CHAPTER III

NICOTINE: SITES AND MECHANISMS OF ACTIONS

CONTENTS

Overview

Nicotine, in tobacco smoking concentrations, is a powerful psychoactive drug (Domino 1973; Kumar and Lader 1981; Balfour 1984). A wide variety of stimulant and depressant effects is observed in animals and humans that involves the central and peripheral nervous, cardiovascular, endocrine, gastrointestinal, and skeletal motor systems. These heterogeneous effects, along with behavioral and psychological variables, result in self-administration of tobacco, tobacco dependence, and withdrawal phenomena with abrupt cessation of tobacco smoking. This Chapter discusses sites and mechanisms of nicotine actions that may help to explain why tobacco products are self-administered.

The first Section of this Chapter provides general summaries of several major effects of nicotine in the body. Following this broad overview, the Chapter presents detailed discussions of sites and mechanisms of nicotine action that may be particularly important to understand tobacco use. Tissue distribution of nicotine, cerebral metabolic effects, and nicotine receptor binding are reviewed. Next, neuroendocrine and endocrine effects of nicotine are discussed. Then, electrophysiological effects of nicotine are presented. Finally, the effects of smoking on psychophysiological reactivity are discussed.

Peripheral Effects of Nicotine

Nicotine exerts its action on the cardiovascular, respiratory, skeletal motor, and gastrointestinal systems through stimulation of peripheral cholinergic neurons via afferent chemoreceptors and ganglia of the autonomic nervous system (ANS) (Ginzel 1967b). Inasmuch as both sympathetic and parasympathetic ganglia are stimulated by levels of nicotine derived from tobacco smoking, the end result depends on the summation of the effects of autonomic ganglion stimulation and reflex effects. The resulting peripheral physiological changes generally resemble sympathetic nervous system (SNS) arousal, but there are also some effects of nicotine and smoking that lead to physiological relaxation. For example, there is usually an increase in heart rate and blood pressure immediately following cigarette smoking. In addition, there is cutaneous vasoconstriction of the distal extremities. In contrast, nicotine can relax skeletal muscles (e.g., reduce patellar reflex) in humans and animals via effects on Renshaw cells (Domino and Von Baumgarten 1969; Ginzel and Eldred 1972; Ginzel l987). But it also can enhance tension in some muscles (e.g., trapezius muscle) (Fagerstrom and Gotestam 1977). Nicotine in small doses can enhance respiration through stimulation of peripheral chemoreceptors. Yet, high nicotine doses can cause respiratory failure. (See Appendix B for a discussion of

nicotine toxicity.) The gastrointestinal effects of nicotine are complex, involving an increase in secretions and reduced motility for a short period of time.

The peripheral actions of nicotine as a cholinergic agonist have made it a valuable pharmacologic tool for studying nicotinic cholinergic actions and functioning in many physiological systems. This Chapter focuses on the mechanisms of nicotine's actions relevant to tobacco use. Several peripheral actions of nicotine, for instance muscular relaxation, may contribute to the habitual use of tobacco products (see smoking and stress in Chapter VI). However, because the central nervous system (CNS) actions of nicotine and resulting neurochemical and electrical effects mediate subsequent biological and behavioral responses, a review of these actions contributes to an understanding of the reinforcing effects of nicotine.

Central Sites of Nicotine Actions

Nicotinic binding sites or receptors in the brain have been differentiated as very high, high, and low affinity types (Shimohama et al. 1985; Sloan, Todd, Martin 1984; Sloan et al. 1985). In the rat brain, when cholinergic muscarinic receptors are blocked, the autoradiographic distribution of ^{3}H-acetylcholine (ACh) and ^{3}H-nicotine are essentially identical (Clarke and Kumar 1984; Clarke, Pert, Pert 1984). However, these brain binding sites differ from peripheral nicotinic receptors in ganglia and skeletal muscle.

Chronic nicotine administration results in up-regulation in regional rat brain ^{3}H-ACh binding sites measured in the presence of atropine to block the muscarinic sites (Schwartz and Kellar 1985). Upregulation of ^{3}H-nicotine binding sites also has been reported after continuous nicotine infusions in mice (Marks, Burch, Collins 1983a). In contrast, most agonists that act on receptor sites in the body, when given chronically, produce a reduction (or down-regulation) in the number of receptors. Both Marks, Burch, and Collins (1983b) and Schwartz and Kellar (1983, 1985) have suggested that nicotinic cholinergic receptors undergo a functional blockade but that sufficient recovery would allow enhanced behavioral responses to low doses of nicotine to occur within 24 hr, as has been shown behaviorally by Clarke and Kumar (1983) and Ksir and coworkers (1985). This phenomenon may help to explain the tolerance to nicotine that develops with repeated exposure. However, the time course of changes in receptor number and other biological effects of nicotine must be carefully compared to determine mechanisms underlying tolerance. (See Chapter II for additional discussion.)

Several investigators have used in vitro autoradiography to identify ^{3}H-nicotine binding sites in the rat brain. These audioradiographic binding studies suggest where nicotine is acting. London, Waller, and Wamsley (1985) have found the most intense localization

of ^{3}H-labeled nicotine in the interpeduncular nucleus and medial habenula.

Cerebral metabolism studies also suggest key sites of action. London and colleagues (1985) have reported that nicotine stimulated local cerebral glucose utilization (LCGU) by 139 percent over that of the control in the medial habenula and by 50 to 100 percent in the superior colliculus and the anteroventral thalamic and interpeduncular nuclei. Other areas of the brain showed moderate or no significant changes. These effects of nicotine were blocked by mecamylamine, a nicotinic receptor antagonist, confirming that they acted via nicotinic receptors. Furthermore, they correlated well with the distribution of ^{3}H-nicotine binding in the brain except in layer IV of the neocortex, which showed nicotine binding but no change in LCGU. Sites that show increased glucose utilization after nicotine administration are probably functionally important loci of nicotinic actions. When nicotine binding and increased energy utilization both occur at a given site, it is likely to be involved in nicotine's actions.

Neuroendocrine Effects of Nicotine

Some of the actions of nicotine result from the release of ACh and other neurotransmitters, including norepinephrine (NE). Nicotinic cholinergic agonists including nicotine, carbachol, and l,l-dimethyl-4-phenylpiperazinium (DMPP) release endogenous ACh from the presynaptic cholinergic nerve terminals in addition to stimulating postsynaptic nicotinic receptors (Chiou 1973; Chiou and Long 1969). Nicotinic agonists also release ACh from rat cerebral cortical synaptic vesicles and can release newly synthesized ^{3}H-ACh from synaptosomes prepared from the myenteric plexus of guinea pig ileum and from mouse cortical synapses (Briggs and Cooper 1982; Rowell and Winkler 1984). These effects are Ca2+-dependent and are blocked by hexamethonium, a quarternary nicotinic receptor antagonist. In addition, nicotine-induced release of ACh in the hippocampal synaptosomes is blocked by the ion channel blocker, histrionicotoxin (Rapier et al. 1987). There is good evidence that nicotine releases ACh by a presynaptic mechanism. In contrast, presynaptic muscarinic receptors, mostly of the M_2-subtype, inhibit ACh release. Nicotine administration increases the amounts of other chemicals in the blood and brain, including serotonin, endogenous opioid peptides, pituitary hormones, catecholamines, and vasopressin (Domino 1979; Gilman et al. 1985; Marty and colleagues 1985). These chemicals may be involved in reinforcing effects of nicotine (see Chapters IV, VI).

Electrophysiological Effects of Nicotine

Nicotine administration is accompanied by brain wave or electroencephalogram (EEG) activation in animals (Domino 1967). The EEG-activating effects of small doses of nicotine occur in intact as well as

brainstem-transected animals. Nicotine acts primarily directly on brainstem neuronal circuits to produce these effects (Domino 1967). However, stimulation of peripheral afferents (Ginzel 1987) and release of catecholamines and possibly neurotransmitters and modulators, such as serotonin or histamine, may enhance the direct central effects of nicotine.

The EKG-activating effects of nicotine result in behavioral arousal (Domino, Dren, Yamamoto 1967). In cigarette smokers, nicotine produces sedative and stimulant effects (Kumar and Lader 1981). Aceto and Martin (1982) have reviewed the large variety of nicotine effects on behavior including facilitation of memory, the increase in spontaneous motor activity, nicotine's antinociceptive properties, and its suppression of irritability. These behavioral and psychological effects are discussed in Chapters IV and VI.

Distribution and Cerebral Metabolic Effects of Nicotine

Nicotine, administered by various routes, rapidly enters the brain and also distributes to specific, peripheral organs. Nicotine produces a distinct pattern of stimulation of cerebral metabolic activity that suggests where nicotine acts in the brain. This Section reviews studies on the distribution of nicotine after its administration to experimental animals, data on the relationship between tissue levels of nicotine and the drug's biological effects, and studies on mapping the cerebral metabolic effects of nicotine in the rat brain.

Distribution of Nicotine

Tissue Distribution of Nicotine: Time Course and Other Considerations

The distribution in the body of exogenously administered nicotine has been a topic of interest for more than a century and has been reviewed several times (Larson, Haag, Silvette 1961; Larson and Silvette 1968, 1971). As early as 1851, Orfila described experiments in which he detected nicotine in various organs (e.g., liver, kidney, lungs) and in the blood of animals after nicotine administration. In the 1950s the development of radiotracer methods led to a reexamination of nicotine distribution in the body.

Werle and Meyer (1950) found that the brain, compared with other organs, contained the highest nicotine levels immediately after injection of a lethal dose in guinea pigs. Tsujimoto and colleagues (1955) found a high concentration of nicotine in the brain after the drug was administered to rabbits and dogs. Yamamoto (1955) observed that 1 hr after a subcutaneous (s.c.) injection of 5 mg/kg in the rabbit, the nicotine content was highest in the kidney. The pancreas, ileum, ventricular muscle, skeletal muscle, lung, spleen, cerebral cortex, omental fat, and liver showed progressively lower

levels of nicotine at 1 hr. None of the tissues had detectable levels at 6 hr. In the dog, the highest level at 1 hr was in the kidney, followed by the pancreas, brain, ileum, liver and omental fat, spleen, heart, muscle, and lung.

Schmiterlow and colleagues used radiolabeled nicotine and whole-body autoradiography to study the distribution of nicotine in several species (Hansson and Schmiterlijw 1962; Appelgren, Hansson, Schmiterlow 1962, 1963; Hansson, Hoffman, Schmiterlow 1964; Schmiterlow et al. 1965; Schmiterlow et al. 1967). After radiolabeled nicotine was administered, radioactivity representing nicotine and its metabolites was concentrated in some organs, particularly the brain. Hansson and Schmiterlow (1962) injected (S)-nicotine-methyl-^{14}C intramuscularly or intravenously (i.v.) in mice. Within 5 min, high concentrations were found in the brain, adrenal medulla, stomach wall, and kidney. Lower concentrations were observed in the liver, skeletal muscle, and blood, but all concentrations were higher in tissue than in blood. Activity was high in the kidney from 5 min to 4 hr after the nicotine injection, with the highest activity occurring within the first hour. The adrenal medulla maintained a high concentration at 1 hr and 4 hr after injection, but little or no activity was observed at 24 hr. At 30 min, the levels were high in the walls of large blood vessels and in the bone marrow. Radioactivity disappeared rapidly from the brain.

Appelgren, Hansson, and Schmiterlow (1962) prepared whole-body autoradiograms of mice and cats given i.v. injections of ^{14}C-nicotine. An initial, heterogeneous accumulation of radioactivity occurred in the CNS. Fifteen minutes after the radiotracer injection, the cat brain showed distinctly more intense labeling of grey than of white matter. Also apparent was a regional distribution within grey matter areas, particularly in the hippocampus. By 30 min, radioactivity was reduced. Studies of mice demonstrated a high concentration of label in the brain at 5 min. By 30 min, the concentration was high in salivary glands, stomach contents, liver, and kidneys, while the brain was almost devoid of radioactivity. The same group also showed the accumulation of ^{14}C-nicotine in the retina of the eye after i.v. administration (Schmiterlow et al. 1965).

Fishman (1963) reported that in rats given randomly labeled ^{14}C-nicotine intraperitoneally (i.p.) and killed 3 hr later, the kidney contained the highest concentration of radioactivity, followed by the lung, liver, brain, skeletal muscle, spleen, and heart. In the dog, more ^{14}C-nicotine was present in the stomach wall than in any other tissue analyzed 3 hr after i.v. injection of radioactive nicotine.

Yamamoto, Inoki, and Iwatsubo (1967) gave mice s.c. injections of 5 mg/kg methyl-^{14}C-nicotine. Five minutes later, they found 0.5 to 1 µg/g (wet weight) of nicotine in various brain regions, including the cerebral cortex, superior and inferior portions of the brain stem, and

the cerebellum. Highest levels were detected 5 to 10 min after injection. Maximum levels in liver and whole blood were observed 2 and 10 min, respectively, after the injection.

Yamamoto, Inoki, and Iwatsubo (1968) studied penetration of ^{14}C-nicotine in rat tissues in vivo and in vitro. They found that 5 mg/kg, i.p., in male Wistar rats produced the following maximum tissue-to-blood ratios of ^{14}C-nicotine activity after 10 to 20 min: kidney, 8.7; liver, 6.7; submaxillary gland, 6.2; cerebral cortex, 3.5; brainstem, 2.4; and heart, 1.8. When they incubated tissue slices with 10^{-4} M ^{14}C-nicotine for 30 min at 37°C, the relative uptake of the label was similar: kidney cortex, 2.6; liver, 2.1; submaxillary gland, 2.1; and cerebral cortex, 2.0. Penetration in slices was unaffected by uncoupling oxidative phosphorylation or blocking metabolic pathways, indicating that the uptake was not by active transport. In vivo, tissue-to-blood ratios were greater than slice-to-medium ratios, indicating that a process other than passive diffusion was involved.

