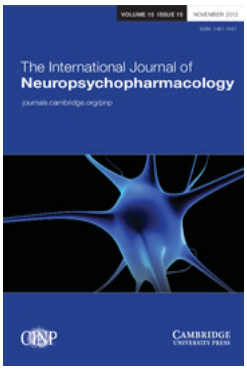

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Monoamine oxidases and tobacco smoking

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Abstract

Although nicotine has been identified as the main ingredient in tobacco responsible for aspects of the tobacco dependence syndrome, not all of the psychopharmacological effects of smoking can be explained by nicotine alone. Accumulating preclinical and clinical evidence has demonstrated that smoking also leads to potent inhibition of both types (A and B) of monoamine oxidase (MAO). Smokers have 30–40% lower MAOB and 20–30% lower MAOA activity than non-smokers. Reduced MAO activity in smokers has been shown by direct measures (platelets, positron emission tomographic studies) or by indirect measures (concentration of monoamine catabolites in plasma or CSF). We examine the hypothesis that chronic habitual smoking can be better understood in the context of two pharmacological factors: nicotine *and* reduced MAO activity. We speculate that MAO inhibition by compounds found in either tobacco or tobacco smoke can potentiate nicotine's effects. Based on this concept, more effective anti-smoking drug strategies may be developed. As a practical consequence of tobacco smoke's MAO-inhibitory properties, comparative psychiatric research studies need to screen and control for tobacco use.

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Introduction

Tobacco smoking is the most prevalent addictive disorder and the leading preventable cause of morbidity and mortality worldwide. The world has an estimated 1.1 billion smokers, approx. one fifth of the world's population (Chapman, 1996). In developed countries tobacco was responsible for 24% of all male death and 7% of all female deaths. The average loss of life attributable to tobacco in 1990 was about 16 years (Peto et al., 1996). In the last 20 years, many efforts have been made to better understand the addictive nature of smoking. Nicotine was identified as the principal drug in tobacco products and tobacco smoke responsible for the dependence-producing effects of cigarette smoking, and it is also responsible for some of the behavioural, mood- and performance-enhancing effects of smoking (American Psychiatric Association, 1994). It was hoped that the accessibility of nicotine replacement therapies (NRT) would promote smoking cessation and drastically reduce rates of smoking. Although NRT significantly outperform placebo in initiating smoking abstinence (Silagy et al., 1994; Tang et al., 1994), their long-term efficacy at maintaining abstinence is less than ideal. All forms of NRT are associated with a high relapse rate in the first 3 months. Minimizing this relapse is important if long-term smoking cessation rates are to be substantially improved (Silagy et al., 2000). Clearly, new research strategies to help nicotine dependent individuals stop smoking are warranted.

This paper reviews evidence that tobacco smoking also leads to monoamine oxidase (MAO) inhibition, and examines the hypothesis that chronic smoking can be better understood in the context of two pharmacological factors: nicotine *and* reduced MAO activity.

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General characteristics of monoamine oxidases

Hare (1928) described a tyramine-degrading enzyme in mammalian liver and called it 'tyramine oxidase'. The large activities of this enzyme in the gut and liver suggested that one of its main biological functions might be the detoxification of exogenous amines by oxidative deamination. Subsequently, the name of the enzyme was changed to monoamine oxidase, and it was localized in most tissues except erythrocytes. MAO (EC 1.4.3.4), a flavoenzyme located in mitochondria, catalyses the oxidative deamination of exogenous and endogenous biogenic amines in peripheral tissues and the brain.

The existence of two types of MAO was proposed, based on inhibitor selectivity (Johnston, 1968; Knoll and Magyar, 1972). MAOA was found to be selectively inhibited by clorgyline, and MAOB was selectively inhibited by deprenyl (selegiline). MAOA preferentially deaminates norepinephrine (NE), serotonin (5-HT) and epinephrine (E), while MAOB preferentially deaminates benzylamine and phenylethylamine (PEA). Dopamine (DA) and tyramine are equally catabolized by both forms of MAO. The highest concentrations of MAO (mainly MAOA) are in the liver, gut and placenta, corresponding to the enzyme's ontogenetic detoxifying function, and it is also estimated that 70% of neuronal MAO is of the A type. MAOB is mainly found in glial cells and thrombocytes.

