10 The Action of Nicotine in the Mammalian Brain

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1. The Cholinergic System in the Brain

Acetylcholine (ACh) is one of the predominant neurotransmitters in the brain. The majority of cholinergic cells are found in the medial septal nucleus, the basal forebrain, the striatum, and the brainstem (Struble et al. 1986). The major projection areas include cortex, hippocampus, striatum, substantia nigra, and medial habenula (Butcher 1995; Woolf et al. 1984). ACh is involved in the regulation of cortical arousal (Semba 1991), attention (Murphy and Sillito 1991), and sleep-wake cycles (Hobson 1990). Thus, the actions of ACh are manifold. The actions of ACh are mediated by two different types of receptors: the ionotropic nicotinic type and the metabotropic muscarinic type. Each of these classes of ACh receptor (AChR) has multiple subtypes with unique structural and functional characteristics, and thus ACh released from a nerve terminal may contribute to a wide variety of brain functions by activating different intracellular pathways depending on the distribution of the receptor types.

Nicotinic sites in the brain were detected long before the receptors were cloned (Clarke et al. 1985); however, the widespread distribution of the different subtypes of nicotinic acetylcholine receptor (nAChR) was not determined until the cloning of a total of 11 different subunits (reviewed in Chavez et al. 1997; Clarke 1993; Delbono et al. 1997; Role and Berg 1996; Sargent 1993). Moreover, the functional significance of these receptors was a mystery for many years largely
because of the inability to record nicotinic currents in neurons in the brain. Recently, it has been shown that nicotine facilitates the release of a number of different neurotransmitters by activating presynaptic or preterminal receptors (Gray et al. 1996; McGehee et al. 1995; Summers and Giacobini 1995; Wilkie et al. 1996). This suggests that nAChRs are acting primarily as modulators rather than as direct mediators of fast excitatory transmission (Clarke and Reuben 1996; Fu and Liu 1997; Wilkie et al. 1996). This modulatory role may be one of the most important functions of these receptors in the brain. These findings also help to explain the difficulties in detecting nicotinic currents in the brain, despite the evidence for widespread distribution of receptors. Perhaps the most compelling reason to believe that the nAChR is an important component of central nervous system (CNS) synapses is the evidence for pharmacological manipulation of behavior with compounds that specifically activate or block nAChR (Dani and Heinemann 1996; McGehee and Role 1996). The behavioral and physiological endpoints known to be manipulated by nicotine include enhanced learning and memory, arousal, concentration, and attention, as well as decreased anxiety and pain perception (Benowitz et al. 1989; Clarke 1993; Rosecrans and Karan 1993).

2. The Action of Nicotine in the Hippocampus

Tobacco smoking in humans as well as acute and chronic administration of nicotine in animals can enhance cognitive function (Levin 1992, 1993; Abdulla et al. 1993; Poincheval-Fuhrman and Sara 1993). Although we now know that the nAChR is important for the addictive properties of nicotine (Picciotto et al. 1998), the mechanism underlying these effects of nicotine, however, is unknown. One possibility is that nicotine-induced cognitive enhancement is mediated by nAChRs in the hippocampus (Gray et al. 1996), a brain area known to be important for learning and memory.