Because the respiratory tract is a major route by which nicotine from tobacco smoke enters the body, Schmiterlow and coworkers (1965) sprayed ^{14}C-nicotine solution directly onto the trachea of mice. Autoradiograms from mice killed at 2 min exhibited a high amount of radioactivity in the respiratory tract and lungs and showed that nicotine enters the CNS rapidly by this route as well. At 15 min, radioactivity still persisted in the lungs, was reduced in the brain, and appeared in large amounts in the kidneys and stomach.

Uptake and distribution of nicotine from tobacco smoke have also been assessed. Harris and Negroni (1965) exposed mice to cigarette smoke and extracted nicotine from the lungs (5 to 25 μg). Mattila and Airaksinen (1966) exposed guinea pigs to the smoke of one 4-g cigar over a period of 40 min, with intermittent ventilation with fresh air, and found that the same tissues which concentrated nicotine administered by other routes also showed nicotine uptake from smoke. Organ-to-blood ratios were lung, 2.0; spleen, 3.0; intestine, 2.9; and brain, 1.1.

The use of positron-emitting radiotracers permits in vivo estimation of nicotine uptake into the brain and other organs, offering the potential of eventually relating nicotine action in the living human brain to behavioral and disease states. Maziere and coworkers (1976) prepared (S)-nicotine-methyl-^{11}C, which they administered by i.v. injection to mice and rabbits. The time course of the radiotracer confirmed earlier studies and showed a maximum concentration in the 5 min following injection, except in the liver and spleen. Highest radioactivity was in kidneys and brain, followed by liver and lungs. The brain activity dropped rapidly, whereas the kidney concentration remained high (8 percent of injected dose) at 50 min after the injection. External imaging by a γ camera showed considerable

radioactivity in the head, kidneys, and liver. Brain activity decreased sharply over 1 hr, while activity remained high in liver and kidneys.

Maziere and coworkers (1979) used ^{11}C-nicotine and positron emission tomography (PET) in baboons and found that ^{11}C-nicotine readily penetrated into the brain and then dropped sharply with time. Radioactivity was high in the temporal lobe, cerebellum, occipital cortex, pons, and medulla oblongata. There was also a high, stable radioactivity level in the retina, consistent with the earlier observation that radioactivity from ^{14}C-nicotine is found in the retina after i.v. administration (Schmiterlow et al. 1965).

Heterogeneity of Nicotine Uptake: Microautoradiographic and Subcellular Studies

Appelgren, Hansson, and Schmiterlow (1963) used a microautoradiographic method to study the localization of nicotine within the superior cervical ganglion of the cat. Most of the radioactivity was localized in the ganglion cells, with little labeling of satellite cells and connective tissue.

Schmiterlow and coworkers (1967), using microautoradiograms of mouse brains after injection of ^{14}C-nicotine and ^{3}H-nicotine, reported that nicotine is concentrated in nerve cells. Brain areas with a high density of nerve cells, such as the molecular and pyramidal cell layers of the hippocampus and the molecular layer of the cerebellum, contained high amounts of radioactivity.

Yamamoto, Inoki, and Iwatsubo (1967) studied accumulation of ^{14}C-nicotine into subcellular fractions (nuclear, mitochondrial, nerve ending, microsomal, soluble) of mouse brain after i.p. injection of 5 mg/kg (20 µCi/kg). Most of the radioactivity was in the soluble fraction. Less than one-tenth of the radioactivity in the soluble fraction was found in microsomes and nerve endings; however, radioactivity levels in microsomes were somewhat higher than in nerve endings.

Effects of Nicotine on Cerebral Metabolism

Following the demonstration that ^{3}H-nicotine binds stereoselectively and specifically in preparations of rat brain (Yoshida and Imura 1979; Martin and Aceto 1981; Marks and Collins 1982), brain binding sites were visualized (Clarke, Pert, Pert 1984) and quantified (London, Waller, Wamsley 1985) by light microscopic autoradiography. However, mapping nicotinic binding sites or identifying specific binding sites for any drug or neurotransmitter does not necessarily mean that receptors are coupled to pharmacologic actions. An example of nonfunctional, stereoselective, specific binding is that of ^{3}H-naloxone to glass fiber filters (Hoffman, Altschuler, Fex 1981). In addition, because the brain is a highly interconnected organ, drugs

may produce effects in brain regions remote from their initial receptor interactions. Receptor maps would show primary binding sites but not sites where important secondary actions might occur.

Functional mapping procedures, such as the use of autoradiographic techniques to measure rates of LCGU and regional cerebral blood flow, are another way to determine the sites of the in vivo effects of nicotine in the brain. The 2-deoxy-D-[l-^{14}C]glucose (2-DG) method for measuring LCGU (Sokoloff et al. 1977) has been used to demonstrate a relationship between local cerebral function and glucose utilization under a wide variety of experimental conditions, including pharmacologic treatments (Sokoloff 1981; McCulloch 1982). The effects of acute, s.c. injections of nicotine on LCGU were examined by London and colleagues (1985, 1986) and by London, Szikszay, and Dam (1986), while Grunwald, Schrock, and Kuschinsky (1987) measured the effects on LCGU of constant plasma levels of nicotine produced by i.v. infusion.

Subcutaneous injections of nicotine stimulated LCGU in specific brain regions (Table 1, Figure l), including portions of the visual, limbic, and motor systems. Effects of nicotine infusion generally paralleled those obtained with s.c. injections. The greatest increase in response to s.c. nicotine occurred in the medial habenula. Marked increases in LCGU were noted in the anteroventral thalamic nucleus, interpeduncular nucleus, and superior colliculus. Moderate increases were seen in the retrosplenial cortex, interanteromedial thalamic nucleus, lateral geniculate body, and ventral tegmental area. No significant effects were observed in the frontoparietal cortex, lateral habenula, or central grey matter. LCGU responses to s.c. injection of nicotine were completely blocked by mecamylamine, indicating the specificity of nicotine effects.

The effects of nicotine on LCGU correlate well with the distributions of ^{3}H-nicotine binding sites (Clarke, Pert, Pert 1984; London, Waller, Wamsley 1985). Areas such as the thalamic nuclei, the interpeduncular nucleus, medial habenula, and the superior colliculus, where there is dense labeling with ^{3}H-nicotine, show moderate to marked nicotine-induced LCGU increases. Areas with less specific binding show smaller LCGU responses to nicotine, and the central grey matter, which lacks specific ^{3}H-nicotine binding, shows no LCGU response. Similarly, nicotine dramatically increases LCGU in the medial but not the lateral habenula, reflecting different densities of ^{3}H-nicotine binding sites. In general, ^{3}H-nicotine binding sites visualized autoradiographically in the rat brain are functional nicotine receptors. However, layer IV of the neocortex displays significant ^{3}H-nicotine binding, but lacks an LCGU response.

In most brain areas, significant LCGU stimulation was obtained with 0.3 mg/kg of nicotine s.c. (London et al. 1986), a dose similar to one used successfully in training rats to distinguish nicotine from

TABLE 1.—R,S-Nicotine effects on glucose utilization in the rat brain

Brain region	Local cerebral glucose utilization (μmol/100 g tissue/minute)	
	Saline control	Nicotine (1.75 mg/kg)
Frontoparietal cortex, layer IV	110 ± 8.1	108 ± 6.5
Retrosplenial cortex, layer I	98 ± 6.5	123 ± 5.1[1]
Thalamic nuclei		
Anteroventral	109 ± 6.5	201 ± 6.1[1]
Interanteromedial	125 ± 8.6	175 ± 12.3[1]
Lateral geniculate body	82 ± 6.8	106 ± 4.4[1]
Interpeduncular nucleus	99 ± 9.8	182 ± 9.3[1]
Medial habenula	70 ± 5.2	167 ± 3.7[1]
Superior colliculus	72 ± 5.2	142 ± 4.6[1]
Central grey matter	66 ± 4.0	77 ± 4.3

NOTE: Results are expressed as the means plus or minus standard deviation for four rats per group.
[1] Significantly different from saline control ($p \leq 0.05$).
SOURCE: London et al. (1985).

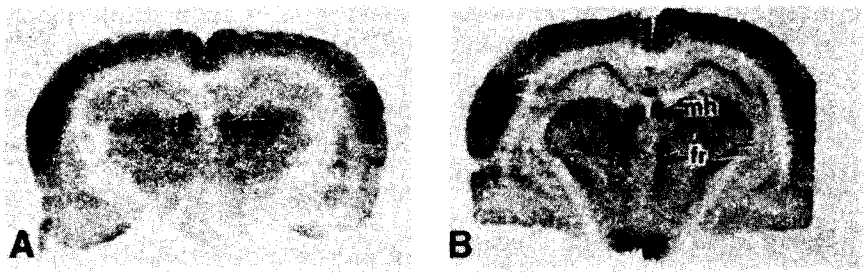

FIGURE 1.—Effect of subcutaneous R,S-nicotine (1 mg/kg, 2 min before 2-deoxyglucose) on autoradiographic grain densities, representing glucose utilization

NOTE: Photographs of x-ray film exposed to 20-μm brain sections from control rat (A) given 0.9 percent sodium chloride (1 mL/kg) and another rat (B) given nicotine; note the increased density in medial habenula (mh) and fasciculus retroflexus (fr).
SOURCE: London et al. (1986).

saline in a T-maze apparatus (0.4 mg/kg, s.c.) (Overton 1969). Nicotine-induced stimulation of LCGU in the ventral tegmental area

and the habenular complex (London et al. 1985, 1986) may relate to the reinforcing properties of the drug (see Chapter IV). These regions of the brain have been implicated in drug- and stimulation-induced reward systems, respectively (Wise 1980; Nakajima 1984). Additional studies, using specific conditions under which nicotine is reinforcing, are needed to elucidate the anatomical loci involved in nicotine-induced reward and to identify the neurophysiological mechanisms by which nicotine acts as a reinforcer.

Nicotine Receptors

Nicotine exerts diverse pharmacologic effects in both the peripheral nervous system (PNS) and CNS. The peripheral actions of nicotine are important, and some may reinforce the self-administration of nicotine. For example, stimulation in the trachea (Rose et al. 1984) seems to be involved in some of the pleasurable effects of smoking. Skeletal muscle relaxation and electrocortical arousal, both stimulated by actions of nicotine in the lung (Ginzel 1967a,b, 1975, 1987), may contribute to habitual tobacco use (Chapter VI). However, it is generally believed that the central actions of nicotine are of primary importance in reinforcing tobacco use (Chapter IV). In animals, the neuropsychopharmacologic effects of this drug are, with few if any exceptions, mediated through central sites of action. These effects are likely to contribute to the drug's reinforcing properties in animals and humans (Clarke 1987b). In addition, the effects of nicotinic antagonists on tobacco smoking in humans (Stolerman et al. 1973) and in rhesus monkeys (Glick, Jarvik, Nakamura 1970) suggest a central site of reinforcement, but do not rule out a peripheral site. To understand these actions, it is important to know exactly where nicotine acts in the body. This Section discusses evidence for nicotine receptors.

Peripheral Nicotine Receptors

In the mammalian PNS, nicotine and muscarine mimic different actions of ACh by acting at different types of cholinergic receptors. Nicotinic cholinergic receptors (nAChRs) have been subdivided according to location and sensitivity to nicotinic antagonists. Receptors of the C6 or "ganglionic" type are found principally at autonomic ganglia, in the adrenal medulla, and at sensory nerve endings; nicotinic cholinergic transmission in autonomic ganglia is selectively blocked by hexamethonium and certain other compounds. Receptors of the "neuromuscular" type (sometimes referred to as C10 type) are located on the muscle endplate, where transmission is selectively blocked by compounds such as decamethonium and alpha-bungarotoxin (*a*-BTX).

Higher doses of nicotine are required to stimulate nAChRs in skeletal muscle than at autonomic ganglia. Ganglionic nAChRs appear to be more sensitive than their neuromuscular counterparts, not only to the stimulant but also to the desensitizing actions of nicotine (Paton and Savini 1968). Doses of nicotine obtained by smoking cigarettes do not appear to affect the muscle endplate directly. Therefore, if the CNS were to possess both types of nAChR, doses of nicotine obtained by normal cigarette smoking might affect only the C6-receptor population. Accordingly, many of the central effects of nicotine in vivo and in vitro are reduced or blocked by nicotinic antagonists that are C6-selective in the periphery. The most widely used C6-selective antagonist is mecamylamine, which passes freely into the CNS after systemic administration. Mecamylamine antagonizes actions of nicotine in the brain and spinal cord, as revealed by behavioral (Collins et al. 1986; Goldberg, Spealman, Goldberg 1981) and electrophysiological experiments (Ueki, Koketsu, Domino 1961) and also by studies of neurotransmitter release (Hery et al. 1977; Chesselet 1984). There have been few attempts to determine whether these central nicotinic actions are also blocked by neuromuscular antagonists, while several studies support the existence of central C6 nAChRs (Aceto, Bentley, Dembinski 1969; Brown, Docherty, Halliwell 1983; Caulfield and Higgins 1983; Egan and North 1986).

The search for putative central *a*-BTX nAChRs has been hindered by several factors, including the central convulsant actions of *a*-BTX antagonists (Cohen, Morley, Snead 1981) and the probable need to deliver locally high concentrations of nicotine. Nevertheless, several studies have demonstrated actions of nicotine or cholinergic agonists that can be reduced or blocked by *a*-BTX, which acts selectively at neuromuscular nAChRs (Zatz and Brownstein 1981; Farley et al. 1983; de la Garza et al. 1987a).

Radioligand Binding to Putative Nicotine Cholinergic Receptors in Mammalian Brain

Many receptors for neurotransmitters in the brain have been identified through the use of radiolabeled probes (radioligands). Attempts to label putative brain nAChRs have used compounds with known potency at peripheral sites (see Table 2).