The structural genes for MAO (A and B) are located on the X chromosome. In 1988, human liver MAO (A and B) were cloned (Bach et al., 1988). The comparison of the deduced amino-acid sequences of MAO (A and B) showed 70% amino-acid sequence identity. The amino-acid sequence of both isoenzymes among mammalian species is strongly conserved which may reflect evolutionary pressure to maintain the specific physiological function of each MAO (Shih et al., 1999). Studies of MAOA and MAOB knockout mice (Cases et al., 1995; Grimsby et al., 1997; Kim et al., 1997b) and studies of humans with specific genetic deficiencies of the A and B isoenzymes (Lenders et al., 1996) have clearly demonstrated that MAO (A and B) have distinct functions.

Measures of MAOB and MAOA in humans

In humans, MAOB activity can be directly assayed in platelets that contain the B form of the enzyme exclusively. Because of their easy accessibility, platelet-derived MAOB activity has been measured across a variety of medical and psychiatric conditions yielding conflicting results (Sandler et al., 1981). Initially, there was some uncertainty as to whether platelet MAOB activity reflected activity of brain MAOB. Chen et al. (1993) determined the nucleotide sequences of human MAOB from frontal cortex and compared it to that of human platelets. They found that the nucleotide sequence of human MAOB cDNA from platelet and frontal cortex were identical, and that cDNA derived from human brain was nearly identical with those copies derived from human liver. Similarly, an earlier in-vivo study measured the reduction of cerebral MAOB activity using positron emission tomography (PET) and found that brain MAOB activity was significantly correlated with the reduction in platelet MAOB (Bench et al., 1991). Taken together then, it appears that platelet MAOB accurately reflects brain MAOB.

MAOA activity in humans can be measured directly in skin fibroblasts; however, this technique is cumbersome and seldom used. Instead, brain MAOA levels have been estimated using PET, or more commonly, have been assessed indirectly in plasma or in cerebrospinal fluid (CSF) by determining catabolites of the various endogenous monoamines.

Norepinephrine

MAOA catabolizes NE to 3,4-dihydroxyphenylglycol (DHPG). DHPG is further metabolized by catecholamine-*O*-methyl-transferase (COMT) to methoxyhydroxyphenylglycol (MHPG). Since DHPG is derived from NE metabolized intraneuronally, and MHPG is derived from NE metabolized extraneuronally (and from DHPG metabolized intraneuronally) (Eisenhofer et al., 1988), brain MAOA activity is probably more accurately reflected by plasma DHPG rather than by MHPG concentrations. Indeed, after inhibition of MAOA by selective inhibitors, plasma DHPG concentrations characteristically decrease (Berlin et al., 1990). The accuracy of measuring MAOA activity can also be enhanced by using the NE/DHPG or sulphate-conjugated normetanephrine/DHPG ratios (normetanephrine is the *O*-methylated amine metabolite of NE) (Lenders et al., 1996).

Dopamine

DA is metabolized by MAO to dihydroxyphenylacetic acid (DOPAC) which is further catabolized to homovanillic acid (HVA) by COMT. Both plasma DOPAC and HVA levels were found to be decreased in the presence of MAOA inhibition (Berlin et al., 1990), or in individuals who lacked a normally functioning MAOA gene (Lenders et al., 1996).

Serotonin

MAOA activity levels also influence the concentration of 5-hydroxy-indoleacetic acid (5-HIAA), the main metabolite of 5-HT (Donnelly and Murphy, 1977). Although MAOA degrades 5-HT more efficiently than MAOB, the neurons that use 5-HT as a neurotransmitter appear to contain primarily MAOB (Westlund et al., 1985).

Physiological factors influencing monoamine oxidase activities

Age effects

In fetal brain, MAOA activity appears before MAOB, and brain MAOA activity peaks in newborns. Since MAOB

activity appears to rise with increasing age (Fowler et al., 1980), MAOB activity levels are greatest in late adulthood. Indeed, the ratio of MAOA:MAOB activity is higher in fetal (2.43) and neonatal (2.39) brain than in the adult brain (0.61) (Lewinsohn et al., 1980). The increase in MAOB activity with ageing has been attributed to the increase in glial cell mass, and not to a direct increase in MAOB activity per se. However, two large-scale studies examining the effects of age on thrombocyte MAOB activity have produced conflicting results. One earlier study reported a doubling of platelet MAOB activity across a 50-yr time-span (Bridge et al., 1985); however, a more recent study found no significant age effects on MAOB activity (Anthenelli et al., 1998). It is noteworthy, however, that only the latter study controlled for the effects of cigarette smoking (see below).

