A. Scope of This Chapter and Historical Introduction

1. Scope of the Chapter

Some of the cholinergic matters that were discussed in earlier chapters are pertinent to the understanding of the cholinergic central nervous system; these include cholinergic cells and their pathways; metabolism of acetylcholine; and central nicotinic and muscarinic receptors. This chapter paints a detailed picture of the system. The scope of this chapter is very wide, and this wide range illustrates well the diversity and the richness of the cholinergic function generally and of the central cholinergic activities specifically.

The subjects to be covered concern three organizational levels. On the neuronal level, the physiological activities of cholinergic neurons and their responses at the pre- and postsynaptic receptor sites to acetylcholine (ACh), cholinomimetics, and anticholinergic drugs are explored; additionally, cholinergic neurons’ pharmacology, that is, their response to noncholinergic transmitters and drugs, is presented. Then the neurons’ dependence on second messenger mechanisms and the molecular biology of the receptor sites are explored. Finally, the interactions among transmitters and modulators are described.

On the system level, this chapter describes physiological functions and responses of the cholinergic pathways or networks to cholinergic and noncholinergic transmitters and drugs. It also describes functions and responses of central areas, which involve both cholinergic and noncholinergic pathways (for example, the basal ganglia and the reticular formation) to the cholinergic and noncholinergic transmitters and drugs. Accordingly, activities and cholinergic and pharmacological responses of the electroencephalogram (EEG) and evoked potentials, respiration, hypothalamic homeostasis, and endocrine functions are depicted in detail.

Behaviorally, a higher level of organization is explored. It concerns cholinergic correlates exhibited through cognitive functions such as learning, addiction, and aggression and less frequently explored behaviors such as imprinting and vocalization. In addition the chapter addresses the pharmacology of these behaviors. Finally, as an excursion into the future, the cholinergic aspect of the mind-brain relation will also be speculated upon.

Because central cholinergic pathways and networks are ubiquitous (see Chapter 2), all functions and behaviors must exhibit cholinergic correlates. In fact, there is no known or measurable function or behavior, including mental disease, that does not exhibit cholinergic aspects, and that does not respond to cholinergic and anticholinergic drugs. However, it is a truism that these behaviors are never purely cholinergic in nature: they are affected by a multitude of noncholinergic transmitters, drugs, and modulators (see Karczmar, 1978a, 1978b and Glowinski and Karczmar, 1979). Indeed, there is a physiological interplay, at both pre- and postsynaptic sites, between the various transmitter and/or modulator systems, and it underlies all functions and behaviors. This interplay is reciprocal; for example, catecholamines affect the release of ACh, and vice versa. This interplay is needed for the subtle control of neuronal activities, behaviors, and functions; for example, ACh, monoamines, peptides, and amino acids interact in rapid eye movement (REM) sleep, seizures, aggression, and cognition.
2. Historical Introduction

a. Discontinuity of the Early Story

The studies of the central cholinergic system do not constitute a continuous or logical sequence of experimental events. The 19th-century findings concerning peripheral effects of physostigmine or the Calabar bean extract preceded Otto Loewi’s demonstration of the presence of cholinergic transmission at the periphery; the 19th- and early-20th-century discovery of the central effects of physostigmine and atropine predate the concept and the demonstration of central cholinergic transmission. Altogether, these findings did not lead to a definition of the site and mechanism of action of these drugs. In fact, the distinguished scientists of the time period in question had as little conception of the mechanism of action of the Calabar bean, physostigmine, or atropine as the Calabar natives who used the bean in their truth ordeals (see Chapter 7 A).

Also, a considerable time gap among qualitative and quantitative site-focused studies must be noted. In the early and mid-19th century, Scottish and German pharmacologists conducted studies that were qualitative in nature; 50 years later, quantitative, site-focused studies were carried out by English, Austrian, German, and Canadian pharmacologists and neurophysiologists. It took another 30 years to conceptually relate the results obtained with physostigmine to Otto Loewi’s demonstration of the peripheral cholinergic transmission. Similarly, the first quantitative studies by Gantt and Freile (1944) and Funderburk and Case (1947) of the central behavioral effects of cholinergic drugs antedate by some 10 years the demonstration of central cholinergic transmission; actually, these investigators referred to the mechanism and site of the central action of ACh as “obscure.”

The 1950s demonstration of central cholinergic transmission by Henry Dale, William Feldberg, Joshua Gaddum, and John Eccles (see below, section A-2b, A-2c), the expansion of this demonstration from the spinal to supraspinal sites (cf. Krnjevic and Phillis, 1963), and the initiation of the definition of the central cholinergic pathways (cf. Chapter 2 DI) led to the multifaceted explosion of the central cholinergic lore.

b. Early Studies of Nicotine, Physostigmine, and Related Substances

The early ethnographic and postethnographic studies of the Calabar bean and its active component, physostigmine, by British government officials and missionaries to Calabar and by Edinburgh’s medical men and masters of Materia Medica were described in detail in Chapter 7 A (see also Simmons, 1956). While many of the actions of these compounds that were described in Edinburgh are peripheral, it must be stressed that many of the effects evaluated in Edinburgh are central in character. For example, Hutchinson, the British consul to the “Calabar Province,” reported that victims of the ordeal both “shook” and foamed at the mouth. In Edinburgh, after self-experimental ingestion of Calabar bean, Robert Christison (1855) felt “torpidity” and sleepiness; paradoxically, his “mind was so active . . . that . . . he was not conscious of sleep”—an early report of REM sleep? Another Edinburghian, Fraser (1863, 1872) experimented with animals and demonstrated that the bean extract causes respiratory depression, miosis, and paralysis, as well as hyperthermia, an early example of hypothalamic action of cholinergic drugs (see below, section BIV-2). Fraser’s work on both peripheral and central interaction among the Calabar bean’s active ingredients and atropine is particularly important. Fraser (1870) also described how the bean’s extract prevents or abolishes strychnine convulsions.

German, British, French, and US investigators extended Fraser’s findings into the second part of the 19th century. This work was helped by the extraction, purification, and crystallization of the active ingredient of the Calabar bean (see Chapter 7 A). These workers confirmed and extended Fraser’s findings regarding the central actions of the bean’s extract. For example, Roeber described the “complete paralysis of the nerve cells . . . concerned with . . . pain” caused by the bean’s extract (1868; cf. Feldberg, 1945). However, the analgesic action of cholinergic drugs (a very interesting effect) was not picked up again until the 1940s (see below, section BV-2). In 1876, Harnack and Witkowski stressed that the active extract induces depressant actions that lead to “central paralysis” and respiratory depression. This effect was sometimes described as the second phase of action,