Agonist Binding

The stereospecific, saturable, and reversible binding of ^{3}H-nicotine to rodent brain is well-described (Romano and Goldstein 1980; Marks and Collins 1982; Costa and Murphy 1983; Benwell and Balfour 1985a; Clarke, Pert, Pert 1984). Most studies have demonstrated the existence of a population of high-affinity binding sites (reflected by a dissociation constant in the low nanomolar range) that is potently

TABLE 2.--Radioligands for putative nicotinic cholinergic receptors in mammals

Antagonists	Bind	Functional antagonism	Sites examined	Agonists
^{125}I-BTX	Yes	Yes	Muscle endplate	^{3}H-nicotine
	Yes	Yes	Autonomic ganglia, spinal cord	
	Yes	Yes	Brain (certain sites only)	^{3}H-methyl-carbachol
^{125}I-naja toxin	Yes	Yes	Muscle endplate	^{3}H-ACh (with excess muscarinic antagonist and AChE inhibitor)
	Yes	ND[1]	Brain	
^{3}H-dTC	ND	Yes	Muscle, spinal cord, ganglia	
	Yes	Yes	Brain	
^{3}H-DHBE	ND	Yes	Muscle, autonomic ganglia	
	Yes	Yes	Brain, spinal cord	
Neosurugatoxin	ND	No	Muscle endplate	
	ND	Yes	Autonomic ganglia	
	Yes	Yes	Brain (inhibits ^{3}H-nicotine)	

[1]ND=no data.

inhibited by nicotinic agonists including ACh. In contrast, most nicotinic antagonists have very low affinity for this site. Binding with similar characteristics has been reported in rat brain tissue with ^{3}H-methyl-carbachol (Abood and Grassi 1986; Boksa and Quirion 1987) and with ^{3}H-ACh in the presence of excess atropine to prevent binding to muscarinic receptor sites (Schwartz, McGee, Kellar 1982).

In the presence of atropine, tritiated nicotine and ^{3}H-ACh probably bind to the same population of high-affinity sites in rat brain. Thus, the two radioligands share the same neuroanatomical distribution of binding (Clarke, Schwartz et al. 1985; Marks et al. 1986; Martino-Barrows and Kellar 1987). Binding of both ligands is inhibited with similar potency by a range of nicotinic agents, is up-regulated by chronic nicotine treatment in vivo, is down-regulated by chronic treatment with acetylcholinesterase inhibitors, and is diminished by disulfide reducing agents in vitro (Marks et al. 1986; Martino-Barrows and Kellar 1987; Schwartz and Kellar 1983). Although less well studied, it appears that sites labeled by ^{3}H-methyl-carbachol are the same as those labeled by ^{3}H-ACh and ^{3}H-nicotine (Abood and Grassi 1986; Boksa and Quirion 1987). High-affinity nicotine binding sites have been found in brain tissue of mice (Marks and Collins 1982), rats (Romano and Goldstein 1980), monkeys (Friedman et al. 1985), and humans (Shimohama et al. 1985; Flynn and Mash 1986; Whitehouse et al. 1986).

Some investigators have reported a second class of sites which are characterized by lower binding affinity and higher capacity for ^{3}H-

nicotine. With no demonstrated differential anatomical distribution or stereoselectivity (Romano and Goldstein 1980; Marks and Collins 1982; Benwell and Balfour 1985b), these low-affinity sites are of questionable pharmacologic significance, but may be the result of post mortem proteolysis (Lippiello and Fernandes 1986). Careful analysis of ^{3}H-nicotine binding conducted in the absence of protease inhibitors has revealed the existence of five affinity sites or states (Sloan, Todd, Martin 1984). Functional studies (Martin et al. 1986) suggest that some of these different sites may represent in vivo sites of action for nicotine, although it is not clear which if any would be activated by nicotine doses obtained from typical cigarette smoking.

Radioligand Binding

Many receptors of different nicotine binding affinities have been reported. It is unclear whether these reflect different conformational states or binding sites of a single type of receptor, distinct receptor populations, or a single type of high-affinity site which has undergone proteolytic degradation. Preliminary evidence supports the existence of distinct receptor subtypes labeled by agonists. Two components of high-affinity ^{3}H-nicotine binding, differing in their affinity for neosurugatoxin, can be distinguished in rat brain. The relative proportion of these two components differs in different regions of the rat brain, suggesting that they are physically distinct receptors (Yamada et al. 1985).

Antagonist Binding

Most studies of nicotine binding in mammalian brain have used radioiodinated *a*-BTX (^{125}I-BTX), which binds with high affinity and in a saturable manner to sites in mammalian brain (Schmidt, Hunt, Polz-Tejera 1980; Oswald and Freeman 1981). This binding is selectively inhibited by nicotinic agents, including nicotine and ACh. Cobra (naja) alpha-toxin, like *a*-BTX, is a selective neuromuscular blocker in the mammal, and appears to label the same sites as *a*-BTX in mammalian brain. Binding is potently inhibited by unlabeled *a*-BTX and has a regional distribution resembling that of ^{125}I-BTX binding (Speth et al. 1977). The antagonist dihydro-beta-erythroidine (DHBE) binds to two sites in rat brain, but the regional distribution of binding differs from that of ^{125}I-BTX (Williams and Robinson 1984). DHBE acts with similar potency at both types of peripheral nAChR in vivo. It is not clear whether ^{3}H-d-tubocurarine binding is selectively inhibited by nicotinic agents. In rat brain, ^{125}I-BTX binds to a distinct population of sites that are not labeled with high affinity (nanomolar kD) by tritiated nicotinic agonists. Radioiodinated *a*-BTX sites have a different neuroanatomical distribution (Marks and Collins 1982; Schwartz, McGee, Kellar 1982; Clarke, Schwartz et al.

1985) and can be physically separated from tritiated agonist binding sites by affinity chromatography (Schneider and Betz 1985; Wonnacott 1986). This type of study helps to determine the location and numbers of nicotine binding sites.

Functional Significance of Nicotinic Binding Sites

High-Affinity Agonist Binding Sites

Brain sites which bind ^{3}H-ACh and ^{3}H-nicotine with high affinity represent nAChRs that respond in some ways like the C6 type of receptor found in the periphery (Clarke 1987a). Studies using the 2-DG technique have revealed that the neuroanatomical pattern of cerebral activation following the systemic administration of nicotine in rats is strikingly similar to the distribution of high-affinity agonist binding demonstrated autoradiographically (London et al. 1985; Grunwald, Schrok, Kuschinsky 1987). Pretreatment with mecamylamine blocks the effects of nicotine on LCGU, suggesting that putative ganglionic (C6-type) receptors in the brain are associated with high-affinity agonist binding.

Most of nicotine's actions on central receptors are blocked by the C6-selective antagonist mecamylamine. The relevant nAChRs are probably those which are labeled with high affinity by tritiated agonists. However, the absence of high-affinity agonist binding sites in PC12 cells (derived from a pheochromocytoma cell line) known to express C6-type receptors (Kemp and Morley 1986) indicates that although central and ganglionic nAChRs have pharmacologic similarities, they may not be identical at the molecular level.

High-affinity agonist binding sites are relevant to long-term effects of human tobacco smoking. Recently, Benwell, Balfour, and Anderson (in press) observed that the density of high-affinity ^{3}H-nicotine binding in post mortem human brain is higher in smokers than in nonsmokers. The increased density of sites in smokers is consistent with studies in animals that show that chronic treatment with nicotine leads to an increased number of nicotinic receptors in the brain (Schwartz and Kellar 1983; Marks, Burch, Collins 1983b).

Alpha-Bungarotoxin Binding Sites

Although *a*-BTX does not block nicotinic actions in all areas of the CNS (Duggan, Hall, Lee 1976; Egan and North 1986), there are several reports of antagonism (Zatz and Brownstein 1981; Farley et al. 1983; de la Garza et al. 1987a). In the rat cerebellum, locally applied nicotine alters single-unit activity in a manner dependent on cell type: nicotine excites interneurons but inhibits Purkinje cells. Both actions are directly postsynaptic (de la Garza et al. 1987, in press(b)). The inhibitory effects of nicotine are blocked by hexame-

thonium but not by *a*-BTX, which does block the excitatory effects (de la Garza et al., in press(a)).

Strain differences exist in mice in the physiological and behavioral effects of nicotine, in the development of tolerance to these effects, and in the regional distribution of ^{125}I-BTX binding density (Marks, Burch, Collins 1983a; Marks, Stitzel, Collins 1986). The genetically determined variation in response is not readily explained by differences in brain nicotinic receptors. However, a classical genetic analysis indicates that the density of ^{125}I-BTX binding sites in mouse hippocampus correlates with susceptibility to seizures induced by high doses of nicotine (Miner, Marks, Collins 1984). These and other considerations (Clarke 1987a) suggest that ^{125}I-BTX may label a subtype of nAChR in the brain and that this receptor is pharmacologically akin to the nAChR found in muscle.

Although ^{125}I-BTX binding sites are found in human brain, the available evidence suggests that nicotine at doses obtained from cigarette smoking does not activate this population of brain nAChRs. Rather, the pattern of neuronal activation that follows the in vivo administration of nicotine in animal experiments, even in doses far greater than those likely to occur during smoking, resembles the neuroanatomical distribution of high-affinity agonist binding sites (London et al. 1985; Grunwald, Schrok, Kuschinsky 1987). However, this issue is not conclusively resolved, and a potential role for bungarotoxin binding receptors in mediating effects of smoking cannot be completely excluded.

Behavioral and Physiological Studies

The effects of mecamylamine on several responses elicited by nicotine in mice have been examined (Collins et al. 1986). The responses are of two major classes: those blocked by low doses of mecamylamine (inhibitory concentrations for 50 percent of mice tested (IC_{50}) ‹ 0.1 mg/kg) (seizures and startle response) and those blocked by higher doses (IC_{50} approximately 1 mg/kg) (effects on respiratory, heart rate, body temperature, and Y-maze activity). Strain differences are also apparent in the sensitivity to mecamylamine blockade. These findings are consistent with the existence of at least two types of central nAChR.

The Neuroanatomical Distribution of Nicotinic Binding Sites in the Brain

High-Affinity Agonist Binding Sites

Rodent

Autoradiographic maps of high-affinity nicotinic binding sites in rat brain are essentially identical for ^{3}H-nicotine, ^{3}H-ACh, and ^{3}H-methyl-carbachol (Clarke, Pert, Pert 1984; Clarke, Schwartz et al.

1985; London, Waller, Wamsley 1985; Boksa and Quirion 1987). Dense labeling is observed (1) in the medial habenula and interpeduncular nucleus, which appear to belong to a common cholinergic system; (2) in the so-called specific motor and sensory nuclei of the thalamus and in layers III and IV of cerebral cortex with which they communicate; (3) in the substantia nigra pars compacta and ventral tegmental area, where labeling is associated with dopaminergic cell bodies (Clarke and Pert 1985); and (4) in the molecular layer of the dentate gyrus, the presubiculum, and the superficial layers of the superior colliculus. Labeling is sparse in the hippocampus and hypothalamus.

Monkey

The autoradiographic distribution of high-affinity ^{3}H-nicotine binding in rhesus monkey brain is similar to that in the rat (Friedman et al. 1985). Dense labeling has been noted in the anterior thalamic nuclei and in a band within cerebral cortex layer III. The latter band is densest and widest in the primary sensory areas. Several other thalamic nuclei are moderately labeled, but as in the rat, the label is sparse in the midline thalamic nuclei. In contrast to findings for the rat, the medial habenula appears unlabeled.

Human

High-affinity agonist binding has not been mapped autoradiographically in human brain. However, assays of a few dissected brain areas suggest the following pattern: nucleus basalis of Meynert > thalamus > putamen > hippocampus, cerebellum, cerebral cortex, and caudate nucleus (Shimohama et al. 1985). Two affinity sites for ^{3}H-nicotine have been detected, and the regional distribution observed reflects the presence of both sites.

Alpha-Bungarotoxin Binding Sites

Because ^{125}I-BTX sites may not be relevant to tobacco smoking, they will be discussed only briefly here. There are clear differences of regional distribution not only between mice and rats, but also between different strains of mice (Marks et al. 1986). The autoradiographic distribution of ^{125}I-BTX labeling in rat brain is strikingly different from the pattern of ^{3}H-agonist labeling, with highest site density in hippocampus, hypothalamus, and superior and inferior colliculi (Clarke, Schwartz et al. 1985). An attempt to map ^{125}I-BTX binding in human brain was hampered by a high degree of nonspecific binding, with diffuse specific labeling in the hippocampus and cerebral cortex (Lang and Henke 1983).

Molecular Biology

Goldman and colleagues have mapped regions in the brain which contain cell bodies expressing RNA that codes for putative nAChRs. The RNA identified is homologous to cDNA clones encoding the alpha subunits of the muscle nAChR and a putative neuronal nAChR (Goldman et al. 1986; Goldman et al. 1987). These and related findings show that a family of genes exists that codes for proteins similar to, but not identical with, the muscle nAChR. The functional role of these putative nAChR subtypes in the CNS is not clear.

Central Nicotinic Cholinergic Receptors: Pre- or Postsynaptic?

Presynaptic Regulation of Neurotransmitter Release

The release of ACh from some nerve terminals in the CNS (Rowe11 and Winkler 1984; Beani et al. 1985) and periphery (Briggs and Cooper 1982) is increased by activation of presynaptic nicotinic "autoreceptors." Preliminary evidence from lesion experiments suggests that some nicotinic autoreceptors in the brain may be high-affinity ^{3}H-nicotine binding sites (Clarke et al. 1986).

Nicotine also modulates the release of certain other neurotransmitters by acting at receptors located on nerve terminals. This form of regulation has been shown for dopaminergic, noradrenergic, and serotonergic terminals (Starke 1977; Chesselet 1984). Lesion studies suggest that these receptors are labeled by ^{3}H-agonists (Schwartz, Lehmann, Kellar 1984; Clarke and Pert 1985; Prutsky, Shaw, Cynader 1987).