Gender effects

Somewhat less controversially, numerous studies have found that men have lower platelet MAOB activity than women (Anthenelli et al., 1998; Berlin et al., 2000; Bridge et al., 1985; Norman et al., 1982, 1987; Saccone et al., 1999; Sandler et al., 1981). This gender difference might be related to the effects of sex steroids on the enzyme's activity, as it has been found that platelet MAOB activity is decreased in women around the ovulatory period when serum oestradiol concentrations reach their peak (Belmaker et al., 1974; Poirier et al., 1985). Further research is needed to better understand hormonal effects on MAO activity and their physiological relevance.

Ethnoracial effects

Bridge et al. (1985) found lower MAOB activities in African–American females and males, compared with gender- and age-matched Caucasians. However, results from the Collaborative Study on the Genetics of Alcoholism (COGA), which controlled for these factors as well as cigarette smoking, failed to confirm any ethnoracial effects on platelet MAOB activity (Anthenelli et al., 1998). Ethnic differences in MAOA activity have not been studied.

Effects of tobacco smoke on monoamine oxidases: preclinical studies

The first report of the effect of cigarette smoke on MAO activity is that of Essman (1977) who exposed mice to cigarette smoke and measured MAO activity in the skin. Cigarette smoke dose-dependently inhibited the deamination of 5-HT as evidenced by an increased skin uptake of 5-HT. Yu and Boulton (1987) measured the effect of cigarette smoke solutions and a cigarette tobacco extract on rat lung mitochondrial MAO activities. Both cigarette smoke solution and cigarette tobacco extract dose-dependently inhibited MAO activity independent of the substrates (i.e. 5-HT, *p*-tyramine, β-phenylethylamine) used. These authors found that the effect was 2-fold greater when 5-HT was used as substrate, indicating that there is a slightly greater inhibitory effect of cigarette smoke on MAOA activity in vitro. In a second experiment, it was found that even after smoking only one cigarette, exposure to human saliva dose-dependently decreased rat lung MAO activity.

Since several epidemiological studies have suggested that smokers may be at lower risk to develop Parkinson's disease, a number of in vitro studies have tested the effect of smoke exposure on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neuronal changes. MPTP, which has been implicated in the pathophysiology of Parkinson's disease, is oxidized by MAOB to give MPP^+ (1-methyl-4-phenyl-pyridinum ion) which is taken up by dopaminergic neurons and ultimately causes cell death. Smoke exposure was found to lessen the diminution in striatal DA (and its metabolite, DOPAC) caused by MPTP exposure (Carr and Rowell, 1990). Another study confirmed that cigarette smoke exposure prevented MPTP-induced decreases in striatal DA levels, and found that both brain and liver MAO activity were inhibited by cigarette smoke (Shahi et al., 1991). When mice were treated chronically with constituents of tobacco smoke such as nicotine, 4-phenylpyridine or hydrazine, none of these individual compounds were found to inhibit MAO activity in cerebral tissue. However, exposure to tobacco smoke caused a marked inhibition of both MAOA and MAOB activity (Carr and Basham, 1991).

Exposure of biogenic amines to aqueous extracts of cigarette smoke results in the formation of amine/smoke adducts. These include m-hydroxy substituted amines (m-tyramine, DA, NE), which form cyanotetraisoquinolines, and indoleamines (5-HT), which form cyanotetrahydro-β-carbolines (Boulton et al., 1988). Adducts of 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4-tetrahydro-β-carboline (THβC) have been found to act as competitive inhibitors for MAOA and MAOB (Mendez-Alvarez et al., 1997; Soto-Otero, 1998).

Pavlin and Sket (1993) measured the effect of cigarette smoke on MAOA and MAOB in single isolated nerve cell bodies from substantia nigra and nucleus reticularis pontis caudalis. Exposing tissues to varying amounts of cigarette smoke progressively increased the degree of MAO inhibition from 37% (1 cigarette) to 100% (4 cigarettes) with MAOA activity being more affected than MAOB. Exposing the animals directly to cigarette smoke also led

to dose-dependent increases in MAO inhibition. However, exposing the animals to the smoke generated by burning cigarette papers had no effect on MAO activities. Furthermore, these authors found that nicotine exposure alone did not inhibit MAO activities.

