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Tobacco Smoking and Nicotine Neuropsychopharmacology: Some Future Research Directions

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Although nicotine is acknowledged as the major pharmacologically active chemical in tobacco that accounts for its continued use, there is a need for much further research. It is necessary to systematically compare the complex pharmacological actions of pure nicotine with those of tobacco, using different routes of administration and, therefore, rates of absorption. Tobacco smoking produces several important behavioral and central nervous system effects. More research is needed to determine the role of nicotine versus the many other substances present in tobacco smoke. Although nicotine is the primary pharmacological agent in tobacco that maintains its use, other chemicals and their biological mechanisms involved in tobacco smoking need to be studied further.
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Much is known about the complex issues involved in tobacco smoking reinforcement. Taste, smell, sensory stimulation of the respiratory tract by the smoke, the psychological set, and the social setting of the smoker are all significant. There is little doubt that nicotine is essential for maintaining tobacco smoking behavior (Larson et al. 1961; Ejrup 1965; Larson and Silvette 1968, 1971; U.S. Surgeon General's Report 1988; Balfour 1984; Adlkofer and Thurau 1985; Ney and Gale 1989; Rand and Thurau 1988; Clarke et al. 1995; Domino 1995a). With each passing year more data are available that describe the complex pharmacology of this intriguing alkaloid. One only needs to peruse the abstracts of the Society for Research on Nicotine and Tobacco meeting in March 1997 and the Society of Neuroscience meeting in October 1997 to appreciate the impressive amount of current nicotinic cholinergic research.

As our knowledge of nicotine pharmacology becomes increasingly more complex, most drug abuse researchers use Occum's razor to explain why a large number of different substances, including nicotine, are reinforcing and, hence, potentially addicting. Most drugs of abuse, including nicotine, release brain dopamine in laboratory rats. Inasmuch as dopamine is the primary neurotransmitter involved in pleasure and reward, the principle of scientific parsimony permits one to conclude that tobacco smoking and dependence are due to nicotine, the resulting dopaminergic neuronal activity and dopamine release (Andersson et al. 1981; Lichtensteiger et al. 1982; Clarke and Kumar 1983a,b; Schwartz et al. 1984; Clarke and Pert 1985; Clarke et al. 1985a, 1988; Grenhoff et al. 1986; Imperato et al. 1986; Grenhoff and Svensson 1988, 1989; Mereu et al. 1987; Clarke 1990; Svensson et al. 1990; Corrigall 1991; Corrigall et al. 1992; Hakan et al. 1993; Bauco and Wise 1994; Nisell et al. 1994, 1995, 1996, 1997). Once the mechanism of nicotine-induced dopamine re-

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lease is well understood, future research directions become individual and administrative choices based upon the needs of society. The purpose of this review is to summarize some of our knowledge and suggest several future directions for nicotine and tobacco research.

A HISTORICAL PERSPECTIVE OF THE RELATIONSHIP OF NICOTINE TO ACETYLCHOLINE

This has been reviewed briefly by Domino (1995b). More than 83 years ago, Dale (1914) compared the actions of various synthetic and endogenous choline (Ch) derivatives, including acetylcholine (ACh), with those of the plant alkaloids muscarine and nicotine. The effects of muscarine were similar to some of the effects of ACh and parasympathetic nerve stimulation. The actions of nicotine were similar to those of ACh after the muscarinic antagonist atropine, as well as after sympathetic nerve stimulation. Dale postulated that ACh was an autonomic nervous system neurotransmitter, and that it had dual actions, i.e., muscarinic and nicotinic.

Nicotine and ACh can exist in remarkably similar molecular forms. ACh is a very flexible molecule compared with nicotine; it can be easily configured to resemble nicotine. The pyridine nitrogen of nicotine is an electronic donor similar to the keto oxygen of the acetyl group of ACh. The positive charge of the quaternary nitrogen of the Ch group in ACh is similar to the positive charge of the pyrrolidine nitrogen of nicotine, which has been emphasized previously (Domino 1979). When using computer graphic techniques, the two molecules are superimposable. At the pH of blood, nicotine exists in both charged and uncharged forms. The latter can readily penetrate the blood-brain barrier, but ACh cannot. Many years ago, tobacco companies began to add ammonia-forming chemicals to tobacco cigarettes, using the basic concept of the Henderson-Hasselbalch equation. With an alkaline pH, nicotine is more unionized and, therefore, better able to penetrate lipophilic cellular membranes. Pankow et al. (1997) studied this phenomenon in relationship to tobacco smoke particles in which the volatility of conversion of nicotine to its nonprotonated free-base form is facilitated at a basic pH.

