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Neuromuscular Blocking & Stimulating Agents Volume I

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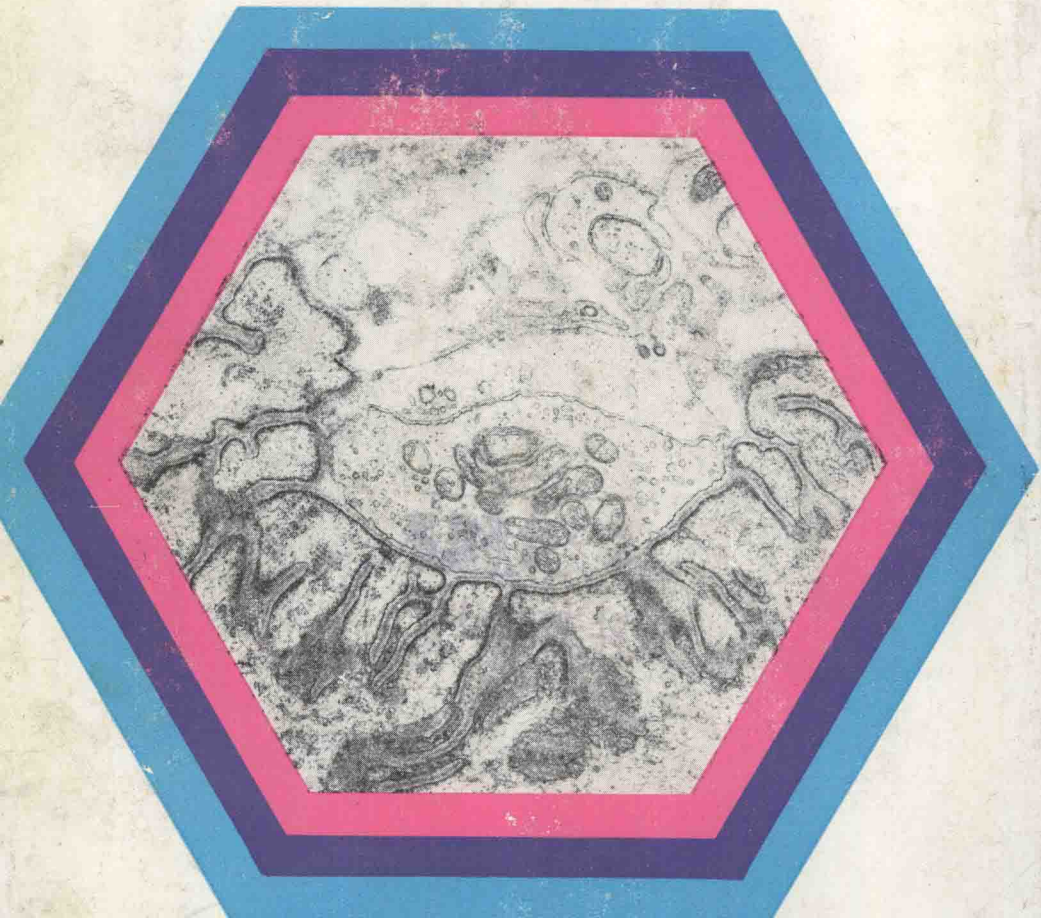
J. Cheymol *Paris*



INTERNATIONAL ENCYCLOPEDIA OF
PHARMACOLOGY AND THERAPEUTICS

NEUROMUSCULAR BLOCKING AND STIMULATING AGENTS

VOLUME I

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PREFACE

For the convenience of the reader, it has seemed appropriate to divide Section 14 into two volumes.

The first volume groups together the chapters relating to the study of the neuromuscular junction and its inhibitors, both natural and synthetic, with those dealing with their pharmacodynamics and their metabolism.

In the second, after a study of the peripheric stimulants, the chapters concerned with the clinical and therapeutic study of the modifiers of both the normal and pathological functioning of the neuromuscular synapse are grouped together.

Lastly, the final chapter enables all those who are interested in general biology to compare the myoneural junction of the vertebrates with that of the insects and the crustaceans.