Somatodendritic Postsynaptic Actions

Much of ^{3}H-agonist labeling probably represents nAChRs located on neuronal cell bodies or dendrites. For example, nicotine excites neurons postsynaptically in the medial habenula, locus coeruleus, and interpeduncular nucleus, all areas of moderate to dense ^{3}H-agonist binding (Brown, Docherty, Halliwell 1983; Egan and North 1986; McCormick and Prince 1987).

Neuroendocrine and Endocrine Effects of Nicotine

Nicotine has direct and indirect effects on several neuroendocrine and endocrine systems (Balfour 1982; Clarke 1987a; Hall 1982). This Section reviews research on the effects of nicotine in animals and humans that are relevant to understanding cigarette smoking. Nicotine effects on cholinergic and noncholinergic nicotinic receptors, as well as on the release of catecholamines, monoamines, pituitary hormones, cortisol, and other neuroendocrine chemicals,

are discussed. Effects on single neuroregulators are emphasized, but it is important to recognize that there are extensive interrelationships among these substances (Tuomisto and Mannisto 1985).

Nicotine has effects on peripheral endocrine as well as on central neuroendocrine functions. In the early 1900s researchers discovered that nicotine stimulated autonomic ganglia (ganglia were painted with tobacco solutions), inducing such effects as the release of adrenal catecholamines (Larson, Haag, Silvette 1961). As the health consequences of cigarette smoking have become clearer, many investigators have sought to determine tobacco's effects on the endocrine system, with the possibility that understanding such effects may help to explain smoking behavior. Nicotine is regarded as the major pharmacologic agent in tobacco and tobacco smoke responsible for alterations in endocrine function. However, there has not been a systematic evaluation of the effects of metabolites of nicotine or constituents of tobacco other than nicotine on the endocrine system.

The functional significance of nicotine-induced perturbations in hormonal patterns and the role of neuroregulators in smoking are poorly understood. Extensive literature using nicotinic agonists and antagonists indicates relationships between cholinergic activity and particular behavioral effects (Henningfield et al. 1983; Kumar, Reavill, Stolerman, in press). Similar strategies have been employed to explore the contributions of catecholamines to smoking-related behavior. However, the exploration of the importance of neuroregulators in the reinforcement of cigarette smoking is still at an early stage.

Cholinergic Effects

Nicotine has cholinergic effects in the PNS and CNS. Nicotine is a cholinergic agonist at peripheral autonomic ganglia and somatic neuromuscular junctions at low doses and becomes an antagonist at high doses (Volle and Koelle 1975). Nicotine also releases ACh in the cerebral cortex (Armitage, Hall, Morrison 1968; Rowe11 and Winkler 1984) and in the myenteric plexus of the peripheral ANS (Briggs and Cooper 1982). Balfour (1982) has suggested that cortical arousal (see Electrophysiological Actions of Nicotine for a detailed discussion) is mediated by ACh release but that behavioral stimulation (see Chapter IV) either is not mediated by ACh release or does not depend on the action of ACh at a muscarinic receptor.

Studies involving intracerebral administration of nicotine have been used to determine the loci of nicotine's action (Kammerling et al. 1982; Wu and Martin 1983). The injection of nicotine into the cerebral ventricles of cats, dogs, and rats produces a variety of effects including changes in cardiovascular activity, body temperature, respiration, salivation, muscle reflex tone, and electrocortical indices

of sleep and arousal; the direction and duration of effects depend on dosage and on baseline response parameters (Hall 1982).

Nicotine's cholinergic actions can affect other neuroregulators in the body (Andersson 1985). Nicotine stimulates NE release in the hypothalamus by a Ca^2+-dependent process that can be inhibited by prior administration of hexamethonium or ACh (Hall and Turner 1972; Westfall 1974). The mechanism resembles nicotine's effects on peripheral adrenergic nerve terminals (Westfall and Brasted 1972). At high dose levels, nicotine stimulates NE release by displacing it from vesicle stores at sites outside the hypothalamus (Balfour 1982). These actions are relevant to understanding the reinforcing effects of nicotine. For example, using drug discrimination procedures, Rosecrans (1987) has demonstrated that intact central NE and dopamine (DA) function were required to elicit the cue properties of nicotine.

Intravenous administration of nicotine modulates the release of both neurohypophyseal and adenohypophyseal hormones (Bisset et al. 1975; Hall, Francis, Morrison 1978). Hillhouse, Burden, and Jones (1975) found that the in vitro application of ACh to the hypophysiotropic area of the rat caused a significant increase in the basal secretion of corticotropin-releasing hormone (as measured by bioassay), which in turn controls, via the anterior pituitary, the release of the pro-opiomelanocortin (POMC) group of hormones--ß-endorphin, ß-lipotropin, melanocyte-stimulating hormone-releasing factor, and adrenocorticotropic hormone (ACTH) (Meites and Sonntag 1981). The humoral mechanism for the release of vasopressin has been traced from the medulla to the paraventricular nuclei of the hypothalamus (Bisset et al. 1975; Castro de Souza and Rocha e Silva 1977). Similarly, Risch and colleagues (1980) have demonstrated a cholinergic mechanism for the release of ß-endorphin.

Modulation of Catecholamine and Serotonin Activity

Dale and Laidlaw (1912) found that the pressor response of the cat to nicotine was due in part to the release of epinephrine from the adrenal glands. Over the past 75 years, a large body of research has confirmed and further investigated this phenomenon. Stewart and Rogoff (1919) quantified the effect of nicotine on adrenal epinephrine release. Kottegoda (1953) observed that nicotine releases catecholamines from extra-adrenal chromaffin tissues. Watts (1961) demonstrated the effect of smoking on adrenal secretion of epinephrine. Hill and Wynder (1974) reported that increasing the nicotine content in cigarette smoke progressively increased the serum concentration of epinephrine, but not NE. Winternitz and Quillen (1977) found that the excretion of urinary catecholamines tended to be higher on smoking days than on nonsmoking days. Several recent studies have focused on the role of nicotine and the mechanisms involved in the

release of catecholamines from cultured chromaffin cells (Forsberg, Rojas, Pollard 1986). Earlier experiments by Douglas and Rubin (1961), using denervated perfused cat adrenal glands, indicated that nicotine augments catecholamine release from chromaffin cells by promoting an influx of extracellular calcium. Forsberg, Rojas, and Pollard (1986) suggested that nicotine-induced catecholamine secretion may be mediated by phosphoinositide metabolism in bovine adrenal chromaffin cells.

The anatomical localization and importance of biogenic monoamines such as serotonin (5-HT [5-hydroxytryptamine]), DA, and NE have been the subject of intense research for the past 30 years. The classic studies of Dahlstrom and Fuxe (1966) revealed that neurons containing these amines were localized in specific ascending projection systems; descending monoaminergic neurons have also been described. The physiological integrity of these systems was further demonstrated by Aghajanian, Rosecrans, and Sheard (1967), who observed that stimulation of 5-HT cell bodies localized in the midbrain raphe nucleus released 5-HT from nerve endings located in the more rostra1 forebrain. The recognition that these amine systems constitute a unique interneuronal communication system has played a central role in understanding underlying neurochemical and behavioral mechanisms.

The cholinergic system has undergone a similar analysis (Fibiger 1982), but the delineation of specific cholinergic pathways has been more difficult because no histochemical method has been available for ACh. It does appear, however, that the cholinergic system is similarly organized and interacts with specific biogenic amine pathways. For example, Robinson (1983) has clearly shown that both 5-HT and DA systems exert tonic inhibitory control over ACh turnover in both the hippocampus and frontal cortex regions. Lesions of the medial raphe nuclei increase the ACh turnover rate in hippocampal sites, while lesions of the dorsal raphe elicit a similar effect in frontal cortical areas. Evidence of DA control comes from the observation that the catecholamine neurotoxin, 6-OHDA, when injected into the DA-rich septal area, facilitated hippocampal ACh turnover. The research of Kellar, Schwartz, and Martino (1987) and others also suggests that nicotinic receptors may occupy a presynaptic site on select DA and 5-HT nerve endings. Westfall, Grant, and Perry (1983), using a tissue slice preparation, have shown that the DMPP-induced stimulation of nicotinic receptors in the striatum will facilitate the release of both 5-HT and DA. This preparation is devoid of cell bodies or 5-HT- and DA-containing axon terminals, suggesting that these nicotinic cholinergic receptors are primarily presynaptic. Further, hexamethonium, but not atropine, attenuated nicotine-induced amine release, confirming that these effects are nicotinic in nature.

Nicotine may have simultaneous actions on many types of neurons. Even though only one kind of receptor may be stimulated, either activation or inhibition of a particular 5-HT, NE, or DA neuron may be the ultimate outcome. Conversely, the activity of specific cholinergic neurons may also be controlled by one of these biogenic-amine-containing projection systems. Nicotine appears to produce its discriminative stimulus effect in at least one major brain area, the hippocampus. This site is rendered insensitive if DA neurons innervating this area are destroyed (Rosecrans 1987). The interrelationships of these amine pathways are important to understand nicotine's effects on behavior and its effects on the neuroendocrine system because of the central role that these amine systems play in the hypothalamic control of the pituitary.

Effects on Serotonergic Neurons

Research evaluating the relationship between nicotine and 5-HT has involved several different approaches. Hendry and Rosecrans (1982) compared the effects of nicotine on conditioned and unconditioned behaviors in rats selected for differences in physical activity and 5-HT turnover. Balfour, Khuller, and Longden (1975) observed that acute doses of nicotine were capable of attenuating hippocampal 5-HT turnover, an effect specific to the hippocampus. Fuxe and colleagues (1987) did not observe any acute changes in 5-HT function following acute nicotine dosing but did observe a significant reduction of 5-HT turnover following repeated doses (3 x 2 mg/kg/hr). This effect, however, was suggested to be due to cotinine, the primary metabolite of nicotine.

In addition to attempts to correlate 5-HT function with some pharmacologic effect of nicotine, investigators have evaluated potential links between 5-HT and neuroendocrine function. Balfour, Khuller, and Longden (1975) showed a relationship between 5-HT and nicotine's ability to induce the release of plasma corticosterone, presumably by activation of the pituitary-adrenal axis. Following acute nicotine injections in the rat, a reduction in 5-HT turnover correlated with an increase in plasma corticosterone. Rats exhibited tolerance to pituitary activation following repeated nicotine doses, but not to the attenuation of hippocampal 5-HT turnover. Stress antagonized nicotine-induced reductions of hippocampal 5-HT. Also, nicotine was reported to inhibit the adaptive response to adrenocortical stimulation following chronic stress (Balfour, Graham, Vale 1986). One interpretation of these data is that nicotine can modify how rats adapt to stress, which may be mediated by changes in hippocampal 5-HT function. At this point, however, it is difficult to draw firm conclusions concerning how nicotine affects 5-HT neurons and whether this neurotransmitter is involved in any of nicotine's

effects on neuroendocrine function. Hippocampal 5-HT turnover appears to be selectively attenuated by nicotine.

Effects on Catecholaminergic Neurons

Studies of the effects of nicotine on NE-containing neurons have produced mixed results. Earlier work suggested that nicotine may affect behavior via a NE component, but recent research has not supported such claims (Balfour 1982). It has been reported that nicotine releases DA from brain tissue (Westfall, Grant, Perry 1983). Lichtensteiger and colleagues (1982) observed that nicotine releases DA through an acceleration of the firing rate of DA cell bodies located in substantia nigra zona compacta when nicotine is administered via iontophoretic application or s.c. (0.4 to 1.0 mg/kg). This activation was marked by a significant increase in striatal DA turnover; DHBE, but not atropine, attenuated nigrostriatal activation. Evidence that nicotine facilitates the firing of DA cell bodies by stimulating nicotinic cholinergic receptors has recently been reported by Clarke, Hommer, and coworkers (1985), who showed a specific effect of nicotine antagonized by mecamylamine on pars compacta cell bodies. Connelly and Littleton (1983) noted that DA release from synaptosomes lacked stereoselectivity but was blocked by the ganglionic-blocking drug pempidine.

Fuxe and coworkers (1986, 1987) have studied nicotine's effects on central catecholamine neurons in relation to neuroendocrine function. These investigators use quantitative histofluorometric techniques that measure the disappearance of catecholamine stores by administering a tyrosine hydroxylase inhibitor (AMPT) to rats receiving various doses of nicotine or exposed to tobacco smoke. Tissues are then exposed to formaldehyde gas, and histofluorescence in AMPT-treated rats is evaluated in comparison to controls.

Nicotine is a potent activator of both DA and NE neuron systems located primarily in the median eminence and in areas of the hypothalamus. These effects result from a stimulation of nicotinic cholinergic receptors, generally antagonized by mecamylamine. Intermittent nicotine dosing (4 x 2 mg/kg, s.c. every 30 min) or tobacco smoke exposure (rats were exposed to one to four cigarettes with a smoking machine-determined nicotine yield of 2.6 mg; rats received 8 puffs at 10-min intervals) results in a decrease of prolactin, thyroid-stimulating hormone (TSH), and luteinizing hormone (LH) and an increase of plasma corticosterone levels. Nicotine doses of 0.3 mg/kg administered i.v. induce an overall activation of the hypothalamic-pituitary axis, causing an increase of both ACTH and prolactin that subsides within 60 min. Tolerance to the corticosterone response develops after repeated nicotine doses, and there is evidence that it develops after a single dose of nicotine (Sharp and Beyer 1986; Sharp et al. 1987). Restraint stress increases

ACTH, corticosterone, and prolactin levels and decreases DA and NE levels in hypothalamic regions. This stressor attenuates nicotine's activation of NE neurons but does not reverse its attenuating effects on prolactin.

