FUNDAMENTALS OF VISCERAL INNERVATION

BUDH DEV BHAGAT
Professor of Physiology and Pharmacology
Saint Louis University
School of Medicine
St. Louis, Missouri

PAUL A. YOUNG
Professor of Anatomy
Saint Louis University
School of Medicine
St. Louis, Missouri

DONALD E. BIGGERSTAFF
Chief, Medical Illustration
Southern Illinois University
School of Medicine
Springfield, Illinois

Recent advances, based on refined biochemical, histochemical and ultrastructural techniques, have added much to the concepts of visceral innervation. Years of experience in teaching and research have gone into the writing of this concise volume on the autonomic nervous system. In preparing this text an effort has been made to update the literature already available, incorporate recent research, present new attitudes, and indicate what appears to be the coming trend. Extensive coverage is given to the most recent advances concerning the mechanism of synthesis, release, and inactivation of neurotransmitters at neuroeffector junctions in the viscera. Every effort has been made to integrate anatomy, physiology and pharmacology in order to present the subject in a unified and logically organized manner. A unique feature of this book is the abundant use of anatomical illustrations as well as physiological and biochemical schemata which will help the reader to grasp the subject more thoroughly and easily.

This book should be on the desk of every medical student and person wanting to learn about the anatomy and physiology of the autonomic nervous system. It will also serve as a valuable aid for teachers in the field who want to emphasize the use of a concept and reasoning rather than a subject matter and fact approach to their teaching.

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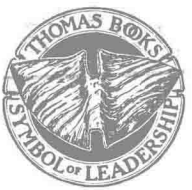

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FUNDAMENTALS OF VISCERAL INNERVATION

This book is dedicated to
our parents
Was Dev and Subdhra Bhagat
Nicholas and Olive Young
Selby and Theda Biggerstaff

PREFACE

THIS ABUNDANTLY ILLUSTRATED BOOK provides a concise exposition of the autonomic nervous system. It is intended to be used as a core text mainly by students. It is not intended to be a reference text for the research worker. The content of the text represents subjects dealing with the anatomy, physiology, and pharmacology of the autonomic nervous system taught to our students in the past two decades. This book should be, therefore, on the desk of every medical student and other persons who want to learn about the anatomy and physiology of the autonomic nervous system.

During the past decade, due to studies in electron microscopy and to the development of specific chemical methods for the identification and measurement of transmitters in tissues, considerable advances have been made in our knowledge of the autonomic nervous system. In preparing this text, an effort has been made to incorporate the results of recent research and newer attitudes and to indicate what appears to be a coming trend. Space limitations prohibit giving references.

We wish to express our appreciation to Mrs. Jo Ann Higdon, Miss Marian F. Parmley, and Mrs. Margaret A. Pomranz for typing the manuscript, and we are especially grateful to Miss Judy Wilson and Miss Ruth Gillies for their secretarial and editorial assistance.

Budh D. Bhagat
Paul A. Young
Donald E. Biggerstaff

CONTENTS

FUNDAMENTALS OF VISCERAL INNERVATION

CHAPTER 1

THE NEURON

ONE OF THE FUNDAMENTAL properties of all animals is the ability to respond to environmental changes. Such responses in higher animals are mediated by specialized tissue that forms the nervous system. Basically, nervous tissue has two main functions: (1) irritability or the capacity to respond to a stimulus, and (2) conductivity or the capacity to transmit impulses rapidly over long distances without any loss of signal strength.

The nervous system of man (and all animals down to the primitive coelenterates) is composed of individual functional units, the neurons, which are arranged in chains that form circuits. Each neuron consists of a cell body, one or more protoplasmic processes, called dendrites (if they conduct toward the cell body) or axons (if they conduct away from the cell body), and terminals. Neurons are morphologically classified in terms of their number of cytoplasmic processes. They are unipolar (one process), bipolar (two processes), and multipolar (three or more processes).