J. Cheymol

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CHAPTER 1

INTRODUCTION

J. Cheymol

Paris

WHY publish a book on the neuromuscular junction when in the same issue of *The International Encyclopedia of Pharmacology and Therapeutics* there is another volume covering in general terms "The physiology and pharmacology of synaptic transmission"?

There are several reasons for this, each of which is enumerated:

AT THE ANATOMICAL LEVEL

The motor end-plate is the simplest form of synapse, the most exposed, "the most vulnerable synapse known" (Estable, 1959),* and the most accessible to investigation. Both the nervous and the muscular tissues are in intimate contact at this point owing to the absence of a myelin sheath, the whole structure being covered by neurilemma only, like a lid.

AT THE PHYSIOLOGICAL LEVEL

Whereas many nervous synapses receive a number of both excitatory as well as inhibitory inputs and in consequence are very difficult to study, the motor end-plate—a simple relay between the directing nerve and the effector muscle—lends itself easily to observation and to experiment. Several eminent research workers have devoted themselves to the study of this particular synapse.

This relative simplicity has made possible investigation into the details of the physicochemical phenomenon of neuromuscular transmission, in which various enzymes, acetylcholine, Na^+, K^+, Ca^{++} and Mg^{++} ions, electrical currents and probably other factors as well are involved.

* Estable, A. (1959) Curare and Synapse, in D. Bovet, *Curare and Curare-like Agents*, Elsevier, Amsterdam, p. 357.

Four recent research techniques have enabled striking advances to be made in this field. Let us simply enumerate them:

the *electronmicroscope* has allowed examination to be carried to the ultrastructural level;

the *microelectrode* has made possible the intracellular recording of the most minute electrical phenomena;

iontophoresis enables the intracellular application of minute amounts of pharmacologically active substances, identical or antagonistic to the chemical mediators, at the physiological dose level;

radioactive isotopes allow the movements of ions, responsible for the membrane potentials, to be followed and the receptors to be localized.

AT THE PHARMACOLOGICAL LEVEL

Although nearly a century has elapsed since Claude Bernard's original work with curare on the neuromuscular junction, contemporary pharmacologists continue to explore this fruitful field of study in its many aspects:

the investigation into an understanding of the fundamental process of neuromuscular transmission—for example, the link between the action potential and the release of acetylcholine;

the preparation of naturally occurring substances of known composition, isolated from the *Chondrodendron* and *Strychnos* species;

an appreciation of the role of the quaternary ammonium group (the presence of one or more such groups in a molecule almost certainly determines whether it shows a curarizing action);

the development of sensitive and specific tests, qualitative as well as quantitative, by which this effect can be followed and understood;

the great interest in the historic, folkloric (strange Indian poisons) and practical aspects (in, for example, anesthesiology, etc.).

Thanks to "scalpels pharmacologiques", research is advancing on two fronts, namely:

(i) An understanding of the structure of neuromuscular inhibitors which possess an optimum spacing between their quaternary ammonium groups (true gold number equals 14 or 20 Ångströms) has enabled a topographical model of specific receptors to be devised. Do the cholinesterases correspond to the cholinergic receptors? A vital question!

(ii) An understanding of the biochemistry of proteins, in which anionic and esterophilic sites are responsible for linkage with the transmitter, involves experiments in which the relatively unstable acetylcholine

is substituted at the giant motor end-plate of *Gymnotus*, by that of the more stable labeled curare-like substance.

AT THE PATHOLOGICAL LEVEL

The aetiology and hence the treatment of myopathies, in particular myasthenia, is still uncertain. This current state of affairs justifies the inclusion of separate chapters.

AT THE THERAPEUTIC LEVEL

Neuromuscular blocking agents have enabled operations previously lasting minutes to extend over hours, as well as inducing temporary relief by the abolition of contractures (tetanus, spastic states, etc.).