A series of studies by Gause and Smaragdova (1938, 1939) and Gause (1941) almost 60 years ago suggested that the mechanism of action of nicotine is related to that of ACh. These investigators studied the toxicity of the optical isomers of nicotine in a large number of invertebrates and vertebrates. In many worms, fish, amphibia, reptiles, and birds, *l*-nicotine is more toxic than *d*-nicotine. In lower forms such as protozoa, coelenterata, platyhelminthes (turbellaria), nemertinea, and trochelminthes (rotatoria), the toxicity of the two isomers of nicotine is equal. Gause (1941) correlated their data with those of Bacq (1935) in animals species that presumably used ACh as a neurotransmitter. The correlation was so impressive that Gause proposed that an optically active receptive substance for nicotine was present in the nervous system of animals that utilized ACh as a neurotransmitter. Hence, Gause in 1941 provided biologic evidence for the existence of a nicotinic cholinergic receptor (nAChR).

BRAIN DISTRIBUTION OF NICOTINIC CHOLINERGIC RECEPTORS

Schwartz et al. (1982), Clarke and Pert (1984, 1985), Clarke et al. (1985b), London et al. (1985), Schwartz and Kellar (1985), and Schulz et al. (1991) described the autoradiographic distribution of nAChRs in rat brain using ^{3}H-nicotine, ^{3}H-ACh, and ^{125}I-α-bungarotoxin binding. ^{3}H-nicotine binds with high affinity. It is displaced selectively by cold *l*-nicotine and ACh and less so by *d*-nicotine. The brain distribution of ^{3}H-nicotine and ^{3}H-ACh is quite different from that of ^{125}I-α-bungarotoxin, indicating major subtypes of nAChRs. Both ^{3}H-nicotine and ^{3}H-ACh binding is highest in the interpeduncular nucleus, most thalamic nuclei, superior colliculus, medial habenula, presubiculum, layers I, III, and IV of the cerebral cortex, substantia nigra pars compacta, and the ventral tegmental area. Deutch et al. (1987) and Swanson et al. (1987) used monoclonal antibodies generated against purified AChR from Torpedo electric organ, or chicken and rat brain, to determine the immunohistochemical localization of nAChR in rat and mouse brain. Again, the pattern of brain distribution is quite different from that of α-bungarotoxin binding but similar to that reported for nicotine binding.

MULTIPLE BRAIN NICOTINE BINDING SITES

In the 1970s and 1980s, researchers characterized rodent brain binding sites for ^{3}H-nicotine. The number of nicotine binding sites found varied considerably. Schleifer and Eldefrawi (1974), Abood et al. (1980), and Martin and Aceto (1981) found only one binding site. However, Yoshida and Imura (1979), Romano and Goldstein (1980), Sershen et al. (1981), and Marks and Collins (1982) reported one or two sites, depending upon the temperature and duration of incubation. On the other hand, Sloan et al. (1983, 1984, 1985a,b,c, 1987, 1988) found that ^{3}H-nicotine binding was very complex. Multiple sties, including a very high, high, low, and very low affinity, as well as a positive cooperativity site, were described. Sloan et al. also pointed out that nicotine ligands that differed in their binding characteristics had different pharmacological effects, data consistent

with the presence of multiple nicotinic receptors. Furthermore, as mentioned above, the brain distribution of the binding sites for nicotine differed considerably from those for α-bungarotoxin as described by Marks and Collins (1982), Clarke et al. (1985b), and London et al. (1985). It should be noted that Abood et al. (1980) provided evidence for a noncholinergic nicotine binding site. Sloan et al. (1987) pointed out that a number of endogenous brain chemicals, especially niacinamide in a concentration of only 10^{-10} mol/L, produced a 17% increase in ^{3}H-nicotine binding by an action at an up-regulatory site. One must conclude that there are multiple binding sites for nicotine in the brain; we need to know far more details of the mechanisms involved.

