GABA IN THE GUINEA-PIG ENTERIC NERVOUS SYSTEM

A thesis submitted for the degree of

Doctor of Philosophy

by

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<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DECLARATION</strong></td>
</tr>
<tr>
<td><strong>ACKNOWLEDGEMENTS</strong></td>
</tr>
<tr>
<td><strong>SUMMARY</strong></td>
</tr>
<tr>
<td><strong>CHAPTER I: GENERAL INTRODUCTION</strong></td>
</tr>
<tr>
<td>History</td>
</tr>
<tr>
<td>Biochemistry</td>
</tr>
<tr>
<td>Physiology and Pharmacology of GABA</td>
</tr>
<tr>
<td>GABA in Peripheral Nervous System</td>
</tr>
<tr>
<td>GABA in Enteric Nervous System</td>
</tr>
<tr>
<td>The Enteric Nervous System</td>
</tr>
<tr>
<td>Functional Organisation</td>
</tr>
<tr>
<td>Myenteric Plexus</td>
</tr>
<tr>
<td>Myenteric Neurons</td>
</tr>
<tr>
<td>Submucous Plexus</td>
</tr>
<tr>
<td>Extrinsic Innervation of the Enteric Plexus</td>
</tr>
<tr>
<td>Intrinsic Innervation of the Enteric Plexus</td>
</tr>
<tr>
<td><strong>CHAPTER II: PHARMACOLOGY OF GABA ACTIONS</strong></td>
</tr>
<tr>
<td>Introduction</td>
</tr>
<tr>
<td>Materials and Methods</td>
</tr>
<tr>
<td>Results</td>
</tr>
<tr>
<td>Discussion</td>
</tr>
</tbody>
</table>
CHAPTER III: LOCALIZATION OF $[^{3}H]$-GABA HIGH AFFINITY UPTAKE SITES BY AUTORADIOGRAPHY

Introduction 37
Methods 40
Autoradiography 42
Staining 43
Results 43
Uptake of $[^{3}H]$ proline and $[^{3}H]$ leucine into myenteric laminar preparations. 43
Myenteric localization of $[^{3}H]$-GABA and $[^{3}H]$-GABA in laminar preparations. 45
Effects of L-GABA, nipevotic acid and ACHC on $[^{3}H]$-GABA uptake. 46
Autoradiographic localization of $[^{3}H]$-GABA of colon and ileum. 47
Discussion 48

CHAPTER IV: MORPHOLOGY OF MYENTERIC NEURONES

Introduction 56
Methods 57
Results 59
Discussion 60

CHAPTER V: UPTAKE AND RELEASE OF $[^{3}H]$-GABA BY MYENTERIC NEURONES

Introduction 63
Methods 65
Identification of $[^{3}H]$-GABA released by stimulation 66
CHAPTER VI: THE EFFECTS OF GABA ANTAGONISM ON INTESTINAL MOTILITY

Introduction 73
Materials and Methods 78
Results 79
Discussion 81

CHAPTER VII: MYENTERIC PURINERGIC NERVES

Introduction 86
Methods 91
Electrical stimulation. 92
Results 93
Responses of the distal colon to ATP. 93
Responses of the ilium to ATP 95
Discussion 97
Distal colon 97
Ileum 98

CHAPTER VIII: GENERAL DISCUSSION AND CONCLUSION 102

BIBLIOGRAPHY 108
SUMMARY

In this thesis a number of criteria for a neurotransmitter have been investigated for γ-amino butyric acid (GABA) in the guinea-pig intestine.

Chapter I is an introductory review of the biochemistry, physiology and pharmacology of GABA nervous transmission in vertebrates and invertebrates. This is followed by a detailed description of the nervous innervation of the mammalian gastrointestinal tract, in particular the small and large intestine, together with structural characteristics of the intestine wall. An overview of the pharmacology of the gastrointestinal tract is also given.

Chapter II is a pharmacological study of GABA actions in the guinea-pig ileum including determination of the chemical specificity of the receptors mediating GABA actions and their associated ionophore. The results confirm and extend the previously published pharmacological studies. GABA stimulation of intrinsic cholinergic motor nerves is via bicuculline sensitive receptors coupled with a Cl⁻ ionophore. The implications of the mode of GABA action is discussed.

Chapter III reports the autoradiographic investigation of a GABA high affinity uptake "inactivation mechanism" in the guinea-pig intestine. Evidence is presented to show the efficacy of [³H] as an autoradiographic marker in laminar preparations of the myenteric plexus. The disposition of [³H]-GABA and [³H] α-alanine accumulating elements were determined by light microscopic autoradiography using specific neuronal and glial high affinity uptake inhibitors in both laminar and paraffin section preparations. [³H]-GABA uptake sites are shown located to neurones of the myenteric plexus and associated nerve fibres ramifying in the circular muscle layer.
In Chapter IV the development of a relatively simple and rapid staining procedure is described, which affords good morphology of neurones in laminar preparations. This method allows delination of nerve types accumulating \(^{3}H\)-GABA, as shown by autoradiography. \(^{3}H\)-GABA labelled only a restricted population of myenteric neurones.

Chapter V describes the investigation of the evoked release criterion, using chromatographic and radiochemical analysis. Electrically evoked \(^{3}H\)-GABA release from laminar preparations of the guinea-pig ileum under various treatments, including neuronal and glial high affinity uptake blockers, tetrodotoxin, and calcium free medium, show \(^{3}H\)-GABA is released by myenteric neurones in a transmitter-like manner.

In Chapter VI current concepts of the mechanisms of peristalsis are discussed, together with results of experiments in which GABA-antagonism interfered with peristalsis, as measured in isolated preparations of the guinea-pig distal colon. The results suggest important implications for studies of intestinal motility.

Acetylcholine is the transmitter of the excitatory nerves stimulated by GABA but the transmitter released by the inhibitory nerves is not known, although it has been proposed to be adenosine 5'-triphosphate (ATP). In Chapter VII pharmacological investigation of this hypothesis using a new class of ATP antagonist is described. Furthermore, the involvement of ATP in transmission from non-cholinergic excitatory nerves was investigated. ATP is not the transmitter of these nerves.

Chapter VIII is an overview of the whole thesis and discussion of the results in regard to the various criteria for identification of a neurotransmitter substance. Conclusions and suggestions for future
research are also presented. It is concluded that GABA is a neurotransmitter in the guinea-pig myenteric plexus.