ELSEVIER

NeuroToxicology 24 (2003) 75–82

NeuroToxicology

Monoamine Oxidase and Cigarette Smoking

Joanna S. Fowler*, Jean Logan, Gene-Jack Wang, Nora D. Volkow

Chemistry Department, Brookhaven National Laboratory, Upton, NY 11973, USA

Received 22 May 2002; accepted 18 July 2002

Abstract

Current cigarette smokers have reduced monoamine oxidase (MAO) and there is evidence that this is a pharmacological effect of tobacco smoke exposure rather than a biological characteristic of smokers. This article summarizes human and animal studies documenting the inhibitory effects of tobacco smoke on MAO and discusses MAO inhibition in the context of smoking epidemiology, MAO inhibitor compounds in tobacco, reinvestigations of low platelet MAO in psychiatric disorders and smoking cessation.

Keywords: Monoamine oxidase; Tobacco; Cigarette smoking; Positron emission tomography; Smoking epidemiology; Smoking cessation

In 1928, Mary Hare isolated a new enzyme which catalyzed the oxidative deamination of tyramine (Hare, 1928). She called it tyramine oxidase and speculated that it ''may be protective and present for the purpose of rapid detoxification of excessive amounts of tyramine absorbed from the intestine.'' Later Blashko et al. showed that this same enzyme also oxidized catecholamines (Blaschko et al., 1937). To reflect this more general reactivity, Zeller proposed the general name monoamine oxidase (MAO) (Zeller, 1938). In the years that followed its discovery, MAO was further characterized along with its role in the regulation of chemical neurotransmitters. In addition MAO has become a molecular target in therapeutic drug development and it genetics have also been studied (Shih et al., 1999).

Monoamine oxidase (MAO; amine: oxygen oxidoreductase (deaminating) (flavin containing); E.C. 1.4.3.4) is an integral protein of outer mitochondrial membranes and occurs in neuronal and non-neuronal cells in the brain and in peripheral organs. It oxidizes amines from both endogenous and exogenous sources thereby influencing the concentration of neurotransmitter amines as well as many xenobiotics (Singer, 1995; Richards et al., 1998). MAO occurs as two subtypes, MAO A and MAO B which have different inhibitor and substrate specificities and which are encoded by separate genes that are closely linked on the X chromosome and share 70% similarity in amino acid sequence (Bach et al., 1988). MAO A preferentially oxidizes norephinephrine and serotonin and is selectively inhibited by clorgyline (Johnston, 1968) while MAO B preferentially breaks down the trace amine phenethylamine and is selectively inhibited by L-deprenyl (Knoll and Magyar, 1972). Both forms oxidize dopamine, tyramine and octopamine (Youdim and Riederer, 1993). Oxidation is accompanied stoichiometrically by the reduction of oxygen to hydrogen peroxide which has been implicated in cellular signaling as well as mitochondrial damage (Vindis et al., 2001; Cohen et al., 1997).

Medical interest in MAO was stimulated in the early 1950s when it was discovered that iproniazide, a drug which was being used to treat tuberculosis, elevated mood in some patients (Selikoff et al., 1952; Crane, 1956). This suggested the possibility of treating depression pharmacologically. Subsequent investigations determined that iproniazide inhibited MAO (Zeller et al., 1955). This revelation, in part, contributed to the hypothesis that monoamine regulation may be related to mood and led to the development and application of MAO inhibitor drugs in the treatment of depression (Schildkraut, 1965). The discovery that

* Corresponding author. Tel.: +1-631-344-4365; fax: +1-631-344-7902.
E-mail address: fowler@bnl.gov (J.S. Fowler).

0161-813X/02/$ – see front matter
PII: S0161-813X(02)00109-2

MAO B occurs in platelets and the accessibility of platelets in living humans peaked interest in the examination of platelet MAO levels as a biological marker for personality and for vulnerability to neurological and psychiatric illnesses. Among the earlier studies was a speculation that low MAO may predict a vulnerability to psychiatric disorders (Buchsbaum et al., 1976). Many other studies linked low platelet MAO to a variety of mental illnesses including depression, schizophrenia and alcoholism. Although the association was not fully appreciated at the time, these are all illnesses in which the rate of smoking is high.

