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NEURAL PHYSIOL

NEURAL PHYSIOPATHOLOGY

Some Relationships of Normal to Altered Nervous System Activity

Edited by

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With Twenty-Eight Participants

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INTRODUCTION

OVER the last few decades remarkable progress has been made in the understanding of the structure and operation of glia, neurons, and neuron nets. New methods and concepts, both theoretical and experimental, have not only made it necessary to ask new questions, but have also further clarified complex problems of both a gross and microscopic nature. These developments have given rise to a new outlook on both the functional activity of the neuron as an entity and on the role in the total organismic picture played by particular neuronal, interneuronal, and multineuronal structural arrangements.

On all levels from the molecular up, the activity of these structures is being related (i.e., attempts are being made to clarify possible relationships) to behavior and disease. As a result of these investigations, it was thought interesting to see what suggestions could be made about what happens in the organism when something goes wrong at a particular level in the nervous hierarchy. The sequence of the contributions follows a scheme starting with peripheral disturbances and moving into and up the central nervous system. In a few cases, certain specific questions were asked.

Examples of these are the contributions of Dr. Grey Walter and Dr. Keith Killam. Dr. Walter was asked to discuss the nervous system as an oscillatory physical system, making an attempt to show what can happen when such a system is not functioning normally. Dr. Killam was posed the question of why and how drugs may correct neural abnormality. In no case was it expected that the answers to such questions were at hand. The basic idea was to bring together available data and analyze it from this point of view, in order to see how far it was possible to

go at the present time, and what ideas for further investigations appeared. With such a synthesis and somewhat unusual approach could one learn anything of changes in the nervous system that accompany learning, or perhaps, derive some clear understanding of such problems as the chemotherapeutic potential in nervous and mental disease?

In other words, by examining abnormal ("unphysiological") phenomena at various levels, perhaps we could increase our knowledge or research potential with regard to the behavioral process of nerve and brain; with regard to the clarification of the substance and activity of "mind"; and finally with regard to the role played by such processes in the integration and maintenance of the total organism.

It is not possible to express my gratitude to all those who have contributed to this symposium. I am deeply indebted to all of the participants for preparing their papers for publication. Particular thanks can be expressed only inadequately to the National Institute of Neurological Diseases and Blindness and its Council whose financial support and encouragement have made this series of volumes possible. To our many friends at The Upjohn Company of Kalamazoo, Michigan, go our thanks for their additional contribution. The Symposium was held under the auspices of the University of Maryland to which we also express our gratitude.

Our brief acknowledgements cannot be terminated without some expression of our thanks and admiration to Mr. Paul B. Hoeber and his staff. Their job of publication was made much more difficult as a result of the editor's sojourn in India. Without the patience, understanding, and efforts of Miss Claire Drullard this book would probably have never appeared at all.

ROBERT G. GRENELL

Trivandrum, India

NEURAL PHYSIOPATHOLOGY

CONTENTS

CHAPTER 1

Some Aspects of the "Abnormal" Neuromuscular Junction

STEPHEN THESLEFF

WE have been studying the effects of motor innervation on the chemical sensitivity of skeletal muscle. Interest in this subject was evoked by the observation that an excess of acetylcholine (ACh) reduced the chemosensitivity of a muscle, and subsequently this has led to an investigation of the opposite phenomenon, i.e., that of denervation supersensitivity.

First, I should like to relate our experimental results and then to briefly discuss their main implications.

Our studies were made on isolated mammalian skeletal muscle with electrical micromethods for drug application and recording. The technique used is illustrated by Figure 1-1. It is possible by an electric current to release iontophoretically constant quantities of ACh from the tip of a fine micropipette (5, 14). By careful manipulation of the pipette a close-range and localized application of ACh to the receptor structure of a single muscle fiber is achieved. At a sensitive "spot" iontophoretically released ACh

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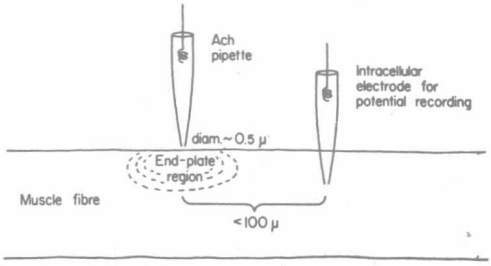

FIG. 1-1. A schematic illustration of the ACh-pipette and the intracellular electrode in their position at the motor end-plate of a single muscle fiber.

produces a transient membrane depolarization with a rapid time course. This potential change is recorded by a capillary microelectrode inserted into the muscle fiber close to the point of drug application. By moving the drug-pipette and the intracellular recording electrode to various parts of a muscle fiber it is possible to determine the distribution and relative sensitivity of ACh receptors in various parts of the fiber.