SUBTYPES OF NICOTINIC CHOLINERGIC RECEPTORS

A great deal of research provided insights into the biological functions of ACh (Mesulam 1994; Reiner and Fibiger 1994) and its muscarinic and nicotinic cholinergic receptor families (Changeaux et al. 1992; Chini et al. 1992; Gerzanich et al. 1993; Lena and Changeaux 1993; Lindstrom et al. 1990; Leutje and Patrick 1991; Sargent 1993; Seguela et al 1993; Sieghart 1992; Steinbach 1990; Tarroni et al. 1992). Muscarinic cholinergic receptors (mAChR) are members of a superfamily of G protein–coupled receptors (Ehlert et al. 1994; Richelson 1994). Nicotinic cholinergic receptors (nAChRs) are members of a superfamily of ligand-gated ion channels with significant molecular diversity (Popot et al. 1976; Conti-Tranconi et al. 1982; Wada et al. 1989; Deneris et al. 1991; Sargent 1993; Arnerić et al. 1995; Bannon et al. 1995). There are now five known muscarinic receptor subtypes (M_1, M_2, M_3, M_4, M_5) that involve, as second messengers, intracellular decreases in cAMP, increases in PI turnover, or increases in K^+ conductance. The number of known nicotinic cholinergic receptor subtypes is increasing. The primary composition of nicotinic cholinergic (Numa et al. 1983) and muscarinic cholinergic (Kubo et al. 1986) receptors were determined by using molecular biological techniques that provided amino acid sequences from cloned DNA. Analysis of hydrophobicity plots of their amino acid sequences suggested that nicotinic receptors traverse the plasma membrane four times and muscarinic receptors seven times.

The specific genes for each subunit of nAChRs all encode proteins that are similar to the skeletal muscle α1 subunit in that they contain cysteine 128 and 142. There are now eight α neuronal genes (α2 through α8). In addition, three neuronal β genes (β2, β3, β4) have been described. The subunit mRNA distribution for each varies considerably throughout the nervous system of different species of animals. The nAChRs are divided into three subfamilies as noted in Table 1.

Although the functional role of nAChRs in synaptic transmission in peripheral autonomic ganglia and at the skeletal neuromuscular junction is well documented, their role in synaptic transmission in the brain is far less documented (Sargent 1993; Zhang et al. 1993; McGehee et al. 1995). Especially interesting is electrophysiological evidence that even in synapses mediated by transmitters other than ACh, there may be presynaptic choline acetyltransferase expression and pre- and postsynaptic nAChRs (Brown et al. 1983; Schwartz et al. 1984; Edwards et al. 1992). Wonnacott et al. (1989) and Wonnacott (1997) summarized the evidence for nAChR presynaptically modulating the release of various neurotransmitters. Vidal (1994) suggested that nicotine potentiation of glutamatergic synapses may explain its effects on cognition. McGehee et al. (1995) provided electrophysiological evidence that nicotine in nmol/L concentrations via nAChRs enhances cholinergic and glutamatergic synaptic transmission by increased presynaptic $[Ca^{++}]_i$.

Table 1. Subfamilies of Nicotinic Cholinergic Receptors

Property	Skeletal Muscle	Autonomic Ganglionic	Central Nervous System
Subunits	α1, β1, ε, δ, γ	α3, α4, α5, α7, β2, β4	α2, α3, α4, α5, α6, α7, α8, α9, β2, β3, β4
Examples of subunit composition as hetero- or homo-oligomers	$(\alpha1)_2$B1εγ(adult) $(\alpha1)_2$B1δγ(fetal)	$(\alpha4)_x7)_y$, $(\alpha4)_x(\beta2)_y$	$(\alpha4)_2(\beta2)_3$, $(\alpha3)_x(\beta2)_y$ $(\alpha7)_5$, $(\alpha8)_5$, $(\alpha9)_5$
Effector	int.$Na^+/K^+/Ca^{++}$ (cond. ps large)	int.$Na^+/K^+/Ca^{++}$ (cond. small to large)	int.$Na^+/K^+/Ca^{++}$ (cond. small to large, high Ca^{2+} perm.)
Selective	$[^3H]$- or $[^{125}]$-α-bungarotoxin	$[^3H]$ cysteine $[^3H]$ methylcarbamyl-choline $[^3H]$ nicotine	$[^3H]$- or $[^{125}]$-α-bungarotoxin $[^3H]$ κ-bungarotoxin
Channel blockers	decamethonium gallamine	chlorisondomine hexamethonium mecamylamine	chlorisondomine mecamylamine

Cond. = conductance; perm. = permeability; ps = picosiemens; x,y = variable numbers not identified.