It seems that nicotine in concentrations found in the blood of smokers does not inhibit MAO activity. For example, when nicotine was incubated with human platelets, MAO inhibition occurred only at nicotine concentrations 2000 times higher (5×10^{-4} M) than those levels which are typically found in the plasma of heavy smokers (Oreland et al., 1981). Furthermore, Fowler et al. (1998a) investigated the effect of nicotine in the non-human primate brain to determine whether brain MAOB is affected by nicotine in vivo. After i.v. administration of 0.3 mg of nicotine to baboons, MAOB concentration, as measured by PET using L-[^{11}C]deprenyl, was not modified in any brain region studied.

Monoamine oxidase-inhibiting properties of other plant extracts

In addition to tobacco, several plants indigenous to South America, Africa and India possessing central nervous system actions have been tested for possible MAO inhibitory activity. Ayahuasca ('vine of the souls') is a hallucinogenic beverage derived from boiling together several Amazonian plants. Some of these plants contain harmine and harmaline, two β-carbolines known to exhibit selective MAOA-inhibiting effects (Kim et al., 1997a). These plants also contain dimethyltryptamine (DMT), a potent hallucinogen. DMT ingested orally is inactive because the compound is degraded by visceral stores of MAO; however, ingestion of β-carbolines together with DMT increases the latter drug's bioavailability and leads to hallucinogenic effects (McKenna et al., 1984).

Kava-kava, a psychaoactive beverage available as an over-the-counter herbal preparation in several countries, has played an important sociocultural role in the South Pacific Islands for many centuries. It is claimed to improve social interaction, to promote sleep, and to possess anxiolytic properties. A recent in-vitro study indicated that kava extract and kava pyrones inhibit platelet MAOB activity more rapidly than L-deprenyl. In fact, these substances were found to inhibit PEA deamination by platelet MAOB at concentrations 10–100 times lower than brofaromine [a MAOA and (less potent) MAOB inhibitor] (Uebelhack et al., 1998).

Areca nuts (*Areca catechu*, or betel nuts) have been used widely on the Indo-Pakistan subcontinent. They are chewed for their psychoactive and antidepressant effects. In preclinical models of depression, *Areca catechu* extracts had similar actions to that of moclobemide, a selective, reversible MAOA inhibitor (Dar and Khatoon, 2000).

Cannabis extract, but not Δ^1-tetrahydrocannabinol, inhibits both MAOA and MAOB activity with a preferential affinity for MAOB (Schurr and Livne, 1976; Schurr and Rigor, 1984). Very recently, several other MAO inhibitor compounds have been isolated from tobacco leaves, all of which have been demonstrated to competitively inhibit both MAOA and MAOB in vitro (Khalil et al., 2000). It appears then that MAO inhibition is a common property among some plant constituents possessing psychotropic effects. To date, these psychotropic actions have generally not been well characterized. These effects may come directly from MAO inhibition or, as is probably the case with Ayahuasca, MAO inhibition might facilitate the bioavailability or pharmacological effects of another compound.

MAO activities in smokers (Table 1)

MAOB

Early studies examining the relationship between smoking and MAO determined almost exclusively the MAOB activity in platelets. Oreland et al. (1981) first demonstrated that platelet MAO activity was significantly lower in smoking women than in non-smoking women. The decrease in MAO activity ranged from 22% (when β-phenylethylamine was used as substrate) to 14% (with tyramine as the substrate). These authors were also the first to show the lack of difference in platelet MAO activity between non-smokers and ex-smokers. Norman et al. (1987) confirmed these results and reported a 24% decrease in smoking women compared with non-smoking women, and a 21% decrease in smoking men compared to non-smoking men. Again, there was no difference in MAO activity levels between non-smokers and ex-smokers. Consistent with the dose-dependent in-vitro effects described earlier, MAO activity was found to be inversely correlated with the number of cigarettes smoked in female smokers, but not in male smokers.

These early results have since been replicated in several more recent studies containing a substantially larger number of subjects. Thus, platelet MAO activity has been found to be approx. 15% lower among regular smokers compared with ex-, non-, or 'irregular' smokers, respectively (Von Knorring and Oreland, 1985). In addition, recent data from the Collaborative study on the Genetic of Alcoholism (COGA) also indicate a dose-dependent decrease in platelet MAOB activity in current smokers which occurs as a function of the reported number of cigarettes smoked per day (Table 1) (Saccone et al., 1999).