Nicotine appears to be associated with neuroendocrine activity by NE and DA activation (Fuxe et al. 1987). Immunohistochemical studies suggest that alterations in NE function are more important for the control of the pituitary-adrenal-axis, while DA turnover appears to be crucial for nicotine's effects on prolactin, LH, and follicle-stimulating hormone (FSH). Moreover, these studies indicate that similar nAChRs are located within both DA mesolimbic and neostriatal systems.

Stimulation of Pituitary Hormones

Nicotine administration and cigarette smoking stimulate the release of several anterior and posterior pituitary hormones. Seyler and coworkers (1986) had human subjects smoke two high-nicotine (2.87 mg) cigarettes in quick succession. Plasma levels of prolactin, ACTH, ß-endorphin/ß-lipoprotein, growth hormone (GH), vasopressin, and neurophysin I increased. No change was seen in TSH, LH, or FSH. The rapid smoking paradigm used by Seyler and coworkers (1986) may have contributed to the effects of nicotine. Growth hormone levels exhibited a prolonged increase after subjects smoked three cigarettes in rapid succession (Sandberg et al. 1973). In experiments conducted by Winternitz and Quillen (1977) with male habitual smokers, GH began to rise after two cigarettes, peaked at 1 hr, and then returned to control levels while smoking continued. Wilkins and colleagues (1982) also found that smoking increases GH levels and presented evidence that the effect is nicotine mediated. Coiro and coworkers (1984) reported that the increase in GH produced by clonidine was greatly enhanced by cigarette smoking, suggesting that nicotinic cholinergic and adrenergic mechanisms might interact in the stimulation of GH secretion.

The TSH plasma levels were not affected when nicotine was administered over a 60-min period to female rats (Blake 1974). In studies involving exposure to cigarette smoke, Andersen and colleagues (1982) reported a lowering of TSH secretion in rats, but as noted, Seyler and coworkers (1986) found no change in human subjects. Thus, the data on the effects of nicotine on TSH release are inconclusive at this time.

ACTH plasma levels increased after i.p. injection of nicotine in the rat (Conte-Devolx et al. 1981). In similar experiments, Cam and Bassett (1983b) found that elevated ACTH levels peaked and rapidly declined to a sustained plateau level. Sharp and Beyer (1986) reported that the effects of nicotine on ACTH in rats show a rapid and marked desensitization. Seyler and coworkers (1984) had male

subjects smoke cigarettes containing 0.48 or 2.87 mg of nicotine. No increases in ACTH or cortisol were detected after subjects smoked 0.48-mg-nicotine cigarettes. Cortisol levels rose significantly in 11 of 15 instances after smoking the high-nicotine cigarettes, but ACTH rose in only 5 of the 11 instances when cortisol increased. Each ACTH increase occurred in a subject who reported nausea and was observed to be pale, sweaty, and tachycardic. Seyler and coworkers (1984) studied smokers and concluded that ACTH release occurs only in smokers who become nauseated.

LH levels were reduced in male rats exposed to unfiltered cigarette smoke, while FSH was unchanged (Andersen et al. 1982). In experiments by Winternitz and Quillen (1977), there were no differences in LH and FSH among male cigarette smokers while smoking as compared with not smoking. Seyler and colleagues (1986) found no change in human LH or FSH levels after smoking. There is no evidence of gonadotropin release stimulated by nicotine or smoking.

Prolactin plasma levels were lowered considerably in lactating rats injected twice daily with nicotine (Terkel et al. 1973). It was suggested that failure of prolactin release following chronic nicotine administration was responsible for low milk production and starvation of pups. Blake and Sawyer (1972) found that, in lactating rats, the rapid suckling-induced release of prolactin into the blood is inhibited by s.c. injections of nicotine. Ferry, McLean, and Nikititovich-Winer (1974) reported that tobacco smoke inhalation in rats delays the suckling-induced release of prolactin. Andersen and coworkers (1982) found that prolactin secretion was reduced in male rats in a dose-dependent manner by exposure to unfiltered cigarette smoke. However, Sharp and Beyer (1986) reported that the effects of nicotine on prolactin in rats shows a biphasic effect, first increasing and then decreasing. Suppressed prolactin levels were found in female smokers who were breast feeding (Andersen et al. 1982). These researchers noted that smokers weaned their babies significantly earlier than nonsmokers. However, Wilkins and coworkers (1982) observed an increased level of prolactin in male chronic smokers.

Arginine Vasopressin

In addition to its antidiuretic effects, arginine vasopressin acts as a vasoconstrictor (Munck, Guyre, Holbrook 1984; Waeber et al. 1984). Arginine vasopressin may also act as a neuromodulator in pathways that affect behavior. It has been shown to promote memory consolidation and retrieval in rats (Bohus, Kovacs, de Wied 1978) and there are reports of memory enhancement following intranasal administration of a vasopressin analog in both normal and memory-deficient humans (LeBoeuf, Lodge, Eames 1978; Legros et al. 1978;

Weingartner et al. 1981). Nicotinic cholinergic receptors in the medial basal hypothalamus and muscarinic cholinergic receptors in the neurohypophysis (posterior pituitary) have been implicated in the release of vasopressin (Gregg 1985). Nicotine has been found to stimulate vasopressin release in a dose-related manner in animals (Reaves et al. 1981; Siegel et al. 1983) and in humans (Dietz et al. 1984; Pomerleau et al. 1983; Seyler et al. 1986). These observations are consistent with the effects of nicotine on cognitive performance (Chapter VI).

The Pro-Opiomeknocorticotropin Group of Hormones

The POMC hormones are released in response to stress and in response to corticotropin-releasing hormone (Munck, Guyre, Holbrook 1984; Krieger and Martin 1981). ACTH has behavioral effects and stimulates the release of steroids such as cortisol from the adrenal cortex. ACTH produces rapid cycling between sleeping and waking as well as sexual stimulation, grooming/scratching, blocking of opiate effects such as analgesia, and the enhancement of attention and stimulus discrimination (Bertolini and Gessa 1981). Endogenous opioids, such as ß-endorphin, potentiate vagal reflexes, cause respiratory depression, lower blood pressure, block the release of catecholamines (Beaumont and Hughes 1979; Schwartz 1981), have antinociceptive effects (van Ree and de Wied 1981), and modulate neurotransmitter systems leading to amnesic effects (Izquierdo et al. 1980; Introini and Baratti 1984). It has been suggested that the primary function of the endogenous opioids is metabolic, serving to conserve body resources and energy (Amir, Brown, Amit 1980; Margules 1979; Millan and Emrich 1981).

Nicotine appears to stimulate the release of corticotropin-releasing hormone from the hypothalamus through a nicotinic cholinergic mechanism (Hillhouse, Burden, Jones 1975; Weidenfeld et al. 1983). Using an isolated perfused mouse brain preparation, Marty and coworkers (1985) demonstrated that nicotine stimulates secretion of ß-endorphin and ACTH in a dose-related manner when applied directly to the hypothalamus but not when applied to the pituitary. The work of Sharp and Beyer (1986) supports this finding; they reported that the secretion of ACTH following nicotine was unaffected by adrenalectomy. Nicotine administration to rats has also been shown to increase the plasma levels of corticosterone, ACTH, and ß-endorphin in a dose-related manner (Conte-Devolx et al. 1981). Termination of chronic nicotine administration reduced hypothalamic ß-endorphin levels (Rosecrans, Hendry, Hong 1985). Hurlick and Corrigal (1987) have also observed that the narcotic antagonist naltrexone inhibits some nicotine-modulated behavior in mice, providing a possible link between nicotine stimulation of endogenous opioid activity and behavioral responses. Acute administration of

nicotine increases levels of plasma ACTH and corticosterone sharply (Cam and Bassett 1983b), while chronic exposure results in complete adaptation (Cam and Bassett 1984). Melanocyte-stimulating hormone was decreased and ß-endorphin was increased by i.p. injections of nicotine in the rat (Conte-Devolx et al. 1981).

Risch and colleagues (1980, 1982) have accumulated evidence for cholinergic control of cortisol, prolactin, and ß-endorphin release in humans. Rapid smoking increases circulating cortisol, ß-endorphin, and neurophysin I (Pomerleau et al. 1983; Seyler et al. 1984; Novack and Allen-Rowlands 1985; Novack, Allen-Rowlands, Gann, in press). Moreover, in a study that examined the role of endogenous opioid mechanisms in smoking, Tobin, Jenouri, and Sackner (1982) observed that mean inspiratory flow rate increases during the smoking of a cigarette but is depressed shortly after smoking. Naloxone had no effect on the initial stimulation of respiration in response to smoking but did significantly blunt the subsequent depression of respiration. The significance of these findings for the control of cigarette smoking remains equivocal (Karras and Kane 1980; Nemeth-Coslett and Griffiths 1986; Chapter IV).

Thyroid

Most of the earlier work (1930s through 1950s) assessing the effects of nicotine on thyroid function involved histological studies of the thyroid glands from animals treated chronically with nicotine. The findings are inconsistent in that some studies suggest elevated thyroid activity and others do not (Cam and Bassett 1983a). In a more recent study of nicotine's action on the plasma levels of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), Cam and Bassett (1983a) found that a single i.p. injection of 200 µg/kg did not alter the level of either hormone, although it did produce an increase in plasma corticosterone. As mentioned earlier, nicotine does not consistently affect TSH in animals or humans (Blake 1974; Seyler et al. 1986).

Adrenal Cortex

Several studies in animals and human subjects have reported that nicotine and cigarette smoking lead to elevated levels of corticosteroids. Kershbaum and colleagues (1968) administered nicotine i.v. to anesthetized dogs and found a 64 percent rise in plasma corticosteroids. In rats, corticosteroid concentrations increased 50 percent after i.p. administration of nicotine. Suzuki and coworkers (1973) also reported adrenal cortical secretion in response to nicotine in conscious and anesthetized dogs. The effects of nicotine on plasma corticosteroids in stressed and unstressed rats were studied by Balfour, Khuller, and Longden (1975). The administration of nicotine to unstressed rats caused a rise in corticosterone which persisted for

60 min. Nicotine did not affect plasma corticosterone concentration in rats stressed by being placed on an elevated platform. Other studies showed increased plasma corticosteroid levels after nicotine administration (Turner 1975; Cam, Bassett, Cairncross 1979; Cam and Bassett 1983b). Andersen and colleagues (1982) exposed male rats to unfiltered cigarette smoke and found a dose-related increase in corticosterone secretion. Filtered cigarette smoke was inactive.

Seifert and coworkers (1984) found that the chronic administration of 0.5 or 1.0 mg/kg of nicotine s.c. twice daily for 8 weeks to rats produced a marked decrease in plasma aldosterone levels. In this study, nicotine had no effect on plasma corticosterone concentration.

Hokfelt (1961) reported increases in plasma cortisol and urinary 17-hydroxycorticosteroids following cigarette smoking in human subjects. Kershbaum and coworkers (1968) reported similar results involving elevations of 11-hydroxycorticosteroids. Hill and Wynder (1974) found that serum corticosteroids were markedly elevated after high-nicotine (2.73 mg) cigarettes were smoked. No increase was seen with cigarettes containing less nicotine. Cryer and colleagues (1976) also found an increase in circulating levels of corticosteroids after smoking. Winternitz and Quillen (1977) reported a sharp increase in circulating cortisol after two cigarettes. The levels were maintained through the smoking period and fell gradually to normal. Wilkins and coworkers (1982) also observed increased levels of cortisol after 2-mg-nicotine cigarettes were smoked. No increases in cortisol were detected after smoking 0.48-mg-nicotine cigarettes, but cortisol rose significantly in 11 of 15 cases smoking 2.87-mg-nicotine cigarettes (Seyler et al. 1984). Consistent with these results is the observation of Puddey and colleagues (1984) that cessation of smoking is associated with a significant fall in cortisol levels.

In contrast to these findings, Tucci and Sode (1972) reported intact diurnal circadian variations of cortisol and unchanged 24-hr 17-hydroxycorticosteroids during smoking. Benowitz, Kuyt, and Jacob (1984) studied 10 subjects who either smoked their usual brand of cigarettes, some of which contained 2.5 mg nicotine, or abstained. Plasma cortisol concentrations throughout the day did not differ during smoking or abstaining. Thus, while the majority of human and animal data indicates that nicotine or smoking elevates corticosteroid levels, the effects appear to be influenced by dose, time, and perhaps other factors.

Many investigators cited above have proposed that nicotine's effects on corticosteroids are mediated by the release of ACTH. Indeed, hypophysectomy abolished the increase in adrenocortical secretion following nicotine administration (Suzuki et al. 1973; Cam, Bassett, Cairncross 1979) and nicotine-induced increase in plasma ACTH precedes the increase in cortisol (Conte-Devolx et al. 1981). However, Turner (1975) found that bilateral adrenal demedullation

abolished the rise in corticosterone in response to nicotine and suggested that the effect of nicotine is mediated via adrenal release of catecholamines and that centrally mediated stimulation is not significant. In contrast, the work of Matta and associates (1987) demonstrates that the effects of nicotine on ACTH secretion are centrally mediated. Rubin and Warner (1975) have also shown that nicotine directly stimulates isolated adrenocortical cells of the cat. The stimulant effect was dose-dependent and required the presence of calcium. These experiments also indicated that nicotine enhances the steroidogenic effect of ACTH.

Androgens

In male beagles, chronic smoking of high-nicotine/tar cigarettes was associated with decreased activity of 7*a*-hydroxylase active on testosterone (Mittler, Pogach, Ertel 1983). Testicular 6ß- and 16*a*-hydroxylases were not altered, while the hepatic androgen 6ß-hydroxylase activity in the testis was stimulated markedly by smoking. Serum testosterone levels were reduced to 54 percent of control levels by heavy smoking. It was concluded that chronic cigarette smoking increased hepatic metabolism of testosterone, resulting in lowered serum testosterone levels. However, it may be that total testosterone is lower while free testosterone is not.