OCCUPANCY, RATE, EFFICACY, AND ALLOSTERY RECEPTOR THEORIES—ACTIONS OF NICOTINE ON ITS RECEPTORS

There are a number of theories regarding drug receptor interactions (Pratt and Taylor 1990; Kenakin 1993). Occupation theory and its extensions include efficacy and allostery models. Classical occupation theory and its extensions involve the mathematical process by which drug molecules bind to the number of their receptors. Rate theory involves the rate of onset and offset of drug molecules binding to their receptor (Paton 1961). As described by Paton, "Instead of thinking of a receptor as, say, a note on an organ, such that as long as it is depressed a note is emitted, we think of it like a piano, one burst of sound and then silence." Rate theory now has few proponents and many feel it has been disproven. Occupancy theory, as developed by Clark (1933), efficacy theory as a modification of occupancy theory Stephenson (1956), and its physical or molecular basis in the allostery model developed by Karlin (1967), Thron (1973), and Lena and Changeaux (1993) are currently the dominant drug-receptor models. Receptor inactivation or desensitization models include those above as well as those described by Katz and Thesleff (1957) and Gosselin (1977). There is a pressing need to explain in mathematical terms the interactions of nicotine with its many different receptors in a unified theory of nicotine receptor activation and deactivation.

TOBACCO AND NICOTINE AS REINFORCERS IN HUMANS

Not only is the amount of nicotine crucial in the reinforcing effects of tobacco, but also its rate of absorption into the systemic circulation. Smokers given nicotine slowly with a 14-h IV infusion (Benowitz and Jacob 1990), or via a transdermal nicotine patch (Foulds et al. 1992), continue to smoke. The additional nicotine produces a substantially greater increase in venous plasma nicotine levels more than the volunteers usually would obtain after smoking ad lib. Furthermore, the subjects smoke less. These findings confirm earlier reports by Johnston (1942) and Lucchesi et al. (1967). The latter found that an IV nicotine infusion reduced the number of cigarettes smoked by only 22%. Recently, a mouth nicotine inhaler has been used as an adjunct to smoking cessation (Leischow et al. 1996). The smoking abstinence rate following its use was 45% compared to 14% ($p < .0005$) for a placebo inhaler at week 6, but by month 12 the rate was 11% and 5%, respectively ($p = .14$). It should be noted that although the type of oral nicotine inhaler used delivers reasonable peak plasma levels of nicotine (Molander et al. 1996), it does not deliver nicotine to the lungs but only to the mouth and throat (Bergstrom et al. 1995).

In 1997, Li et al. and Winchell et al. from the Food and Drug Center for Drug Evaluation and Research reported on all phase III clinical trials related to nicotine products in new drug applications in the United States. A total of 1,953 tobacco smokers were examined for quit rates between nicotine replacement and placebo treated groups. The 4-week quit rates were 37.2% for the nicotine treated versus 22.1% for the placebo group ($p < .0001$). After 12 months, the quit rates were 14.9% for the nicotine and 11.1% for the placebo group ($p < .05$). Nicotine underdosing was not associated with poorer smoking cessation rates among the nicotine treatment groups with different levels of salivary cotinine. *Although the differences between placebo and nicotine replacement therapy groups were statistically significant, the clinical success of nicotine replacement is clearly unimpressive*. At 4 weeks, about one of three smokers quit and after 1 year of continuous nicotine therapy only 15 of 100 smokers quit, whereas 85 ex-smokers are back to smoking. Why is nicotine replacement therapy so poorly effective if tobacco smokers are addicted to nicotine? The quantitative data on the rate of nicotine absorption by Armitage et al. (1975) and the pharmacokinetic considerations by Benowitz (1990) following smoking provide clues. Russell et al. (1995) proposed that tobacco smokers regulate their pattern of puffing and inhalation of cigarette smoke to obtain an increase (which they called a boost) of about 10 ng/ml venous blood within a period of less than 10 min. The blood nicotine boost is defined as the trough concentration before to the peak concentration just after smoking a tobacco cigarette. The nicotine arterial/venous concentration ratio is about 8–10 just after smoking a cigarette (Armitage et al. 1975; Henningfield et al. 1993). Therefore, the arterial nicotine boost delivered to the human brain must be in the order of 80–100 ng/ml, with a decline to about 25 ng/ml within 10 min. Arterial/venous equilibration of nicotine is incomplete 10 min after finishing smoking a cigarette (Henningfield et al. 1993).

