Opioids
Past, Present and Future

Symposium to celebrate the 80th birthday of
Hans W. Kosterlitz FRS
Churchill College, Cambridge, 11 April 1983

Edited by
J. Hughes, H.O.J. Collier, M.J. Rance and M.B. Tyers

Taylor & Francis
London and Philadelphia
1984
**Contents**

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td></td>
<td>v</td>
</tr>
<tr>
<td>1</td>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>H. W. KOSTERLITZ: A THUMB NAIL SKETCH</strong></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td><em>A. T. McKnight</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contributors to the symposium</td>
<td>xiii</td>
</tr>
<tr>
<td>1</td>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>G. M. Lees</strong></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>REFLECTIONS ON OPIOID PEPTIDES</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td><em>J. Hughes</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Historical aspects</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Biogenesis of the opioid peptides</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Actions and functions of opioid peptides</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Concluding remarks</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>OPIOID AGONISTS AND ANTAGONISTS</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td><strong>W. R. Martin</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>A steric theory of opioid agonists, agonist-antagonists, partial agonists</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>and competitive antagonists</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>MULTIPLE OPIOID RECEPTORS</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td><strong>E. J. Simon and J. M. Hiller</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Properties of opioid binding sites</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Multiplicity of opioid receptors</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Concluding remarks</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>OPIATES AND NERVE CELL MEMBRANES</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td><strong>R. A. North</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Opiates open membrane potassium channels</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Conclusions</td>
<td>58</td>
</tr>
</tbody>
</table>
6. ELECTROPHYSIOLOGICAL STUDIES ON THE ACTIONS OF OPIOIDS,
WITH PARTICULAR REFERENCE TO THE PRODUCTION OF
ANALGESIA
R. G. Hill, R. Morris and C. M. Pepper
Introduction 61
Sites of action for opioid analgesia 62
Sites of action within the CNS 63
The importance of multiple opiate receptor sub-types 71
Endogenous opioids and the production of analgesia 73

7. OPIOID PEPTIDES IN THE HYPOTHALAMIC-PITUITARY AXIS
A. Herz and M. J. Millan
Introduction 79
Families of opioid peptides: biosynthetic origins and localization 79
Opioid peptides and neurohypophyseal vasopressin and oxytocin 82
β-Endorphin: localization, modulation and possible roles 87
Concluding comments 95

8. OPIATE TOLERANCE AND PHYSICAL DEPENDENCE:
ASSESSMENT AND MECHANISMS
E. L. Way and A. Rezvani
Introduction 103
General considerations in opiate tolerance and physical dependence 103
Possible role of calcium in opiate tolerance and physical dependence 103
Assessment of tolerance and physical dependence in vitro 106

9. CELLULAR ASPECTS OF OPIOID TOLERANCE AND DEPENDENCE
H. O. J. Collier
Tolerance and dependence 109
Physiological basis of opioid dependence 113
Cellular site of opioid dependence 114
Molecular mechanism of dependence 120
Summary 123

10. OPIOID PEPTIDES: FUNCTION AND SIGNIFICANCE
A. Goldstein
Introduction 127
Function deduced from the distribution of an opioid peptide 130
Function deduced from the receptor type selectivity of an opioid peptide 133
Function deduced from the change in level of an opioid peptide 135
Function deduced from the administration of a specific antibody 137
Function deduced from the administration of an opioid peptide 137
Function deduced from the effect of naloxone 138
Concluding remarks 139

11. OPIOID SYSTEMS: ANATOMICAL, PHYSIOLOGICAL AND
CLINICAL PERSPECTIVES
S. J. Watson, H. Akil, H. Khachaturian, E. Young and M. E. Lewis
Introduction 145
Endogenous opioids: basic relationships 146
Physiological and clinical studies 158
Conclusions 170
Contents

12. OPIOID PEPTIDES IN HUMAN CEREBROSPINAL FLUID 179
   L. Terenius, F. Nyberg and A. Wahlström
   Introduction 179
   The early methodological approach and some applications 180
   Chemical characteristics of CSF endorphins 183
   Recent functional studies using the refined methodology for CSF
   analysis 185
   Work in progress and possible future directions 188
   Conclusions 189

13. ENKEPHALIN BIOSYNTHESIS: FOCUS ON ENKEPHALIN
    CONVERTASE 193
   S. H. Snyder and L. D. Fricker
   Introduction 193
   Demonstration of enkephalin convertase 194
   Detection of enkephalin convertase in the adrenal gland 195
   Tissue distribution and regional variations of enkephalin convertase
   within the brain 196
   Purification of enkephalin convertase 199
   Selectivity of enkephalin convertase towards arginyl and lysyl enkephalin
   hexapeptides 201
   Inhibitors 201
   Conclusions 203

Appendix. PUBLICATIONS OF H. W. KOSTERLITZ 207

Subject index 223