NERVE DEGENERATION

In an innervated muscle ACh produces depolarization only when applied to the end-plate region of a muscle fiber (Fig. 1-2

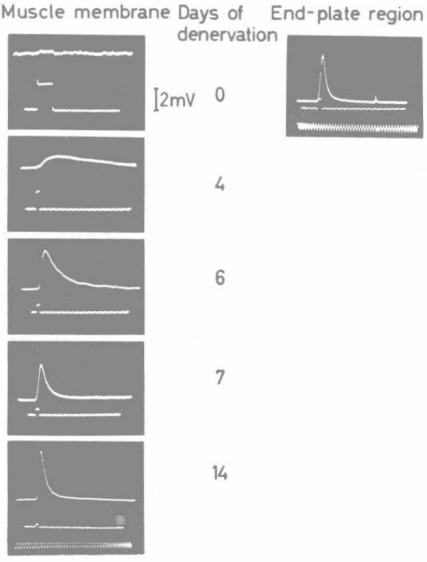

FIG. 1-2. An illustration of the sensitivity of innervated and denervated muscle fibers (cat's tenuissimus) to iontophoretically applied ACh. The membrane potential of the fiber is recorded in the upper tracing, and the current passing through the pipette in the lower tracing of each record. In an innervated muscle ACh produces membrane depolarization only when applied to the end-plate region (*upper right record*) but has no effect when released outside this area of the membrane (*upper left record*). After denervation the whole muscle becomes sensitive to ACh, which, wherever applied to the membrane, causes a potential change (*subsequent records*). Time marker, 100 c/s (2).

and lower records in Fig. 1-3). The area sensitive to ACh is small and covers normally not more than 1 mm. of the fiber length.

Following motor denervation, however, the entire muscle membrane becomes sensitive to locally applied ACh (2, 9). A few days after denervation iontophoretically released ACh produces depolarizations outside the former end-plate region, and one week later the whole muscle membrane is uniformly as

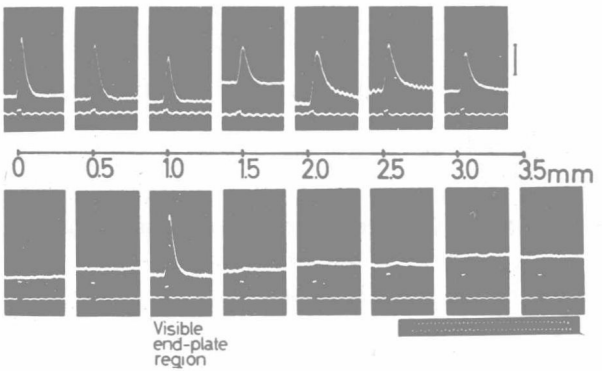

FIG. 1-3. The sensitivity of a muscle fiber of the cat's tenuissimus to locally applied ACh was tested by moving the tip of an ACh-pipette close to the cell membrane at points separated by distances of about 0.5 mm. In an innervated fiber (*lower records*) only the visible end-plate region is sensitive to ACh. In a 14-day denervated fiber a constant pulse of ACh produced a potential change at each point of the membrane, as is shown in the upper records. Time marker, 100 c/s; voltage calibration, 2 mV (2).

sensitive to ACh as the former end-plate region (Figs. 1-2 and 1-3).

The spread of chemosensitivity occurs from the end-plate toward the tendons. The sensitivity of the end-plate region to ACh is not increased by denervation. It retains about its original responsiveness to the drug and it is not affected by the process which renders the rest of the cell membrane equally sensitive to ACh.