Estrogens

Cigarette smoking is associated with antiestrogenic effects in women, including earlier menopause, lower incidence of breast and endometrial cancer, and increased osteoporosis. MacMahon and colleagues (1982) reported lower urinary estrogen levels in premenopausal smokers than in premenopausal nonsmokers and suggested that the low estrogen secretion reflected lower estrogen production, based on decreased estrone, estradiol, and estriol. However, 2-hydroxyestrogens, the major metabolites of estradiol in women, were not measured. Jensen, Christiansen, and Rodbro (1985) presented evidence for increased hepatic metabolism of estrogens as a result of smoking based on an observation of decreased serum estrogen levels in postmenopausal smokers receiving exogenous hormone therapy. This study examined 136 women treated for 1 year with different doses of estrogen. Reduction of serum estrogen was most pronounced in the highest estrogen-dose group. There was a significant inverse correlation between the number of cigarettes smoked daily and changes in serum estrogen. Michnovicz and colleagues (1986) found a significant increase in estradiol 2-hydroxylation in premenopausal women who smoked at least 15 cigarettes/day. They concluded that smoking exerts a powerful inducing effect on the 2-hydroxylation pathway of estradiol metabolism, which is likely to lead to decreased bioavailability of hormone at estrogen target tissues.

Pancreas and Carbohydrate Metabolism

The body weight of smokers is consistently lower than that of nonsmokers, and smokers tend to gain weight after cessation of smoking (see Chapter VI for a detailed discussion of these relationships). These phenomena are thought to contribute to tobacco use. Glauser and coworkers (1970) and Hofstetter and coworkers (1986) suggested that a change in metabolic rate is partially responsible for these effects. Schechter and Cook (1976) and Grunberg, Bowen, and Morse (1984) showed that rats which were administered nicotine lost body weight without reducing food intake, although the body weight changes were not as great as when eating behavior declined as well (Grunberg 1982). Grunberg (1986) has pointed out that differences in body weight between smokers and nonsmokers result from changes in energy consumption (via changes in specific food consumption) and changes in energy utilization. Recently, Grunberg and coworkers (1988) have reported reductions of insulin levels accompanying nicotine administration in rats which could result in an increase in the utilization of fat, protein, and glycogen. This finding is consistent with work of Tjalve and Popov (1973), using rabbit pancreas pieces, and studies by Florey, Milner, and Miall (1977) of human smokers versus nonsmokers. Grunberg and coworkers (1988) have suggested that the effects of nicotine on insulin levels also may be involved in the nicotine-induced decrease of sweet food preferences.

Electrophysiological Actions of Nicotine

Electrocortical Effects

The brain responds to electrical as well as to chemical stimuli. Therefore, measurements of the electrophysiological actions of nicotine complement studies of its chemical effects. In addition, electrophysiological activity reflects function that may relate to sensory and cognitive changes observed in humans after smoking (see Chapter VI). In animals, nicotine produces changes ranging from subtle latency decreases in the primary auditory pathway to seizures. The electrophysiological actions of nicotine may help to relate the anatomical and receptor data (discussed earlier in this Chapter) with sensory and cognitive data (discussed in greater detail in Chapter VI).

The human studies on electrocortical effects of nicotine have some methodological limitations. Most of the human studies had subjects smoke cigarettes and did not measure blood levels of nicotine. Also, most studies were performed on smokers whose immediate and long-term smoking history was determined by questionnaires which may not accurately reflect tolerance and physical dependence (Chapter IV). In some studies the subjects were deprived of cigarettes, but no objective measures such as expired carbon monoxide or blood

nicotine levels were collected to verify compliance with the deprivation conditions.

Spontaneous Electroencephalogram

Historically, nicotine and ACh were used in animal experiments to study the cholinergic mechanisms in the midbrain and thalamus which produced EEG and behavioral activation (Longo, von Berger, Bovet 1954; Rinaldi and Himwich 1955a,b). The administration of nicotine produced EEG activation, consisting of desynchronized low-voltage, fast activity, and behavioral arousal or alerting. These EEG and behavioral responses resembled those produced by electrical stimulation of the midbrain reticulomesencephalic activating system (Moruzzi and Magoun 1949). With the discovery by Eccles, Eccles, and Fatt (1956) of nicotinic receptors in the Renshaw cell of the spinal cord, other investigators began to study the precise pharmacology of the EEG and behavioral alerting produced by nicotine and electrical stimulation of the midbrain. Cigarette smoking in humans also produced EEG desynchronization (Hauser et al. 1958; Wechsler 1958; Bickford 1960) or EEG desynchronization with an increase in alpha frequency (Lambiase and Serra 1957). By the late 1950s and early 1960s it was generally known that nicotine or tobacco smoke caused EEG and behavioral arousal in animals and humans, but several important issues were unresolved.

The central effects of nicotine were originally thought to result from its action on the cardiovascular system (Heymans, Bouckeart, Dautrebande 1931). Early studies found that EEG desynchronization occurred when the subjects smoked nicotine cigarettes, nicotine-free cigarettes, or sucked on glass tubes filled with cotton (Hauser et al. 1958; Wechsler 1958). Schaeppi (1968) injected nicotine into the vertebral artery, carotid artery, and third and fourth ventricles of a cat's brain and was able to dissociate the effects of nicotine on the EEG from those on the cardiovascular system. Kawamura and Domino (1969) demonstrated that the EEG changes induced by nicotine could be obtained in animals whose blood pressure increase was blocked. Prevention of release of catecholamines in reserpine-pretreated animals did not interfere with the EEG desynchronization produced by nicotine (Knapp and Domino 1962).

Inhaled tobacco smoke (2-mL samples with about 2 µg/kg of nicotine) and 2 µg of nicotine injected every 30 sec in a cat encephale isole preparation produced EEG desynchronization. EEG and behavioral activation after cigarette smoke inhalation was also observed in unanesthetized cats with implanted electrodes (Hudson 1979). Lukas and Jasinski (1983) found that i.v. doses (0.75 to 3.0 mg) in human smokers resulted in dose-dependent decreases in alpha (8 to 12 Hz EEG activity) power and EEG desynchronization. In an inpatient study where nicotine deprivation was carefully controlled and

monitored by measurement of expired carbon monoxide, the smoking of non-nicotine cigarettes did not change the EEG (Herning, Jones, Bachman 1983), but EEG changes did occur when subjects smoked nicotine-containing cigarettes. These studies confirm that nicotine has a direct action on the CNS separate from the cardiovascular effects and that the effects are produced primarily by the nicotine in inhaled tobacco smoke.

As experimental physiological manipulations, EEG recording, and EEG quantification techniques improved, the specific nature of the nicotine-induced cortical EEG changes and their relationship to behavior were found to be more complex than originally thought. The desynchronization produced by nicotine (20 to 100 μg/kg) in the cat was blocked by anterior pontine transections, but not by midpontine transections (Knapp and Domino 1962). The midbrain reticular activating system was needed for the cortical EEG desynchronization produced by nicotine. However, larger doses of nicotine injections also produced synchronous slow high-voltage EEG activity in the hippocampus (hippocampal theta). Injections of the muscarinic agonist arecoline (20 to 40 mg/kg) in the anteriorly transected midbrain preparations still produced the hippocampal theta activity without the cortical desynchronization. Atropine (1 mg/kg) and mecamylamine (1 mg/kg), but not the ganglionic antagonist trimethidinium (1 mg/kg) block the nicotine induced EEG desynchronization in an intact animal. The convulsions observed after nicotine injections (1 to 5 mg/kg in cats; 0.05 to 0.25 μg/g in mice) (Laurence and Stacey 1952; Stone, Meckelnburg, Torchiana 1958; Stumpf, Petsche, Gogolak 1962; Stumpf and Gogolak 1967) appear to be due to nicotine's ability in large doses to stimulate muscarinic cholinergic receptors in the hippocampus. Because a high concentration of labeled nicotine binds to hippocampal cells of the cat (Schmiterlow et al. 1967) and areas adjacent to the hippocampus in the rat (Clarke, Pert, Pert 1984), the possibility that nicotine-induced limbic electrical activity contributes to its behavioral effects cannot be discounted.

Nicotine's alerting effect on the brain may also involve a peripheral component. Electrocortical and behavioral arousal occurs in the cat within 1 to 2 sec after injection of 10 to 15 μg/kg into the right atrium of the heart, originating in vagal pulmonary C fiber afferents (Ginzel 1987). The human counterpart to this finding is the observation by Murphree, Pfeiffer, and Price (1967) that an initial EEG change occurred within 5 sec after cigarette smoke inhalation, which is shorter than a chest-to-head circulation time. Another input from the periphery arises from nicotinic sites in the arterial tree. Injection of small amounts (2 to 4 μg/kg) of nicotine, even as far away from the brain as into the lower aorta or femoral artery, causes instantaneous arousal from all types of sleep (Ginzel and Lucas 1980).

The nicotine-induced release of ACh (MacIntosh and Oborin 1953; Mitchell 1963) may be responsible for the EEG desynchronization in animals (Armitage, Hall, Sellers 1969). The effect does not appear to be due to the direct action of nicotine on the cortex because the cortical cholinergic receptors are largely muscarinic (Kuhar and Yamamura 1976; Rotter et al. 1979). Lower doses of nicotine (20 µg/kg/30 sec for 20 min) induced EEG desynchronization and ACh release in the cat, whereas higher doses (40 µg/kg/30 sec for 20 min) produced either an increase or decrease in EEG desynchronization with corresponding increase or decrease in ACh release (Armitage, Hall, Sellers 1969). The effect of nicotine on the EEG was short lived relative to the release of ACh. Two separate pathways have been proposed to explain these results: an ascending cholinergic pathway mediating the cortical desynchronization and a limbic pathway mediating the ACh release.

In one strain of mice, C57BL, nicotine increased cortical high-voltage activity and decreased homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenthyleneglycol (MHPG) production in a perfused brain preparation (Erwin, Cornell, Towel1 1986). The decrease in HVA and MHPG levels reflects an increase in brain DA and NE levels. In intact C57BL mice, nicotine decreased locomotor activity (Marks, Burch, Collins 1983a). Thus, at least in one strain of mice, nicotine induces an increase in cortical EEG synchronization, a decrease in locomotor activity, and an increase in brain catecholamines. Little evidence relates the cortical desynchronization observed in animals and humans to an increase in catecholamine changes in the brain.

As trends in neuroscience research have shifted away from spontaneous EEG recording in animals to intracellular recording, receptor localization, and binding techniques, the precise quantification of the nicotine-induced EEG desynchronization and hippocampal synchronization has not been done. This type of quantification has been done in humans by power spectral analysis. This technique quantifies the EEG by the distribution and amplitude of brain waves at different frequencies. Alpha power includes EEG activity in the 8- to 12-Hz frequency range. Theta power includes EEG activity in the 4- to 7-Hz frequency range. Beta power includes EEG activity in the frequency range of 13 Hz and higher.

The comparison of nicotine-induced EEG changes in animals and humans is complicated by an important methodological difference. Animals usually have not previously been given nicotine, while in studies of humans, the subjects always are experienced tobacco smokers. Moreover, in human studies that included a deprivation period, nicotine abstinence may have produced electrophysiological changes that are reversed by smoking or nicotine.

EEG desynchronization or increased beta power was observed in smokers after smoking a tobacco cigarette (Hauser et al. 1958; Wechsler 1958; Bickford 1960; Ulett and Itil 1969). These findings essentially replicated the animal studies of nicotine. Using power spectral analysis, Ulett and Itil (1969) also observed a decrease in theta power and an increase in alpha frequency. The increase in alpha frequency was previously noted with visual inspection by Lambriase. However, the increase in theta was not. The subjects in the study by Ulett and Itil had smoked one pack or more of cigarettes/day and had been deprived of tobacco cigarettes for 24 hr when the baseline EEG was recorded. Comparisons of the postsmoking EEG were made with this baseline period. Therefore, the decrease in alpha frequency and increase in theta power relative to the data from the postsmoking session may be the result of nicotine deprivation (Chapter IV).

Knott and Venables (1978) compared the alpha frequencies of nonsmokers, 12-hr nicotine-deprived smokers, and nondeprived smokers. They observed a decrease of about 1 Hz in the dominant alpha frequency of the deprived smokers relative to the nonsmokers and nondeprived smokers in a passive eyes-closed situation. An active behavioral task and other frequencies of the EEG were not studied. Knott and Venables hypothesize that smokers were constitutionally different from nonsmokers. The slower alpha frequency was interpreted as an arousal deficit, and smoking as compensation to reduce the arousal deficit. Knott and Venables (1978) and Ulet and Itil (1969) both found an attentional deficit during tobacco deprivation.

Herning and coworkers (1983) investigated the EEG changes related to cigarette smoking in a hospitalized group of healthy smokers who smoked at least a pack and a half of tobacco cigarettes with a machine nicotine delivery of 0.8 mg or more. A serial subtraction task was administered and EEGs were recorded from subjects in an eyes-open state. Alpha frequency was not affected by periods of smoking and deprivation. However, theta and alpha power increased during periods of deprivation and decreased after smoking tobacco but not placebo cigarettes. The effects were most pronounced on theta power. Increases in theta power occurred as early as 30 min after the last cigarette, and were of the same magnitude as those after 10 to 19 hr of nicotine deprivation. The increase in EEG theta was interpreted to be a sign of tobacco deprivation (Chapter IV).

An indirect method of observing an increase in cortical activation was the measurement of alpha power changes after tobacco smoking. A number of investigators reported a decrease in alpha power or abundance with cigarette smoking (Murphree, Pfeiffer, Price 1967; Philips 1971; Caille and Bassano 1974, 1976; Murphree 1979; Herning, Jones, Bachman 1983; Cinciripini 1986), with nicotine

polacrilex gum (Pickworth, Herning, Henningfield 1986, in press), and with i.v. doses of nicotine (Lukas and Jasinski 1983). In spite of differences in the number of cigarettes regularly smoked by the subjects, the length of tobacco deprivation, the type of tobacco cigarette smoked during the experiment, and the route of administration, nicotine reduced alpha power.