Some special features of neurons are their ectodermal origin, their inability to reproduce new neurons, their extreme dependence on a constant supply of oxygen and glucose, and the trophic nature of their cell bodies.

Cell Body

The nerve cell is surrounded by a plasma (cell) membrane formed by three lipoprotein layers with an overall thickness of 70 to 80Å. Localized specializations occur at synaptic and adhesive junctions and at the initial segment of the axon.

The nucleus of a nerve cell is within the cell body and is usually centrally located. In many autonomic neurons, however, nuclei are eccentric in location. The nucleus contains dust-like chromatin rich in DNA, and one or more prominent nucleoli, rich in RNA. In neurons of females, a small nucleolar satellite rich in DNA is frequently attached to the periphery of the nucleolus and is thought to represent an X chromosome.

Ultrastructurally, the nucleus is surrounded by a nuclear envelope consisting of two membranes, inner and outer. Each is about 70Å in diameter, and they are separated from each other by a space of varying diameter. The inner membrane is smooth, whereas the outer is ruffled and frequently continuous with the endoplasmic reticulum. The membranes are periodically interrupted by pores which occasionally appear to be closed by a thin membrane. The nucleolus consists of an interwoven mass of granules (pars amorpha) and fine filaments (nucleonema).

Within the cytoplasm of the perikaryon and large dendrites are Nissl bodies consisting of plates or cisterns of rough endoplasmic reticulum and free ribosomes; both are the sites for protein synthesis. These Nissl bodies are absent in the axon hillock. In addition, smooth endoplasmic reticulum known as the Golgi apparatus, is present and is believed to be concerned with secretion of intracellular material such as enzymes and structural macromolecules. Although the Golgi apparatus is usually perinuclear in position, it may extend into the proximal parts of larger dendrites. Mitochondria, which occur throughout the nerve cell body and its processes, present the same morphological features as in other cells. In addition to oxidative phosphorylation, neuronal mitochondria perhaps incorporate amino acids into protein. Thus, the cell body containing the nucleus and many constituents involved in metabolic processes, is re-

sponsible for maintaining the metabolism of the neuron including its growth and repair.

Neurofibrils, readily demonstrated by reduced silver methods as elongated structures extending throughout the cytoplasm of the cell body and its processes, are thought to be aggregates of microtubules and neurofilaments. Microtubules, elongated tubular structures from about 200 to 300Å in diameter, are more abundant in dendrites, whereas neurofilaments, tubular structures about 100Å in diameter, are more prevalent in axons. In addition to providing cellular support, the neurofibrils may enhance cytoplasmic flow from the cell body to the distal parts of the neuronal processes. It has been shown that disruption of the neurofilament impairs the axoplasmic flow of many neuronal constituents. Features of the nerve cell body are presented in Figure 1.