It is of interest that nicotine in gums, skin patches, and inhalers is not pleasurable to most people, in contrast to its use in tobacco. Nicotine skin patches are readily available over the counter in the United States without a prescription and are not abused, probably because they do not provide the short duration nicotine boosts that tobacco smoking does. Is this the only reason most people do not find pure nicotine-containing preparations reinforcing? It should be noted that an extensive series of studies by Jasinski, Henningfield, and colleagues found that IV pulses or smoked nicotine were as pleasurable as cocaine, morphine, or heroin in polydrug abusers (Henningfield et al. 1981, 1983, 1985, 1987; Henningfield and Jasinski 1988; Jasinski and Henningfield 1988; Jasinski et al. 1984; Keenan et al. 1995). Such studies must be repeated in normal nonsmokers and smokers, although significant ethical issues need to

be settled first. At present, pure nicotine abuse is almost nonexistent compared with tobacco smoking. Why?

Another major area of research concern is the impact of individual differences and the role of psychopathology in human smoking behavior. Gilbert (1995) stressed the issue of individual differences in relationship to a large variety of psychological and biological factors. Pomerleau (1997) reviewed the extensive evidence that psychological/psychiatric co-morbidity with tobacco smoking is present in patients with anxiety disorders, attention deficit-hyperactivity disorders, bulimia/bingeing, and mental depression. Nicotine and other chemicals in tobacco smoke are probably used by such patients as self-medication. Especially pertinent are the studies by Freedman and colleagues, using the positive auditory evoked potential of about 50 ms as an electrophysiological marker for schizophrenia. This positive potential (P1, also known as P50) has been used as an index of processing auditory input in schizophrenic patients (see Adler et al. 1982, 1992; Freedman et al. 1983, 1987, 1991; Waldo et al. 1991). The testing paradigm they used is related to prepulse inhibition of the startle response. Tobacco smoking/nicotine transiently reversed this deficit in sensory gating in schizophrenic patients and some of their mentally normal relatives. Freedman et al. (1983) demonstrated that the P1 gating mechanism involves a nicotinic cholinergic mechanism via an α-bungarotoxin sensitive receptor. It is of interest that Knott (1989) summarized data that the P1 potential is enhanced in mentally normal volunteers by tobacco smoking.

The mechanism by which nicotine in combination with haloperidol is a treatment of Tourette's syndrome (Silver and Sanberg 1993) needs further study, as does the relationship of nicotine to Parkinson's and Alzheimer's diseases (Smith and Giacobini 1992).

NICOTINE ALONE IS REINFORCING IN ANIMALS

There is no question that nicotine is a positive reinforcer in animals. The first report by Deneau and Inoki (1967) indicated that monkeys self-administer nicotine. Perhaps because nicotine is not as reinforcing in animals as cocaine there was early disagreement among investigators as to how reinforcing nicotine really was. The early literature is well summarized in the U.S. Surgeon General's report in 1988. Since then, the evidence that nicotine alone is a positive reinforcer in animals is overwhelming. In addition, animals readily discriminate nicotine in appropriate behavioral paradigms (Stolerman 1989; Rosecrans et al. 1995). Strain differences are important, indicating genetic factors must be considered.

Genetic factors in rats are impressive (Shoaib et al. 1997). For example, Corrigall and Coen (1989) studied Long-Evans rats that show robust self-administration of nicotine, whereas Dworkin et al. (1993) studied Wistar rats that do not. Rosecrans (1971) showed that female rats selected for activity differences differ in their behavioral and 5-hydroxytryptamine brain effects. Individual differences are marked (Rosecrans 1995). Furthermore, nicotine stimulus discrimination varies markedly among different rat strains (Rosecrans et al. 1995). Although genetic factors are very important in nicotine reinforcement, the conditions in which rats were previously trained to drugs like cocaine (Tessari et al. 1995) are an indication of important conditioning, etc., factors (Shoaib et al. 1997).

