Synapse formation

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Cover photograph

Temporal axons stained with rhodamine-B-isothiocyanate growing on a striped membrane carpet. The temporal axons grow preferentially on the stripes of anterior tectal membrane, leaving the stripes of posterior membrane free of neurites. Photograph by Bernhard Müller (see pp. 29–46).
ACKNOWLEDGEMENTS

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Synapse formation

Synapses lie at the heart of neuronal function: they are the vital points of contact between neurones in the central nervous system and between motor neurones and muscle fibres at the neuromuscular junction. The precision with which information is transmitted throughout the central nervous system depends upon the specificity of these synaptic connections. The rapid development of techniques, such as confocal and epifluorescence microscopy, immunocytochemistry and the use of in vitro systems, along with the more traditional methods such as transplantation and lesioning, has produced a mass of new information about synaptic plasticity and specificity. This volume draws attention to recent work in the field of synapse formation and provides an authoritative review of the factors that influence synapse development in the embryo and synapse re-formation following damage to the mature nervous system. It presents a fund of essential material for researchers and students of neurobiology.

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PREFACE

This volume had its origin in 1988 when John Treherne joined a group of distinguished neurobiologists on a visit to China, organized by Ren-Ji Zhang and John Nicholls. The group taught and gave practical advice to many scholars and students, and extended its work by means of informal conversation, from which both sides benefited greatly. John Treherne was particularly struck by the dedication and enthusiasm of the Chinese scientists, by their ability to carry on their work despite limited money and equipment, and by their isolation from much current research and opinion. John was not a man who could shrug his shoulders and accept as inevitable the problems of others; he decided to help. He began on the spot by arranging for a young PhD student to transfer his studies to Cambridge, where the equipment he needed was available. He made sure that copies of the journals published by the Company of Biologists were available free of charge to many Chinese scientists, and he was determined to involve Chinese researchers in the meetings of international scientists that, as Editor of this journal, he was instrumental each year in organizing. Albert Aguayo and John Nicholls willingly agreed to help, and preliminary arrangements were in train for a meeting of neurobiologists in China when the events of June 1989 made this impracticable, and Batam in Indonesia was chosen instead. Travel difficulties at the last moment reduced the participation of Professor T. P. Feng and Dr Ren-Ji Zhang to written communications. The meeting provided, nonetheless, an opportunity for scientists from ten countries to meet and discuss their most recent findings on aspects of synapse formation.

John Treherne died before the final arrangements for the meeting could be made and he did not see the completion of his work. This volume is dedicated to his memory.

E. A. Howes
INTRODUCTION

In the ‘enchanted loom’ of development the interweaving of different fibres creates the multitude of patterns that make up the nervous system. The final touch that gives it function is the formation of synapses.

The way in which specific connectivity is generated and the ability of synapses to respond to changing patterns of activity and to re-develop after injury are topics of interest to neurobiologists and neurologists because they provide cues to the understanding of normal function and behaviour, neural disease and repair processes. The papers presented in this review volume reflect current opinions on how axonal growth and synapse formation first develop, are subsequently modified and can be restored after injury.

Although it is likely that a constant turnover of synapses occurs in the adult animal in response to changing patterns of activity (Raisman and Field), the process of synaptogenesis can be readily investigated either during development when synapses are first formed (e.g. Fraser and O’Rourke; Singer; So, Campbell and Lieberman) or following damage to the immature or adult central nervous system (CNS) when repair processes lead to the establishment of new synapses (e.g. Hamori; Frank and Mendelson; Kawamura, Murase and Yuasa; So et al.; Aguayo, Bray, Rasminsky, Zwimpfer, Carter and Vidal-Sanz). An elegant addition to studies of the injured CNS is the use of mutant mice, where patterns of cerebellar connectivity are changed as a result of gene mutation (Sotelo). A further approach is to study synapse formation and function in vitro (Nicholls, Liu, Payton and Kuffler; Feng and Dai; Müller, Stahl and Bonhoeffer), where the multiple constraints imposed by the environment of the CNS are removed and factors affecting synapse formation can be studied in isolation.

From all these approaches it has become clear that synapse formation is influenced by a number of factors, some inherent to the presynaptic cell (Magill-Solc and McMahan; Zhang, Zhu, Wang, Zhang and Zou), some dependent on molecular interactions with other cells (Trisler; Müller et al.) and some related to influences from postsynaptic targets (Frank and Mendelson).

The study of target molecules that attract or repulse selected populations of growing axons (Müller et al.) and the investigation of molecular gradients that can specify positional information (Trisler) provide new insights on possible mechanisms that influence the topographic distribution of certain nerve fibre projections in the brain. Although little is known about what determines the location, differentiation and maintenance of postsynaptic structures in the CNS, the postulated role played by the molecule agrin at the neuromuscular junction is a remarkable example of how presynaptic influences may affect postsynaptic components (Magill-Solc and McMahan).

Recent work in many laboratories has been directed towards investigating the effects of activity on the formation of synapses. Studies in the visual system
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indicate that, although early stages of development are not dependent upon neural activity, the final sorting of axons at targets is influenced by such activity (Kalil). When there is a balance of activity in both pre- and postsynaptic elements, and when postsynaptic depolarization is sufficient to allow activation of NMDA-receptor-gated conductances, synaptic contacts may be strengthened, leading to selective stabilization of elements with correlated activity (Singer). In his paper, Jones demonstrates that neural activity in the primate cerebral cortex regulates gene expression and thus controls the appearance of various transmitters and peptides. Changes in activity can rapidly affect the production of neuroactive molecules in both young and adults and could thus influence the development and subsequent plasticity of the cortex. Activity-dependent recruitment and regulation of synapses have similarly been demonstrated in identified crustacean motor neurones (Atwood and Govind).

The crustacean preparation also allows observation of identified neurones at many stages during development and ageing and shows progressive changes in synapse organization and location. Recently developed techniques of epifluorescence microscopy have enabled the growth of a single optic nerve fibre in living tadpoles to be visualized directly and the changing morphology of the nerve terminal arborizations to be followed from day to day. Grafting experiments coupled with these techniques have helped to demonstrate that positional cues play an important role in the formation of axonal projections. In the retinotectal system of these animals cell-autonomous cues appear to override other influences such as competition or association with other retinal projections (Fraser and O'Rourke). Another example of the ability of amphibian neurones to find their appropriate targets is provided by the anatomical and electrophysiological studies of Frank and Mendelson. These show that interrupted spinal axons from brachial dorsal root ganglia regrow into the cord along unusual, albeit short, courses to terminate in their appropriate fields of innervation.

Finally, it is becoming increasingly clear that regenerating (Aguayo et al.) or sprouting axons (Raisman and Field) in the adult mammalian CNS can accomplish some of the steps required for the restoration of functional synaptic connections when presynaptic and postsynaptic elements are, or can be, brought close together. Although there are indications that such connections are not randomly restored, it has yet to be shown whether the formation of normal connections that occurs during mammalian development and after regeneration in anamniotes can also be accomplished in the injured CNS of mature mammals.