Table 1. Monoamine oxidase (B and A) activities in current smokers compared to non-smokers

Reference	Difference in MAOB activity between smokers and non-smokers (%)
Oreland et al. (1981)	−14 to −22 with different substrates
Norman et al. (1982)	Men: −12
	Women: −21
Von Knorring and Oreland (1985)	−15
Norman et al. (1987)	Men: −21
	Women: −24
Berlin et al. (1995a)	−53
Fowler et al. (1996)	−40 (PET scan)
Anthenelli et al. (1998)	Men: −18
	Women: −22
Saccone et al. (1999)	1–10 cigarettes/d: −16
	11–20 cigarettes/d: −24
	21–35 cigarettes/d: −27
	36+ cigarettes/d: −37
Simpson et al. (1999)	−39 schizophrenic patients
	Difference in MAOA activity between smokers and non-smokers (%)
Berlin et al. (1995a)	−19 (plasma DHPG)
	−36 (plasma DOPAC)
Fowler et al. (1996b)	−28 (PET scan)
Geracioti et al. (1999)	−54 (HVA in CSF)

MAOB activity was measured ex vivo in blood platelets with the exception of the study of Fowler et al. (1996a). Changes in plasma DOPAC and CSF HVA concentration may result from both MAOB and MAOA activities although the predominant enzyme is thought to be MAOA.

Further support for the dose-dependent effects of cigarette smoke on MAOB activity levels in humans come from studies examining the relationship between indirect measures of tobacco smoke exposure (e.g. plasma thiocyanate or cotinine levels) and platelet MAOB which have found a substantial inverse correlation between these variables (Berlin et al., 2000; Norman et al., 1982).

The findings of lower MAOB activity levels in the platelets of smokers have been confirmed and extended using PET. Fowler et al. (1996a) reported an overall 40% decrease in brain MAOB activity of current smokers compared with non-smokers or former smokers. In some smokers, brain MAOB activity was almost as low as that found after the adminstration of L-deprenyl at a dosage of 10 mg/d for 1 wk. This degree of inhibition is of the same order of magnitude as that found in the platelets of heavy smokers in our own studies (Anthenelli et al., 1998; Berlin et al., 1995b). The reduction in brain MAOB activity measured by PET was widespread (i.e. reductions of 49% in the basal ganglia, 47% in the pons, 42% in the thalamus, 41% in the cingulate gyrus, 40% in the cerebellum, 39% in the frontal cortex, and 44% in the occipital cortex) (Fowler et al., 1998b).

More recently, the same authors measured the effect of a single cigarette on brain MAOB activity in 8 non-smokers (Fowler et al., 1999). PET studies were performed before and 5–10 min after smoking. No significant change in MAOB was observed. However, the study was limited because the subjects experienced nausea and vomiting, and most of them were unable to inhale the smoke to the extent that expired air carbon monoxide levels were lower than 10 ppm in all but 1 subject. Among the 4 subjects who achieved plasma nicotine concentrations in the range of smokers (i.e. 15–18 ng/ml), 3 subjects exhibited decreased brain MAOB levels while 1 subject had an increase in activity.

Taken together then, there is convincing evidence that MAOB activity is lower in current smokers, but then returns to the levels of non-smokers when smokers quit (Berlin et al., 1995a; Fowler et al., 1996a; Norman et al., 1987; Oreland et al., 1981; von Knorring and Oreland, 1985; Saccone et al., 1999). Normalization of platelet MAOB activity after stopping smoking takes several weeks (Berlin et al., 1995b). Since cigarette smoke irreversibly inhibits platelet MAOB (Carr and Basham, 1991; Yu and Boulton, 1987), the return of platelet MAOB activity to normal levels probably depends upon two factors: (i) the turnover rate of thrombocytes (as is

the case with the inhibition of cyclooxygenase by aspirin), and (ii) the rate of synthesis of MAOB. Human platelets have an estimated life-span of about 10 d, and the synthesis rate of MAOB is slow with a half-life of approx. 40 d (Fowler et al., 1994). Therefore, measures of MAOB activity in platelets may reflect longer-term exposure to tobacco smoke. This suggests that determination of ex-vivo MAOB activity in thrombocytes might, theoretically, be used as a biological index of direct and/or environmental tobacco smoke exposure.

