was characterised in rat, sheep, cow, pig and in man. A novel, highly specific and sensitive radioreceptor assay was developed to measure tissue contents and plasma levels of CGRP. The implications of the findings and possible future research are discussed in the final chapter.

I have demonstrated the presence of not only α-CGRP and β-CGRP in man, but also its multiple immunological and molecular weight forms in tissues, plasma and in CSF. The demonstrated distribution of CGRP and its receptors are consistent with the postulated functions of CGRP. This is the first study to demonstrate the full expression of the α- and β-CGRP gene in normal tissues in man. To understand the mechanism of action of CGRP at the molecular level, this study is being further extended to the purification of the CGRP-receptor and the cloning of its gene. In the long term, one might envisage the eventual development of receptor-based peptide and non-peptide CGRP-mimetic analogues for clinical use in man.