Brown (1968) measured the resting EEG for heavy smokers and nonsmokers. No cigarettes were smoked. The EEG of the heavy smokers had less alpha and more beta activity. Twelve hours of nonconfirmed deprivation in the heavy smokers did not change the EEG patterns.

The EEG of neonates of mothers who smoke is not different from that of neonates of control mothers (Chernick, Childiaeva, Ioffe 1983). Whether acute periods of smoking may affect the EEG of the child before birth is not known.

In limited animal and human work, individual or species differences in the effects of nicotine on the EEG have been observed. Nicotine produced a dose-dependent cortical EEG desynchronization in C3H mice and an increase in synchronized EEG similar to hippocampal theta activity in C57BL mice (Erwin, Cornell, Towel1 1986). Both effects have been observed at different doses in the same preparation (Kawamura and Domino 1969). Lower doses produce EEG desynchronization, and higher doses produce hippocampal theta. Tobacco cigarette smoking decreased EEG alpha power in Type A subjects and increased theta power in Type B subjects deprived of nicotine for about 4 hr (Cinciripini 1986). The relationship between hippocampal theta in animals and cortical theta in humans is not yet understood. In nondrugged animals cortical desynchronization and hippocampal theta activity often occur simultaneously. Nicotine at low doses produces cortical desynchronization and at high doses produces both types of EEG activity. Animal data indicate that nicotine has effects on at least two systems in the brain: a midbrain area responsible for EEG desynchronization and a limbic system generating hippocampal theta activity. These findings are consistent with the observation that some smokers indicate that they smoke for nicotine's stimulating effects and others smoke for its sedating effects.

Sensory Event-Related Potentials

In animals and humans, the brainstem auditory-evoked potential technique provides a noninvasive method for studying the effects of nicotine on primary auditory sensory function. In the rat, nicotine reduced the amplitudes of Waves III and IV of the brainstem auditory-evoked response (BAER) (Bhargava and McKean 1977; Bhargava, Salamy, McKean 1978; Bhargava, Salamy, Shah 1981). Serotonergic mechanisms may mediate the nicotine-induced reduc-

tion in latency. Lavernhe-Lemaire and Garand (1985) found essentially the opposite. Nicotine increased Waves I-III and did not decrease Waves IV and V of BAER.

Auditory event-related potentials (AERPs) recorded directly from the cortex of rat have provided conflicting information about nicotine's effects on auditory transmission from the inferior colliculus to the cortical areas. Guha and Pradhan (1976), using pentobarbital anesthesia, found a dose-dependent increase in Pl (40 ms) and N1 (110 ms) of the AERP. Bhargava, Salamy, and McKean (1978), using chloralose anesthesia with atropine pretreatment, reported no nicotine-related change in P1 (11 ms), N1 (28 ms), P2 (75 ms), and N2 (121 ms) of the AERP.

After smoking, the Pl (50 ms) of the human AERP is increased during passive tasks at all intensity levels and the Nl (110 ms) is increased in both passive and active tasks (Knott 1985). The N2 (about 215 ms) to P2 (about 260 ms) component of the AERP recorded during a passive task was reduced after cigarette smoking when compared with data from the baseline deprivation test (Friedman and Meares 1980). P2 was also reduced by nicotine in the study by Knott (1985). These components also increased in amplitude as the tobacco deprivation period was lengthened. Any attempt to relate this finding to results in the anesthetized rat would be speculative because AERPs recorded from the cortex of unanesthetized animals and humans are difficult to compare (Wood et al. 1984). Alterations in AERP components in the 75- to 150-ms latency range have been attributed to change in attention. The decrease in the later N2-P2 component is more likely to reflect reduced habituation to auditory stimuli.

The effects of nicotine on visual event-related potentials (VERPs) are more complicated than those on the AERPs. In unaesthetized rabbits, i.v. nicotine (0.025 to 0.500 mg/kg) produced a complex VERP change (Sabelli and Giardini 1972). At 2 min, nicotine depressed the Pl (100 ms) and the Nl (250 ms). At 5 min, these components were enhanced. At doses below 0.050 mg/kg, the Nl was again depressed from 10 to 20 min after the injection. Pretreatment with catecholamine inhibitors diminished the nicotine-induced VERP changes. The authors suggested that the effect of nicotine on VERPs was mediated in part by catecholaminergic mechanisms.

The effects of nicotine on the human VERP using multiple flash intensities were the focus of four studies. The studies were designed to test Buchsbaum and Silverman's (1968) concept of stimulus intensity control and its modulation by nicotine. According to their theory, sensory processing in different individuals varies in at least two ways. Some persons, "augmenters," are more sensitive to higher intensities than to lower intensities, and others, "reducers," are more sensitive to lower than to higher intensities. Smokers might be

one particular type of stimulus processer and may smoke to alter or normalize stimulus intensity. In all studies the comparison was between results after 12 hr or more of unconfirmed tobacco deprivation and those after recent smoking. Components of the VERP increased after smoking in three studies (Hall et al. 1973; Friedman and Meares 1980; Woodson et al. 1982) but decreased in another study (Knott and Venables 1978). The increases and decreases occurred in components of the same latency range (75 to 250 ms) after flash onset. The fourth study differed only slightly from the others in that it used a between-subjects and not within-subject experimental design. Using a single flash intensity, Vasquez and Toman (1967) also observed a decrease in components IV (^{14}0 ms) and V (170 ms) of the VERP when compared with results after 36 hr of tobacco deprivation. Two studies found a nicotine-induced increase at earlier components (III-IV and IV-V) for the lower intensities only. The other study reported an increase in later components (V-VI and VI-VII) at the higher flash intensities. Knott and Venables (1978) observed the decrease after smoking in the middle components (IV-V and V-VI) for the lower intensities. Because of these divergent results, it is premature to conclude that smokers are exclusively augmenters or reducers who are attempting to optimally adjust stimulus intensity by smoking.

Cognitive Event-Related Potentials

Cognitive event-related potentials reflect neural events which appear to be related to different aspects of cognition, such as attention and stimulus evaluation. They usually follow the sensory components of event-related potentials when human subjects are performing active behavioral tasks. They provide information not normally available from performance measures such as reaction time. Increases or decreases in these potentials after smoking can aid in our understanding the effects of nicotine on performance.

When two task-relevant stimuli are separated by a short interval (1 to 3 sec), a negative slow wave develops between them. In particular, this contingent negative variation (CNV) develops in warned or cued reaction times, successive discrimination, and some language processing tasks. The CNV appears to reflect brain preparation to process and respond to the second stimulus. Smoked tobacco and i.v. nicotine either increase or decrease the CNV (Ashton et al. 1973, 1974, 1980; Minnie and Comer 1978). Extraverted smokers took longer to smoke and nicotine increased the CNV. Introverted subjects smoked faster and nicotine decreased the CNV. Reaction time was inversely correlated with CNV amplitude; that is, shorter reaction time was associated with larger CNV. With i.v. doses of nicotine (12.5 to 800.0 μg), larger doses produced a decrease and small doses produced an increase in the CNV in the same

subject. O'Connor (1982) studied the effects of smoking on the orienting (O wave) and expectancy (E wave) components of the CNV in introverted and extraverted subjects. The O wave was not affected by smoking. The E wave, recorded in frontal areas, was increased in extraverted subjects after smoking. The E wave has been interpreted by some investigators as cortical preparation for a response. Smoking decreased a positive parietal E wave in introverts. Nicotine's effect on the E wave suggests the possible enhancement of motor preparation in the extraverted subjects. The decrease of parietal positivity indicates a possible enhancement of stimulus-processing capacities in the introverts.

Poststimulus components P2(00) and P3(00) were affected by cigarette smoking and nicotine polacrilex gum. P2 is thought to be an index of habituation (Hillyard and Picton 1979), and P3 an index of stimulus evaluation (Johnson 1986). Both components were reduced in deprived smokers after smoking (Knott 1985; Herning and Jones 1979). Knott (1985) interprets the reduction in P2 as a more efficient habituation of sensory screening of relevant stimuli. The reduction in P3 amplitude after smoking indicates a poorer evaluation of task-relevant stimuli. The P3 latency and reaction time were reduced only by cigarettes with higher machine-tested nicotine yields (Edward et al. 1985). Such data indicate faster stimulus and response processing. These authors did not report any P3 amplitude changes. If none were present or P3 was reduced, the argument for enhanced stimulus processing would be weak. Herning and Pickworth (1985) reported both dose-dependent increases and decreases in P3 amplitude as a function of background noise levels when deprived smokers chewed nicotine polacrilex gum (4 mg and 2 mg doses). The respective increase or decrease was blocked by mecamylamine pretreatment. Thus, the effect of nicotine on stimulus evaluation remains unclear and is perhaps confounded by cognitive deficits after periods of nicotine deprivation.

Motor Potentials

O'Connor (1986) investigated the effect of tobacco smoking on motor potential and motor performance. Smoking increased the motor readiness potential in extraverts, but not in introverts. These results are consistent with his earlier finding of an increased E wave in extraverts after smoking. For introverts, smoking improved task performance, but did not increase the motor readiness potential.

Other Peripheral Effects Relevant to Tobacco Use

In addition to vast central and peripheral effects, cigarette smoking and nicotine have other peripheral effects that may contribute to tobacco use. These additional factors have received less

research attention, mainly because they involve relatively new theory or methodological approaches. For example, there is evidence that direct stimulation of the trachea is important for cigarettes to satisfy smokers (Rose et al. 1984) (Chapter IV). There is also evidence that nicotine acts directly on the lung to stimulate afferent neurons that, in turn, result in skeletal muscle relaxation and electrocortical arousal (Ginzel 1987). These effects may contribute to the relationship between smoking and stress (Chapter VI). Other research indicates that smoking affects psychophysiological reactivity, an integrative mechanism that is different from the classic, physiological approach of examining individual systems or pathways. Therefore, psychophysiological reactivity and its relevance to smoking are discussed.

Psychophysiological Reactivity and Smoking

Psychophysiological reactivity is emerging as a useful construct in smoking research, linking basic biological processes (genetic vulnerability, central neurochemical factors) to behavioral coping and other psychosocial factors. Psychophysiological reactivity refers to a physiological response to a specific stimulus or as a result of the absence of stimulation. This response can, in some cases, act as a stressor. Within the broader conceptual framework of a stress-coping model of smoking addiction (Shiffman and Wills 1985), smoking behavior can be viewed both as a potential stimulus and as a coping response that modulates psychophysiological reactivity.

Studies of psychophysiological reactivity illustrate the value of controlled laboratory procedures to study person-environment interactions. Psychophysiological reactivity reflects an interaction of the organism and the environment. It is affected by individual differences in multiple response modes (physiological, cognitive, behavioral) and takes into account the genetic and learning history and current state of the organism.

This Section reviews two separate but interrelated lines of psychophysiological reactivity research with humans. The first is the effect of smoking on psychophysiological reactivity. Related issues include identification of mechanisms that may help to reveal why some individuals smoke and the relationship between smoking and coronary heart disease (CHD). The second research line addresses the relationship among situational events (general and drug-specific), psychophysiological reactivity, and relapse.

The effects of smoking on the cardiovascular aspects of physiological reactivity have been well documented and appear to be primarily due to effects of nicotine and carbon monoxide (Suter, Buzzi, Battig 1983; Koch et al. 1980; Rosenberg et al. 1980). In individuals with no cardiovascular disease, some of the typical effects of smoking and nicotine are elevated heart rate and blood pressure and a fall in

fingertip temperature and capillary blood flow (Richardson 1987; Ashton et al. 1982; Epstein and Jennings 1986; Henningfield et al. 1983).

Accompanying cardiovascular reactions to smoking are cognitive reactions, including perceptions of relaxation, and anxiolytic, antinociceptive, euphoric, stimulative, and dysphoric effects (Kozlowski, Director, Harford 1981). Although there is consistency in the literature with regard to the self-reported emotional changes experienced as a result of smoking, there are clear differences in response and direction of effects between individuals and within individuals over time (Best and Hackstian 1978; Gilbert 1979; Gilbert and Welser, in press). Smoking can produce physiological changes that are concurrent with subjective tranquilizing effects (Nesbitt 1973; Shiffman and Jarvik 1984; Gilbert 1979). This phenomenon has led investigators to emphasize the importance of incorporating physiological, psychological, and environmental factors into more biobehavioral models to better understand the cognitive and physiological components of reactivity to smoking (Pomerleau and Pomerleau 1984; Baum, Grunberg, Singer 1982; Abrams et al. 1987; Grunberg and Baum 1985). For example, nicotine has direct and indirect actions on central neuroregulatory systems and has biphasic effects of both stimulation and blockade. These factors can help explain effects such as the anxiolytic and antinociceptive phenomena (Pomerleau 1986) at a cognitive and neurochemical level, while at the same time resulting in increased heart rate and blood pressure and decreased perception of muscle tension (Epstein et al. 1984).

In addition to dosage, biphasic, and physiological factors, the influence of setting and expectancy set, the current state of the individual (smoking, deprived, stressed, not stressed), and individual differences in dependence, genetic, demographic, and learning history can all influence psychophysiological reactivity. For example, smoking a 1.3-mg-nicotine cigarette under conditions of mild sensory isolation produced consistent arousal effects (i.e., elevations in heart rate and skin conductance level with decreases in EEG alpha waves) in smokers compared with sham smoking or a situational control group. However, under conditions of stress, as induced by intermittent noise bursts, a mixed stimulant (heart rate) and depressant (EEG, skin conductance) response was observed (Golding and Mangan 1982). Woodson and coworkers (1986) also reported that during noise, smoking induced cardiovascular stimulation (i.e., heart rate acceleration, peripheral vasoconstriction) but electrodermal depression (i.e., lowered skin conductance response amplitude). These findings are consistent with the conclusions of Gilbert and Welser (in press) that unidimensional models are inadequate to explain the effects of smoking.