IS TOBACCO SMOKING ADDICTION DUE TO NICOTINE ALONE?

A hypothesis championed by proponents of the tobacco industry is that the effects of tobacco cigarette smoking are more complex than those due to nicotine alone. Perhaps an appropriate nicotine boost, as well as the possible effects of the thousand or more other chemicals in tobacco smoke, is involved in maintaining tobacco smoking behavior. It is not the purpose of this communication to review the chemistry of tobacco and its smoke (see Schmeltz and Hoffman 1976). Jarvik's review (1979) includes a short list of substances in the gas and tar phase of cigarette smoke, which is a cesspool of chemicals that may have some biological effects. What substances in tobacco smoke besides nicotine have behavioral, nervous system, or other actions throughout the body? Almost everybody agrees with the widely held belief that the primary pharmacologically active agent in tobacco is nicotine. However, other chemicals in tobacco smoke contribute to its smell, taste, and complex biological effects. It is essential to compare the effects of pure nicotine with those of tobacco smoke on various biological and psychological measures. As described above, one must keep in mind the route and speed by which tobacco versus nicotine is taken into the body. The various tobacco/nicotine delivery systems are compared in Table 2.

The rate of absorption and dose of nicotine are crucial variables that determine its pharmacological actions. There are rapid but variable rates of desensitization of various nicotinic cholinergic receptors, which lead to differential tachyphylaxis and tolerance. It makes little pharmacological sense to compare the effects of the inhalation of tobacco smoke with those produced by a nicotine patch. One must compare the effects of tobacco and pure nicotine via the same route of administration and same rate of absorption. Skin absorption of both is the slowest, oral gum slow, snuff and nasal spray a little faster, and pipe smoking and mouth inhalation intermediate. Cigarette smoking and aerosol inhalation produce the fastest absorption of active compounds. Nicotine aerosol inhalers developed

Table 2. Tobacco/Nicotine Delivery Systems

Tobacco	Nicotine	Absorption
Mouth (oral snuff)	Gum	Slow
Skin contact	Patch	Slowest
Nasal snuff	Nasal spray	Intermediate
Enema	Enema	Intermediate
Cigar, pipe	Mouth inhaler	Intermediate
Cigarette	Aerosol inhaler	Fast
Not applicable	Injection, SC, IM, IV	Intermediate to fastest

years ago (Herxheimer et al. 1967; Domino and Lutz 1973) were very irritating and not practical in delivering pure nicotine via lung absorption. With new propellants and the technologies used in current asthmatic inhalers, this problem should be overcome. One can also use pure nicotine injections SC, IM, and IV. The rates of absorption from these routes are intermediate to very fast. It is not very practical, but tobacco has been used by local skin application and rectal administration. Inasmuch as ulcerative colitis is a disease primarily of nonsmokers, and transdermal nicotine patches are helpful, Green et al. (1977) developed a nicotine polyacrylic carbomer administered by enema to treat patients with active disease. In the case of ulcerative colitis, it appears that the beneficial effects of tobacco smoking are those due to nicotine itself and not other chemicals in tobacco.

Dramatic visual evidence from the human positron emission tomography (PET) imaging study by Fowler et al. (1996) shows that there is more to tobacco smoke than nicotine. It was known for many years that something in tobacco smoke inhibits monoamine oxidase (MAO; Essman 1977; Oreland et al. 1981; Norman et al. 1982, 1987; Yu and Boulton 1987; Boulton et al. 1988; Berlin et al. 1995). There are two types of MAO involved in the oxidative deamination of biogenic amine chemical modulators and neurotransmitters. Fowler et al. (1996) showed more reduced brain MAO_B than MAO_A binding in tobacco smokers compared with nonsmokers. Nonsmokers were pretreated with nonradioactive deprenyl to inhibit their brain MAO_B as a control. In neither the deprenyl-treated nonsmokers nor the tobacco smokers was ^{11}C-deprenyl taken up as well by the brain. Nicotine itself is not an MAO inhibitor. Something else besides nicotine in tobacco smoke produces MAO inhibition. Is the percentage of inhibition in vivo sufficient for a functional decrease in MAO activity? The time has come for more research on this issue.