The intriguing question remains, however, whether low MAO activity levels are solely related to the inhibiting effects of tobacco smoke, or whether low MAO activity might be related to personality traits predisposing individuals to various forms of 'disinhibitory psychopathology' that might include nicotine dependence (Oreland and Shaskan, 1983). For example, Buchsbaum et al. (1976) described the 'vulnerability hypothesis' of low platelet MAOB activity which postulated that individuals with low MAO activity levels were more vulnerable to certain psychiatric disorders that included schizophrenia and bipolar disorder. Subsequently, a number of studies found associations between low platelet MAO activity and other disorders such as alcoholism and antisocial personality disorder. In all of these cases, however, more recent studies have found that cigarette smoking, which was typically more prevalent among the patient populations than in the controls, was confounding the results. Several studies have found inverse correlations among MAO activity levels and personality traits such as extroversion, impulsiveness and sensation seeking. While some authors argue that these associations are present even after controlling for smoking (Oreland et al., 1999), others have found no such association once factors such as smoking and gender are considered (Daw EW, personal communication: December 1996). The pros and cons of the 'low MAOB activity–personality traits–smoking relationship' largely exceeds the aims of this review.

MAOA

Compared with studies in smokers measuring platelet MAOB, data concerning MAOA activities in smokers are relatively scant. This relates to the relative inaccessibility of this isoenzyme compared with platelet MAOB, and some concerns whether peripheral measures of monoamines actually reflect those in the brain. Nevertheless, plasma DHPG has been found to be diminished by 20%, and DOPAC by 37%, in heavy smokers smoking at least 20 cigarettes per day as compared to non-smokers (Berlin et al., 1995a). Geracioti et al. (1999) have found a significant 54% decrease in HVA in the CSF of smokers (which can reflect decreases in both MAOA and MAOB activities), but found no difference in plasma HVA concentrations in the same subjects. The comparison of brain MAOA activities using PET in 15 non-smokers and 16 current smokers demonstrated an overall decrease of 28% in smokers (Fowler et al., 1996b). As was the case for MAOB, these authors found that MAOA levels were significantly lower in smokers than in non-smokers in all brain regions studied, ranging from a 38% decrease in the occipital cortex, to a 22% decrease in the basal ganglia. The smoking-related decrements in MAOA activity were less than that observed with tranylcypromine (an irreversible, non-selective MAO inhibitor, 10 mg/d for 3 d) which led to a decrease of 58%. Presently, no data are available as to the time-course of reversibility of MAOA inhibition in smokers. Since selective inhibition of MAOA, but not MAOB, results in mood-enhancing effects, more studies are needed to better clarify the role of reduced MAOA activity in smokers.

Hypothesized role of inhibited MAO activity in smokers

To date, the drug most strongly linked to the dependence-producing properties of cigarette smoking has been nicotine (American Psychiatric Association, 1994). However, there are several lines of evidence that nicotine intake alone does not adequately explain all aspects of the nicotine dependence syndrome. First, the abuse liability of the nicotine patch is less than that of nicotine nasal spray or the nicotine vapour inhaler – all of which have a substantially lower abuse liability than smoking cigarettes (Pickworth et al., 1994; Schuh et al., 1997). While the routes of drug administration and related pharmacokinetic differences might explain some of the variance in the abuse potentials of the various nicotine products, they are unlikely to explain the whole picture. Secondly, there is general agreement that NRT only partially mimic aspects of the tobacco dependence syndrome such as the dependence-producing effects, and cognitive- and mood-altering effects associated with smoking. Thirdly, nicotine administration only incompletely ameliorates withdrawal symptoms and signs such as the urge to smoke and craving for cigarettes after cessation of smoking. In fact, de-nicotinized cigarettes have been found to reduce craving and withdrawal signs, indicating that agents other than nicotine are involved with this syndrome (Pickworth et al., 1999). Thus, it is unlikely that all of the behavioural, mood- and performance-enhancing effects of smoking are simply related to nicotine intake.