The new ACh receptors which are formed in the muscle membrane after denervation have properties similar to those at an innervated end-plate (2). Thus, in a denervated muscle ACh

displaces the membrane potential toward an equilibrium value of about —10 mV. The reaction between ACh and the receptors proceeds even when no sodium is present and in the absence of a resting potential, as shown at the innervated end-plate by del Castillo and Katz (6). Furthermore, the mode of action of drugs such as carbachol and tubocurarine is not altered by denervation. However, drugs with anticholinesterase activity do not potentiate the effects of locally applied ACh in a denervated muscle. Presumably the denervated muscle membrane is, in a practical sense, devoid of cholinesterase (2).

EFFECTS OF BOTULINUM TOXIN

The conversion, following denervation, of the muscle membrane into an ACh-sensitive surface is presumably due to the absence of some influence exerted when the motor innervation is intact. To elucidate whether or not the chemical transmitter agent provided such an influence, use has been made of botulinum toxin (18).

Characteristic of botulinum poisoning is a lack of transmitter release from cholinergic nerves while otherwise nerve and muscle are unaffected by the toxin (13, 15, 20). As shown by Professor B. Katz the ultrastructure of motor nerve terminals is not altered by botulinum toxin, and electrophysiological results indicate that the toxin selectively blocks the mechanism responsible for the release of the chemical transmitter from the motor nerve (18).

When transmitter release is blocked by botulinum toxin the muscle fibers become sensitive to applied ACh along their entire length. About two weeks after the administration of the toxin, ACh released from the tip of a micropipette produces depolarizations with a rapid time course wherever applied to the muscle membrane (Fig. 1-4, upper records). The whole surface of the membrane becomes as sensitive to ACh as the end-plate which maintains its original responsiveness to the drug. The uniform sensitivity of the muscle membrane to ACh is similar to that which is observed in chronically denervated muscles.

When transmitter release is reduced but not completely abolished, as shown by the occurrence of spontaneous miniature end-plate potentials at a slow rate, the receptor area is enlarged but it does not cover the whole muscle fiber (Fig. 1-4).

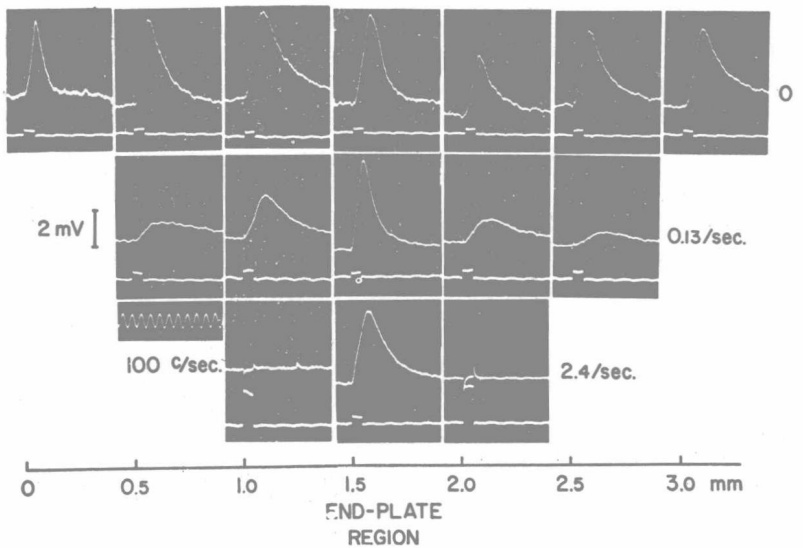

FIG. 1-4. In a tenuissimus muscle of the cat, intoxicated three weeks earlier with a small amount of botulinum toxin, muscle fibers were observed in which the ACh-sensitive surface varied in size. The fiber illustrated by the upper records was uniformly sensitive to applied ACh over a distance of at least 1.5 mm. at each side of the end-plate. The size of the ACh-sensitive surface in two other fibers was smaller (*middle and lower records*). The respective frequency of miniature end-plate potentials is shown by right-hand figures (18).

Since, as mentioned, botulinum toxin is without effect on the morphological structure of motor nerve endings it may be concluded that lack of transmitter release and not nerve degeneration is responsible for initiating the process which causes the high and uniform chemical sensitivity of chronically denervated muscles.

EFFECTS OF DECENTRALIZATION

The possibility that the extension of chemosensitivity, following denervation, was due to inactivity has been investigated by