TOLERANCE, SENSITIZATION, AND WITHDRAWAL TO NICOTINE AND TOBACCO SMOKING

Nicotine is well known to produce rapid (tachyphylaxis) and slower tolerance. Any person who smoked a first tobacco cigarette knows the initial effects of smoking may be very unpleasant with subsequent tolerance. Interestingly, even regular tobacco smokers lose some tolerance overnight to the side effects of the first cigarette smoked in the morning. There are very important differential genetic components to nicotine-induced tolerance and nAChR changes as described by Marks et al. (1986) in four different inbred mouse strains. In contrast to C57BL, BALB, and DBA animals, C3H mice did not develop tolerance to nicotine effects on Y-maze activity, rearing, and body temperature. However, C3H mice showed tolerance to nicotine on acoustic startle. None of the four strains developed tolerance to nicotine effects on respiration. Only the BALB mice showed tolerance to nicotine-induced bradycardia. All four strains had increased [^{3}H]nicotine binding in six different brain regions with slight strain differences in α[^{125}I]bungarotoxin binding to chronic nicotine. The significance of the paradox of increased nAChR upregulation with chronic nicotine has been reviewed by Wonnacott (1990).

Damsma et al. (1989) found no tolerance to nicotine-induced dopamine release in nucleus accumbens. Such animal studies have important implications for the effects of nicotine and tobacco smoking in humans and may help explain some of the individual differences and perplexities of tobacco smoking. Detailed studies on the tolerance development to different pharmacological effects of nicotine are needed, similar to those described by Porchet et al. (1987, 1988) on heart rate.

One of the simplest behavioral effects of nicotine in rodents is alteration of locomotor activity. In mice, nicotine produces either an increase or decrease of activity, depending upon the dose and the genetic strain. Very marked pharmacogenetic differences to nicotine are observed in pure bred mouse strains (Bovet et al. 1969; Collins et al. 1988). When nicotine is given in a single dose to most strains of naive adult rats, locomotor activity is reduced. However, when nicotine is given daily, tolerance occurs to its depressant effects both on locomotor activity as well as in various operant paradigms (Morrison 1967; Morrison and Stephenson 1972; Domino and Lutz 1973; Stolerman et al. 1973; Rosecrans et al. 1989; Belwell and Balfour 1992; Villaneuva et al. 1992). On repeated administration, nicotine induced rat behavioral stimulation becomes very apparent (Morrison and Stephenson 1972; Clarke and Kumar 1983a,b; Ksir et al. 1985, 1987; Hakan and Ksir 1988, 1991; Johnson 1995). In addition, the sensitivity of rat frontal cortical neurons is increased by chronic nicotine (Abdulla et al. 1995). The same daily nicotine treatment schedule does not cause dramatic behavioral sensitization in hemiparkinsonian monkeys, suggesting important species or brain pathological differences (Domino et al. 1998). Hence, the need for more research. Does nicotine-induced behavioral sensitization, so easily observed in rats, occur in primates, and especially in humans?

The 1988 U.S. Surgeon General's Report summarized the evidence that abrupt withdrawal from nicotine/tobacco resulted in an abstinence syndrome. There is a significant interrelationship between conditioned and primary reinforcement in the maintenance of tobacco smoking (Rose and Levin 1991), but also in the extent of its withdrawal signs and symptoms. Hildebrand et al. (1997) used centrally and peripherally acting nicotinic antagonists to precipitate an abstinence syndrome in rats given nicotine, 10.27 mg/kg/day for 7 days. They concluded that central as well as peripheral nicotinic receptors contribute to the withdrawal syndrome. Abdulla et al. (1996) found that chronic nicotine given to rats produced regional brain increases in [^{3}H]-nicotine binding in some areas such as the frontal, entorhinal, and dorsal hippocampus, but not in other areas such as the posterior cingulate or ventral hippocampus. Nicotine clearly improved the rate of learning. These investigators studied the relationship between upregulation of nicotine binding sites and the cognitive enhancement after acute or chronic nicotine. Nicotine, given only for 1 day 11 days earlier, increased the rate of learning, but only marginally increased nicotinic receptor binding in the entorhinal cortex and not in other brain areas. Entorhinal and dorsal hippocampal nicotinic binding was positively correlated with the rate of learning. Clearly, much more research needs to be done on the relationship of improvement in learning and the significance of differential regional upregulation of both active and desensitized nAChRs, and which ones. Lake et al. (1997) reported in an abstract that in rats given a SC nicotine infusion in a dose of 9 mg/kg/day for 7 days, abrupt termination, injection of nicotine, the SC injection of mecamylamine, dihydro-β-erythroidine, or cerebral intraventricular (IVT) hexamethonium, but not scopolamine, induce an abstinence syndrome. The animal data indicate that nicotinic cholinergic antagonists such as mecamylamine precipitate a withdrawal syndrome in nicotine-dependent rats. However, mecamylamine, in doses up to 20 mg orally, does not precipitate a withdrawal syndrome in chronic tobacco smokers (Eissenberg et al. 1996). Perhaps much larger doses of mecamylamine are needed, but this will result in significant side effects due to mecamylamine alone. Obviously, much more research is needed to pursue this important issue.