Recent studies have found that nicotine primarily exerts its effects via presynaptic nicotinic acetylcholine

receptors (nAchRs). These receptors, situated on axon terminals, modulate rather than transduce fast synaptic transmission (Vizi and Lendvai, 1999). Accumulating evidence suggests that the most important function of presynaptic nAchRs is to increase transmitter (NE, DA, 5-HT) release initiated by axonal firing. However, nAchRs participate in both synaptic and non-synaptic signal transmission, and some essential brain functions are carried out by both synaptic impulse transmission, and by non-synaptic communication that is also subject to presynaptic modulation. Neurons, without making synaptic contact, can communicate with each other by varicosities around the axon terminals. Neurotransmitters released from both synaptic and non-synaptic sites reach target cells by diffusion. In this case, the response of the target cell will depend on the concentration of the diffused neurotransmitter and the sensitivity of its specific receptors. In this way, because of the widespread presence of nAchRs, nicotine can modulate also the function of neurons that do not have specific nAchRs.

The pharmacodynamic effects of nicotine are linked to the release of the various neurotransmitters, each of which appear to be associated with different functions. Thus, increases in DA release have been associated with increased pleasure; NE release has been associated with increased levels of arousal and appetite suppression; increased acetylcholine transmission with cognitive enhancement; 5-HT release with mood modulation and appetite suppression; and vasopressin release with memory enhancement (see the extensive review of Benowitz, 1999).

We hypothesize that the dependence-producing properties of smoking are due not only to the actions of nicotine, but also, to the effects of other, not yet clearly identified substances, possessing MAO-inhibiting properties. In this 2-component model, the main effect of nicotine is on neurotransmitter release, while the MAO-inhibiting components of smoke may lead to the potentiation of nicotine's effects by slowing down the catabolism of the neurotransmitters NE, DA and 5-HT. This would partly explain why nicotine, when given in pharmaceutical forms, leads to less dependence-proneness as compared to the effects of tobacco smoke, where nicotine is present along with MAO-inhibiting compounds.

Further indirect evidence for this 2-component model comes from the clinical efficacy of non-nicotine agents in helping individuals stop smoking. The therapeutic effectiveness of bupropion (a NE and DA re-uptake blocker), and nortriptyline (mainly a NE re-uptake blocker) as smoking cessation aids has been established in randomized, placebo-controlled trials (Hall et al., 1998; Hurt et al., 1997; Jorenby et al., 1999; Prochazka et al., 1998). The effectiveness of MAO inhibitors for smoking cessation has not yet been established; however, some promising preliminary results exist (Berlin et al., 1995b). Thus, inhibition of NE and DA re-uptake, or inhibition of these neurotransmitters' catabolism, either in the absence or presence of nicotine, may mimic some of the effects of smoking. Co-administration of re-uptake inhibitors or MAO inhibitors with nicotine may be a promising therapeutic intervention in smoking cessation. In support of our hypothesis, the best results obtained to date have occurred with the co-administration of bupropion and the nicotine patch, which was found to be more effective than the patch alone (Jorenby et al., 1999).

DA plays a key role in reward mechanisms and has been implicated in the mechanisms of action of almost all drugs of abuse (Altman et al., 1996). Cocaine and amphetamine increase extraneuronal DA (and NE) availability by blocking the DA (and NE) transporter, resulting in increased dopaminergic (and noradrenergic) neurotransmission in ways similar to the effects of nicotine administration. Epidemiological studies have consistently found that cigarette smoking, alcoholism, and other drug use disorders frequently co-exist. Thus, smoking-induced MAO inhibitory effects might lead to boosts in DA (and NE) availability contributing to an individual's vulnerability to developing other substance use disorders.

Because tobacco smoking is associated with reduced MAO activities and this is of the same magnitude as MAOA inhibition of reversible MAOA inhibitors (Berlin et al., 1990) but somewhat less than that of irreversible MAOB inhibitors (Fowler et al., 1996a) psychiatric studies have to screen for and control routinely use of tobacco (Hughes and Howard, 1997).

Several questions remain to be answered:

(1) What is the MAO inhibiting substance(s) in smoking?
(2) Is the effect of smokeless tobacco similar to that of smoked tobacco?
(3) What is the pharmacodynamic effect of the associations of nicotine–MAOA, and nicotine–MAOB inhibitions, respectively?
(4) Is there a genetic polymorphism of MAOA and/or MAOB predisposing individuals to smoking?
(5) Does reduced MAO activities by smoking render vulnerable smokers for other drugs of abuse?
(6) What is the contribution of MAO activities to behaviour, mood and cognitive performance regulation in smokers?
(7) Can determination of platelet MAOB activity be used to measure ex vivo direct and environmental smoke exposure?

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