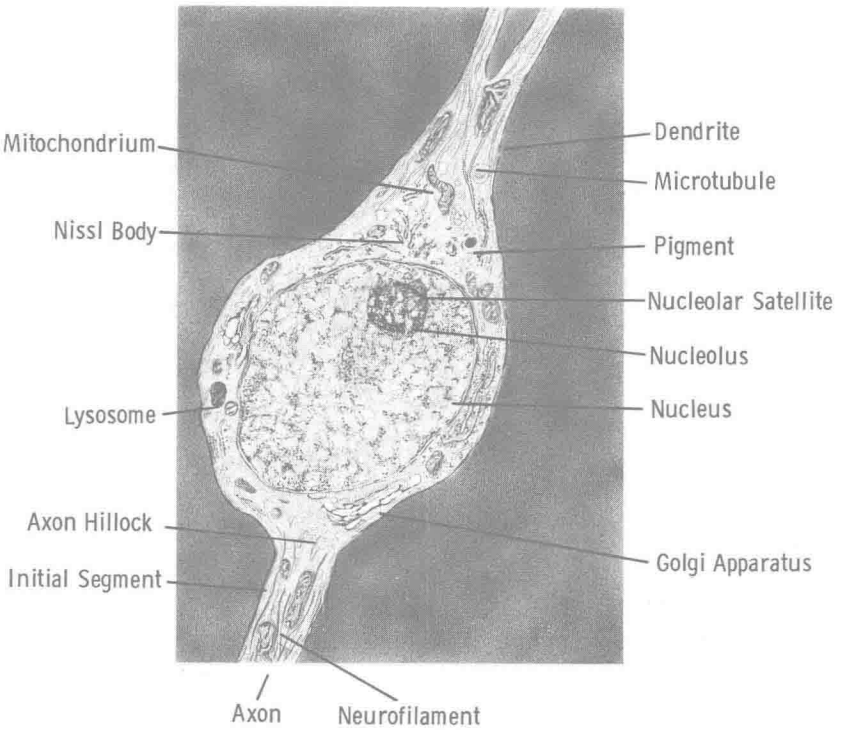

Figure 1. Illustration showing the ultrastructural features of a neuron.

Axons

The axon is the protoplasmic process that carries the nerve impulse away from the cell body. Characteristically they are longer than dendrites and do not taper. Also, axons are covered whereas dendrites are naked. A comparison of axons and dendrites is given in Table I.

TABLE I
COMPARISON OF AXONS AND DENDRITES

Feature	Axon	Dendrite
Length	Longer	Shorter
Diameter	Uniform	Tapers
Branching	Collaterals at right angles	Profuse and at acute angles
Surface	Smooth	Spiny
Coverings	Neurolemma in PNS Myelin in PNS & CNS	Naked
Nissl	None	Present in larger
Ultrastructure	Longitudinal neurofilaments	Longitudinal microtubules
Conduction	Away from soma	Toward soma

The axon emanates from the neuronal soma at the axon hillock. The first part of the axon is called the initial segment. In myelinated axons the initial segment extends as far as the beginning of the myelin sheath. Branches of axons, referred to as collaterals, are few in number and usually arise at right angles to the axon.

The axolemma, or plasma membrane of the axon, has the same characteristics as the unit membrane. It is modified at the initial segment, at nodes of Ranvier, in paranodal regions,. and at synaptic sites.

The axoplasm contains mitochondria, neurofilaments, microtubules, agranular endoplasmic reticulum, and various vesicles. However, it does not contain granular endoplasmic reticulum or ribosomes. In contrast to dendritic cytoplasm, axoplasm contains relatively few microtubules and many neurofilaments. Both

of these are oriented parallel to the long axis of the axon. In contrast to both dendrite and cell body, the axon possesses no apparent synthesizing capacity of its own. It is believed that the cell body synthesizes all the necessary macromolecules for the axon, and axoplasmic flow carries them from the cell body to all distal parts of the axon.

Axons may be either myelinated or nonmyelinated. Myelinated axons are surrounded by a sheath of fatty material known as myelin. This layer of lipid material is of variable thickness. The myelin sheath in the central nervous system is formed in the oligodendrocytes, whereas in the peripheral nervous system, it is formed in the Schwann cells. In both cases, it develops by a spiral wrapping of the respective cell around the axon. At intervals varying from 0.2 to 1 mm, the myelin sheath is interrupted by short gaps called the nodes of Ranvier (Fig. 2).

Unmyelinated axons in the peripheral nervous system are located in troughs, or gutters, in Schwann cells. In the brain and spinal cord, they are related to glial elements.

In the peripheral nervous system, individual myelinated and unmyelinated fibers are invested by loosely arranged connective tissue, the *endoneurium*. Groups of these fibers are gathered in variable sized bundles and are surrounded by a dense and lamellated connective tissue sheath, the *perineurium*, which continues to surround the bundles, even after they branch. Groups of bundles are loosely held together by an external connective tissue covering, the *epineurium*. This entire assembly is called a nerve.