In addition to research on the impact of smoking on psychological and physiological processes, studies have also examined the combined cardiovascular effects of smoking and stress. In this context the concept of cardiovascular psychophysiological reactivity is used to help clarify the relationship among stress, smoking, and CHD (Epstein and Jennings 1986). MacDougall and colleagues (1983) randomly assigned 51 male smokers to smoking versus sham smoking and stress versus no stress conditions in a 2 x 2 factorial design. The stressor was a difficult video game performed under challenging conditions. Subjects who sham smoked under no stress showed minimal cardiovascular response. Subjects who smoked under no stress or who sham smoked under stress evidenced similar degrees of response of about a 15-bpm increase in heart rate, a 12-mmHg increase in systolic blood pressure, and a 9-mmHg increase in diastolic blood pressure. Subjects in the combined smoking and stress condition had larger increases in all cardiovascular measures. The combination of mild stress and smoking produced effects that were twice those of either condition alone. Smoking and stress combined to increase cardiovascular response in men.

In a followup study of women, using the same 2 x 2 factorial design, Dembroski and colleagues (1985) found that the combined effect of stress and smoking produced blood pressure and heart rate increases that exceeded the sum of the individual effects. However, because modifications were made in dosage and psychological challenge, the two studies were not identical. The gender differences noted could therefore reflect methodological differences, uncontrolled factors, or possibly differences between the sexes in response to the stress and smoking stimuli. Indeed, it has been noted that females may be more likely than males to smoke to regulate affect (Ikard and Tomkins 1973), are more likely to relapse after quitting (Gritz 1986), may differ in biological factors relating to stress reactivity/sensitivity (Abrams et al. 1987), and show greater changes in body weight and eating behavior in response to nicotine (Grunberg, Bowen, Winders 1986; Grunberg, Winders, Popp 1987). (See Chapter VII for a discussion of treatment implications of these possible sex differences.)

In a conceptually related study, the relationship between physiological responses to cognitive (mental arithmetic) and physical (cold pressor) stressors was examined in female smokers and nonsmokers who either used or did not use oral contraceptives (Emmons and Weidner, in press). All subjects showed some physiological response (heart rate and blood pressure responses) to the stressors, but in smokers oral contraceptive use significantly enhanced the systolic blood pressure response to cognitive stress. This finding may be related to the fact that smokers who use oral contraceptives are 5.6-times more likely to have a myocardial infarction than are smokers

who do not use oral contraceptives, 9.7-times more likely than nonsmoking users, and 39-times more likely than nonsmokers who do not use oral contraceptives (Shapiro et al. 1979; Jain 1976; Ory 1977).

In studies of psychophysiological reactivity, it is critical to identify, measure, and control for factors that might confound or alter the intended impact of the independent variables. For instance, time since last drink and beliefs, expectations, and setting are important variables to consider in the study of alcohol addiction (Abrams and Wilson 1979; Abrams 1983; Marlatt and Rohsenow 1980). The 2 x 2 balanced placebo design (Marlatt, Demming, Reid 1973), where expectancy set (told to expect the drug or told to expect no drug) and actual content (drug versus placebo) are fully controlled, has been used extensively in the alcohol addiction field to isolate the separate and interactive elements of cognitive and pharmacologic effects. With smoking, little is known about the separate and interactive impacts of expectations of cigarettes' effects versus their actual pharmacologic effects. This is partially because it is difficult to find a method of administration that closely resembles smoking but where the required manipulations to achieve a credible balanced placebo design can be accomplished.

Another methodological concern is control over the dosage of nicotine absorbed by the smoker. Nicotine is thought to be the most important tobacco constituent responsible for the acute effects of smoking on reactivity, attention and task performance, mood, and withdrawal following cessation (Perkins et al., in press; Pomerleau, Turk, Fertig 1984; Hughes et al. 1984). However, in tobacco smoking, nicotine is accompanied by more than 4,000 other compounds (Dube and Green 1982) and smokers are known to smoke in individualized ways (Epstein et al. 1981) (Chapter IV). The coaching of puff frequency and other attempts to standardize intake of smoke are imperfect (Perkins et al., in press). An aerosol nasal spray appears to be a promising alternative to smoking in studies of behavioral and physiological effects. It allows for rapid uptake through inhalation, and a dose-response study indicates patterns of heart rate, blood pressure, and serum nicotine levels that are very similar to those obtained by smoking cigarettes of equivalent nicotine content (Perkins et al., in press).

Perkins and coworkers (in press) studied the separate and interactive effects of nicotine administered by nasal aerosols and stress on psychophysiological reactivity. The authors note that the previous studies (MacDougall et al. 1983; Dembroski et al. 1985) could be confounded because smokers usually smoke more under stress and therefore they may inhale more nicotine or alter their smoking in other ways when stressed (Mangan and Golding 1978; Rose, Ananda, Jarvik 1983) (Chapter VI). In other words, the additive effects of

stress and smoking on physiological responses could have resulted from uncontrolled changes in smoking pattern between the smokers in the no-stress and stress conditions. Perkins and colleagues (in press) studied 12 male smokers in a repeated-measures design, where subjects received all 4 conditions (stress plus nicotine, stress plus placebo, rest and nicotine, and rest and placebo) on separate days with the order of condition counterbalanced within subjects. Following the methodology of previous studies of psychophysiological reactivity, the researchers used an active stressor consisting of a video game under conditions of competitive challenge. Nicotine was administered in measured l.0-mg doses by the aerosol nasal method (Perkins et al., in press). Consistent with observations of MacDougall and coworkers (1983), results were additive for heart rate reactivity. However, effects were less than additive for systolic and diastolic blood pressure.

Taken together, the studies of the effects of smoking cigarettes and of nicotine aerosol stimuli on the physiological responses of adult males demonstrate a consistent effect for the stimuli alone, additive in combination with stress on heart rate, and additive or less than additive with stress on blood pressure. There is some suggestion that effects may be more than additive for women, but this finding requires replication.

Psychophysiological Reactivity, Smoking Cessation, and Relapse

Psychophysiological reactivity also serves as a conceptual framework to study relapse after cessation from smoking (Shiffman 1986b; Abrams 1986). Individual differences in psychophysiological reactivity and associated coping responses, as a function of general and smoking-specific stressful stimuli, have been hypothesized to mediate relapse. For example, smokers who smoke more when stressed might be particularly vulnerable to relapse (Pomerleau, Adkins, Pertschuck 1978). This idea is consistent with the observation that relapse may be triggered by life stress events and other psychosocial demands (Ockene et al. 1982) and by high-risk situations including negative emotions, social conflicts and pressures, and the presence of alcohol or smoking cues (Marlatt and Gordon 1985; Shiffman 1979, 1982, 1984, 1986a; Abrams et al. 1986). If certain psychophysiological reactivity responses distinguish potential abstainers from relapsers, cessation may be better maintained by identifying “relapse-prone” individuals (Chapter VII).

Stressful environmental demands, sensitivity of the individual to these demands, and the repertoire of coping responses are important factors in relapse (Shiffman and Wills 1985; Abrams et al. 1987). These same factors also may contribute to initiation of smoking among adolescents. Wills (1985) provides evidence for the stress-

coping model of smoking in adolescence, relating both stress and coping patterns to substance use. Results are consistent with other findings that, in addition to peer pressure to smoke, adolescents actively seek methods of coping with their perceptions of stress (Wills 1985; Friedman, Lichtenstein, Biglan 1985; Botvin and McAlister 1981). Although these survey studies are consistent with the notion of smoking as a means of coping with psychophysiological reactivity to environmental demands, research has not yet measured reactivity in adolescents prior to smoking onset.

Observational and retrospective studies of relapse have identified other smoking-specific stressful stimuli and cognitive/psychophysiological measures of reactivity that are relevant to relapse. Situations or stimuli that cue smoking and are associated with relapse include pharmacologic dependence and withdrawal symptoms (Jarvik 1977; Pomerleau and Pomerleau, in press; Hughes et al. 1984), stimuli previously associated with smoking (e.g., coffee drinking, alcohol) (Shiffman 1984, 1986a; Best and Hakstian 1978), and urges to smoke (Myrsten, Elgerot, Edgren 1977). Situational stimuli may or may not have previously been paired with smoking and may or may not include smoking cues as a trigger for relapse.

Substance use cues themselves (e.g., the sight and smell of cigarettes) also may precipitate relapse, perhaps in combination with other stressful stimuli or in a vulnerable individual (Shiffman 1986b; Abrams et al. 1987). Models of how substance use cues are related to relapse have been proposed on the basis of classical, operant, and social learning principles. Reactions may be conditioned to stimuli repeatedly paired with smoking, resulting in craving and physiological reactivity in their presence and moderated by dependence, tolerance, and nonpharmacologic withdrawal (Siegel 1983; Cooney, Baker, Pomerleau 1983; Gritz 1980). Psychophysiological reactivity to smoking cues could mimic the prior drug response (Wikler 1965), result in a drug-opposite (compensatory) response (Siegel 1983), or have other effects on psychological processes such as perceived anxiety, urges to smoke, and self-efficacy in resisting relapse according to a social learning model of relapse (Marlatt and Gordon 1985).

Abrams and colleagues (1987) studied the psychophysiological reactivity and behavioral coping responses of male and female relapsers and quitters in four simulated situational contexts: general social situations, smoking-specific negative emotional and interpersonal role-plays, high-demand social stress, and relaxation. Compared to abstainers, relapsers had higher heart rates and higher perceived anxiety and were rated as less skillful at coping in the smoking-specific intrapersonal (negative affect) situations. There were no differences on any measures in the high-performance-demand general-social-stress procedure. There were some differences

in heart rate and self-reported anxiety in the general social situations and in heart rate in the relaxation interval, with relapsers having higher levels than abstainers. Abstainers and relapsers did not differ in heart rate, perceived anxiety, or coping skills in the high-demand social anxiety procedure, but they did differ in the other situations. The results suggest that selected situational demands prompt situation-specific psychophysiological changes.

Rickard-Figueroa and Zeichner (1985) used a within-subjects design to examine the responses of smokers to a confederate of the experimenter lighting and smoking the subject's preferred brand of cigarette behind a glass window. Cigarette paraphernalia were placed adjacent to the subject but smoking was not permitted until after the session. The cue exposure manipulation resulted in higher urges to smoke, increased systolic and diastolic blood pressure, and increased heart rate variability compared with a no-cue condition. Urges were significantly positively correlated with diastolic blood pressure, the use of active mastery to cope with urges, and the more rapid smoking of a standard cigarette after the trial.

In a study that shows some evidence for a conditioned response, Saumet and Dittmar (1985) measured finger-pulse amplitude, a measure of peripheral vasoconstrictive activity, while subjects placed an unlit cigarette into their mouths and waited for it to be lit. Heavy smokers showed an anticipatory vasoconstrictive response to the cigarette compared with light smokers and nonsmokers.

Abrams and colleagues (in press) used smoking cues and a social stressor to simulate an interpersonal situation with high risk for relapse. Relapsers, abstainers, and never smokers were examined for psychophysiological reactivity. Compared with controls (never smokers), relapsers had significant heart rate reactivity, stronger urges to smoke, and subjective anxiety. Trained raters, unaware of subject smoking status, judged relapsers as having significantly less effective coping skills to resist smoking. In a second study, the same assessment was used prospectively in a treatment outcome context to determine whether patterns of psychophysiological reactivity could discriminate between quitters who maintain abstinence from those who do not. Both heart rate reactivity and subjective anxiety were greater in quitters who relapsed at 6-month followup compared with those who continued to abstain. The groups did not differ with regard to urges to smoke or behavioral judgments of coping skill. Thus, the two studies were consistent for heart rate and perceived anxiety but not for urges or objective ratings of coping effectiveness.

In a reanalysis of the heart rate data from Abrams and coworkers (in press), Niaura and colleagues (in press) examined beat by beat event-related heart rate during the period immediately before and for the 10 sec following the lighting of a cigarette by a confederate (subjects did not smoke throughout). Prospective relapsers showed a

strong decelerative trend at the point of lighting, whereas prospective abstainers did not. The results may reflect a conditioned compensatory response (Siegel 1983) or some other information processing/attentional phenomenon (Sokolov 1963; Knott 1984). In another treatment study, Emmons (1987) examined smokers' cardiovascular reactivity to mental arithmetic or deep knee bends before and 6 months after smoking cessation. There was no change in reactivity (heart rate, systolic and diastolic blood pressure) to either stressor before and after quitting. Heightened pretreatment heart rate reactivity significantly discriminated relapse at 6-month follow-up.

Individual differences in psychophysiological reactivity may influence the likelihood of relapse. This possibility is discussed in Chapter VII.

Summary and Conclusions

1. Nicotine is a powerful pharmacologic agent that acts in the brain and throughout the body. Actions include electrocortical activation, skeletal muscle relaxation, and cardiovascular and endocrine effects. The many biochemical and electrocortical effects of nicotine may act in concert to reinforce tobacco use.
2. Nicotine acts on specific binding sites or receptors throughout the nervous system. Nicotine readily crosses the blood-brain barrier and accumulates in the brain shortly after it enters the body. Once in the brain, it interacts with specific receptors and alters brain energy metabolism in a pattern consistent with the distribution of specific binding sites for the drug.
3. Nicotine and smoking exert effects on nearly all components of the endocrine and neuroendocrine systems (including catecholamines, serotonin, corticosteroids, pituitary hormones). Some of these endocrine effects are mediated by actions of nicotine on brain neurotransmitter systems (e.g., hypothalamic-pituitary axis). In addition, nicotine has direct peripherally mediated effects (e.g., on the adrenal medulla and the adrenal cortex).

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