Finally, what relationships can be drawn between the anatomy and physiology of the neuromuscular junction of insects, crustacea and of higher animals? This study is far from being entirely academic. Has it been established that the lethal action of the powerful organophosphorous insecticides is by virtue of their anticholinesterase property, as established in higher animals? A better understanding of the basic mechanism would enable a more rational employment of these insecticides, so useful in the protection of man's food, and a move in the direction of less dangerous substances for the consumer.

All these facts and many others which are contained in this volume dictated the need for a separate article. The authors hope that basic scientists and clinicians will find the information they need in these two volumes (Vol. I, Chaps. 1–15; Vol. II, Chaps. 16–21).

Subsection I

THE NEUROMUSCULAR JUNCTION

CHAPTER 2

STRUCTURE AND CYTOCHEMICAL CHARACTERISTICS OF THE NEUROMUSCULAR JUNCTION

R. Couteaux

Paris

2.1. INTRODUCTION

The neuromuscular junctions where transmission of the impulse from a motor nerve to striated muscle takes place are characterized by a very short distance separating in these regions the plasma membrane of the motor axon from the plasma membrane of the muscle fiber, by the absence of other cytoplasms between these membranes, as well as by a certain number of structural and cytochemical peculiarities exhibited by the nerve fiber and the muscle fiber in the junctional region.

These are the only regions of the muscle where the interrelationship between the motor axons and the muscle fibers is so direct. Everywhere else the sheaths which surround the axons separate them from the muscle fibers.

The nerve fiber and the muscle fiber exercise an inductive influence one on the other in the region of their junction. During their development this leads to a sort of localized differentiation, which gives to the terminal portion of the nerve fiber and to the adjacent region of the muscle fiber their own morphological character.

The neuromuscular junction comprises both cytoplasms and nuclei belonging to cells of very different types: nerve cells, muscle cells, Schwann cells, and connective cells.

The special character of the nerve cells and the muscle fibers in the region of the junction adds further to the complexity of this ensemble composed of four tissues.

Although the nervous and muscular cytoplasms are intimately linked at the point of the junction, they constitute regions which are completely

distinct one from the other both anatomically and physiologically, each being limited by a plasma membrane and an extracellular basal lamina. The juncture of the nerve fiber and of the muscle fiber takes place between the two basal laminae and leaves a distance of some hundred Ångströms between the two plasma membranes. These two regions correspond to the presynaptic and postsynaptic portions of the junction.

One of these portions, the presynaptic, trophically depends on the nerve cell, whilst the other, the postsynaptic, depends on the muscle fiber. However, as regards the maintenance of their particular character in the synaptic zone each also depends one on the other and the proof for this may readily be shown for the postsynaptic portion. After section of the motor nerve, the disappearance of the nerve terminal takes place approximately at the same time as that of the distal segment of the motor axon and leaves apparently intact the muscle fiber including the postsynaptic portion of the junction. However, this portion soon demonstrates morphological and histochemical changes which finally lead to the disappearance of the characteristics which makes it a differentiated zone of the muscle fiber.

Induced by the action of the motor nerve fiber during the development this differentiation thus still remains dependent, for its maintenance, on the influences exerted by the nerve fiber.

The intimate union of the two portions of the junction has naturally been the source of great technical difficulties in localizing the phenomena for which they are both, respectively, the site.

Similar difficulties have been counted in the localization of the chemical constituents, and particularly the enzymes, and these difficulties have not yet been entirely overcome. It is not always easy to technically achieve the required precision to distinguish two sites only separated by a few hundred Ångströms.

The trophic interdependence of the two portions, nervous and muscular, of the junction also greatly complicates the study of the pathogenesis in neuromuscular diseases, since a lesion which initially is confined to one of the two zones, presynaptic or postsynaptic, of the junction more or less rapidly leads to an alteration of the other portion.

Only a very general approach to the neuromuscular junction will be considered here. More detailed information can be found in recent reviews and papers dealing with the morphology and cytochemistry of the neuromuscular junction (Andersson-Cedergren, 1959; Coërs and Woolf, 1959; Lehrer and Ornstein, 1959; Robertson, 1960; Birks *et al.*, 1960; Couteaux, 1960; Zacks, 1964; Csillik, 1965; Coërs, 1967).