Terminals

Interneuronal

Except for unipolar and bipolar nerve cells in the cerebrospinal ganglia, the soma and dendrites of virtually all other neurons have a vast number of terminal endings from axons of other neurons. These junctions between neurons are called synapses and serve to transmit the impulses from one neuron to another. Synapses are dynamically polarized so that the im-

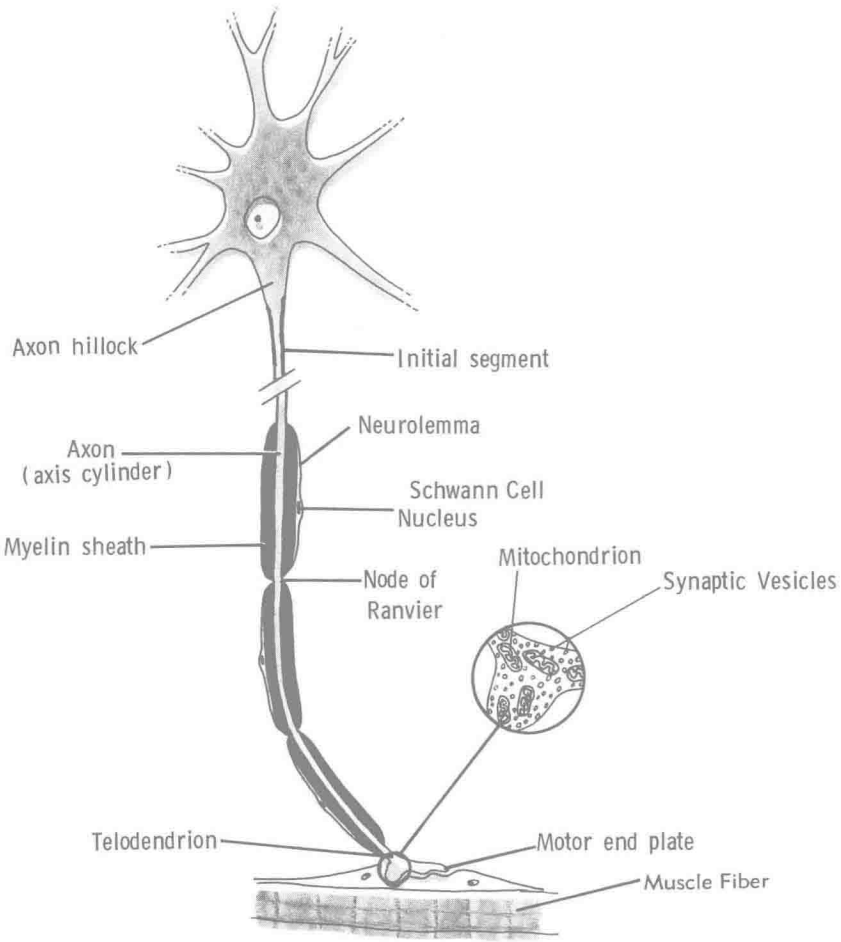

Figure 2. Illustration of motor nerve fiber.

pulses always pass from the terminal ending of the first neuron to the surface of the second neuron.

With light microscopy the terminal axons exhibit a wide variety of forms, the most common being round end-loops called boutons. Electron microscopy has revealed that the axon terminal, or bouton, is filled with large numbers of membrane-bound vesicles and numerous mitochondria.

The synaptic surface of the bouton possesses a distinct presynaptic membrane which is separated from the postsynaptic part of the target neuron by a gap, or synaptic cleft. Variations in the width of the synaptic cleft characterize synapses as either electrical or chemical (see Fig. 4 below.) Electrically coupled synapses commonly show fusion of the pre- and postsynaptic membranes. Chemically coupled synapses possess gaps that measure between 200 to 600Å. During the process of chemical transmission, an electrical signal in the presynaptic membrane causes the release of a transmitter into the synaptic cleft where it interacts with a specific site (called a receptor) on the postsynaptic membrane to initiate an action potential.