NEED FOR APPROPRIATE COMPARISON STUDIES WITH NICOTINE ALONE AND VARIOUS TOBACCO PRODUCTS

Russell et al. (1995) concluded that a similar venous blood nicotine boost occurs within 10 min with both smokeless oral tobacco snuff and nicotine spray, but not with nicotine gum or patches. The best method of duplicating the puff by puff inhalation of tobacco smoke is the use of a nicotine aerosol. Until a nonirritating nicotine aerosol is developed, which can deliver nicotine to the lungs, the inhalation method of administering nicotine is not an option.

Pure nicotine solutions have been given to humans via various routes of injection including IV, IM, or SC. However, such methods of administration require an investigational new drug application to the U.S. Food and Drug Administration and, therefore, are of limited availability. Furthermore, institutional human use committees are far more concerned with protocols that deal with nicotine by injection than by patch, gum, or nasal spray. Obviously, computer programmed intravenous injections of nicotine that mimic the blood concentrations of nicotine obtained from inhaling tobacco smoke are of special interest. If an average tobacco smoker obtains about 10 total 0.1 mg/puff doses of nicotine in about 5 min, appropriate computer programming of small, very rapid bolus IV injections could mimic cigarette smoking. To do so, the injection system must deliver an IV nicotine bolus within 2 s. Corrigall and Coen (1989) used a pneumatic pump which delivered a 1-s pulse of nicotine each time a rat pressed an operant bar. A modified system using a microdialysis pump is being developed by Matta and colleagues from the Minneapolis Medical Research Foundation (personal communication 1997). Such a technique is still highly experimental and not a U.S. FDA approved method for humans. Therefore, from a practical point of view, at the present time intranasal administration of nicotine seems to be the only reasonable approach to compare pure nicotine with tobacco smoke inhalation. Fortunately, the FDA in 1996 approved a nicotine nasal spray device. This device delivers 0.5 mg/spray. Nicotine can easily be administered in doses of 1–2 mg total with one to two sprays into each nostril. Obviously, the next studies to be done are to compare the effects of intranasal nicotine with the results obtained with tobacco smoking.

FUTURE DIRECTIONS

We humans usually have free choice to decide on the harm/benefit of most behaviors that directly affect us. Much is known of the harmful effects of tobacco smoking, but a lot less about its benefits, which many in our society feel are none. Jarvik (1991) described some of the beneficial effects of nicotine. From a scientific point of view, society must do far more in providing support for studying the latter. Developing safer tobacco smoking devices is the job of the tobacco industry, but developing substitutes for the positive reinforcing effects of tobacco smoking is the job of motivated scientists and the pharmaceutical industry. The tobacco problem will not go away with a prohibition on smoking. Current agreements and negotiations among private, state, and

federal representatives and the tobacco industry are heading in the direction of allowing the tobacco industry to survive but be far more regulated. One can conclude that the 21st century will have many people well informed of the hazards of tobacco smoking who will continue to smoke. Hence, safer tobacco products, as well as much more scientific knowledge on why people smoke, need to be obtained through research. Agreements between legislative bodies and the tobacco industry should include funds to support such research, or more taxes on tobacco products should be designated for research.

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