Neuromuscular

The terminal parts of motor axons assume specialized forms where they synapse on skeletal or smooth muscle.

In the case of the somatic system, the motor axon loses its myelin sheath and divides into numerous branches immediately before it reaches the muscle fibers to be innervated (Fig. 3). A single axon may innervate hundreds of muscle fibers. The alpha motor neuron, its axon, and the muscle fibers it innervates is a motor unit. The size of motor units varies tremendously, since a single somatic motor axon may supply from twenty or thirty to over a thousand or more muscle fibers.

The region of the muscle fiber which makes contact with the motor nerve is called a motor end-plate (Fig. 5). The axon terminal is discretely isolated from the surface of the muscle by a synaptic cleft.

Terminals of autonomic axons on smooth muscle are far more complex and differ from somatic motor terminals in the following ways:

1. the autonomic terminal axon becomes varicose as it approaches the effector cell, whereas the somatic axon does not;
2. relatively few of all the fibers of a smooth muscle bundle receive a terminal twig, whereas every skeletal muscle fiber has a motor end-plate;
3. the autonomic terminal axon is within a bundle con-

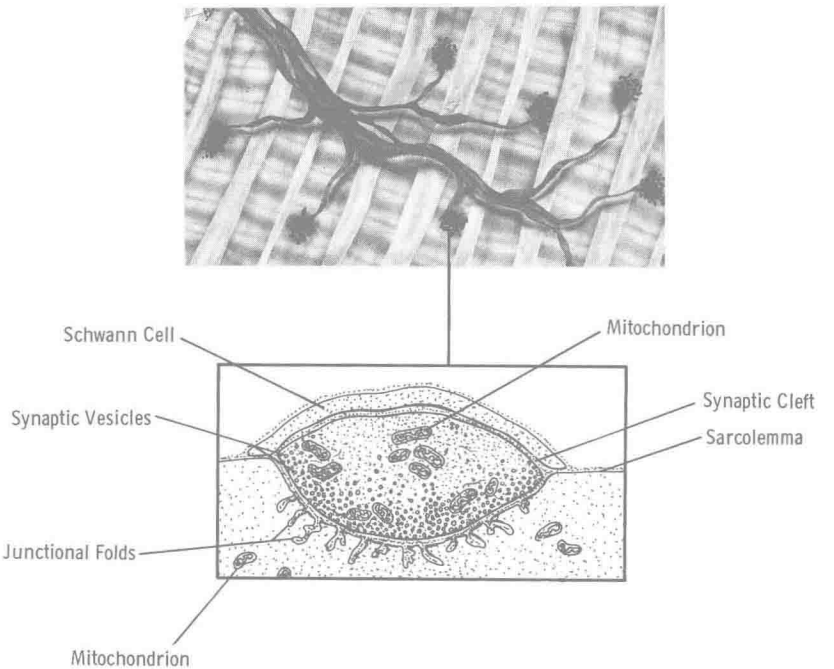

Figure 3. Illustration and schematic drawing of a myoneural junction. Motor nerve fiber within a nerve trunk originates from an alpha motor neuron. Just before it reaches the muscle it innervates, the axon loses its myelin sheath and divides into a number of branches. Each branch terminates on a single muscle fiber. The region of the muscle fiber with which the nerve makes contact is known as the end-plate. An alpha motor neuron and the muscle fibers it innervates is a motor unit.

taining terminals from many axons. Thus, a smooth muscle fiber may be innervated by terminals of different axons, whereas a somatic muscle fiber is innervated by only one axon.

A feature of all chemical nerve terminals both interneuronal and neuromuscular, is the presence of intracellular synaptic vesicles. These vesicles measure from 200 to 800Å in diameter. Some have an electron-dense core while others have an electron-translucent core. These vesicles are the storage sites for chemical substances.