In this article we will review studies linking low MAO A and B levels and smoking, including the pharmacodynamics of brain MAO inhibition by smoke, speculation that MAO inhibition by tobacco smoke may account for some of the epidemiological features of smoking, recent re-investigations of links between low platelet MAO and psychiatric disorders, the isolation of MAO inhibitors from tobacco and the utilization of MAO inhibition as a strategy for smoking cessation. We note that another review on this same topic was published recently (Berlin and Anthenelli, 2001).

MAO LEVELS IN SMOKERS: HUMAN AND ANIMAL STUDIES

Several early human studies reported that cigarette smokers have lower platelet MAO levels than non-smokers (Coursey et al., 1979; Oreland et al., 1981; Norman et al., 1982; von Knorring and Oreland, 1985) though it was not known at the time whether this was due to decreased MAO B synthesis in smokers, the presence of MAO inhibitory compounds in smoke or whether low MAO individuals are more vulnerable to smoking. However, a later study reporting normal MAO levels in former smokers provided evidence that low MAO B may be a pharmacological effect of the smoke rather than a biological characteristic of smokers (Norman et al., 1987). Although the early studies in human cigarette smokers focused MAO B, in the mid-1990s a study comparing plasma catecholamine metabolite levels in smokers and non-smokers provided evidence that tobacco smoke exposure also inhibits MAO A (Berlin et al., 1995a).

Tobacco smoke-induced reduction in MAO is also supported by animal studies. Yu and Boulton (1987) reported that extracts of tobacco smoke inhibit MAO in rat lung and that saliva from human smokers inhibits MAO. A very early study reported that exposure of rodents to cigarette smoke inhibits MAO in mouse skin (Essman, 1977). Later Carr and Basham (1991) reported brain MAO inhibition in the mouse exposed to cigarette smoke. In another study, it was reported that exposure of animals to cigarette smoke but not to burning cigarette paper produced a dose dependent inhibition of MAO (Pavlin and Sket, 1993).

Positron emission tomography (PET) imaging studies in 1996 were the first to document low brain MAO A and B in smokers relative to non-smokers and former smokers (Fowler et al., 1996a,b). MAO A and B activities are measured using carbon-11 labeled clorgyline ([^{11}C]clorgyline) and carbon-11 labeled deuterium substituted L-deprenyl ([^{11}C]L-deprenyl-D2), respectively, as radiotracers and positron emission tomography (PET). These radiotracers label MAO A and B in vivo through the irreversible covalent attachment of the tracer to the enzyme during catalysis (Fowler et al., 1987, 1995). Carbon-11 has a 20.4 min half life and decays by positron emission. The two 511 keV photons arising from positron decay are detected by a PET scanner which records the spatial and temporal concentration of carbon-11 in living tissue. MAO A and B activities are calculated from the kinetics of the movement of the radiotracers in brain and in arterial plasma using a three-compartment model which provides model terms which are related to blood flow (K_1) and MAO activity (λk_3) (Fowler et al., 1995, 1996a).

Human brain MAO A and B inhibition in smokers is partial, with average reductions of 30 and 40% being observed for MAO A and B, respectively (Fig. 1A and B). For perspective, treatment with a therapeutic dose of L-deprenyl (10 mg per day) for 1 week produces a >90% inhibition of human brain MAO B (Fowler et al., 1994) and treatment with a low dose (3 mg per day) of the non-selective irreversible MAO inhibitor parnate (tranylcypromine) for 3 days produces a 58% reduction in MAO A (Fowler et al., 1996a). The degree of MAO B inhibition in smokers relative to non-smokers is quite variable between subjects, ranging between 17 and 67%. The degree of inhibition was not accounted for by the smoking duration or frequency (Fowler et al., 1996b). Large variability was also observed for the more recent replicative study in six subjects where the coefficients of variation (S.D./mean, expressed as percentage) were 33 and 19.8% for smokers and non-smokers, respectively (Fowler et al., 2000). Similar to the first study, there was also no correlation between MAO B levels and amount smoked. Since it is well known that the smoker can manipulate the dose of nicotine (and presumably other substances in smoke) on a puff by puff basis rather than by the number of cigarettes smoked (Benowitz, 1988) we also assessed

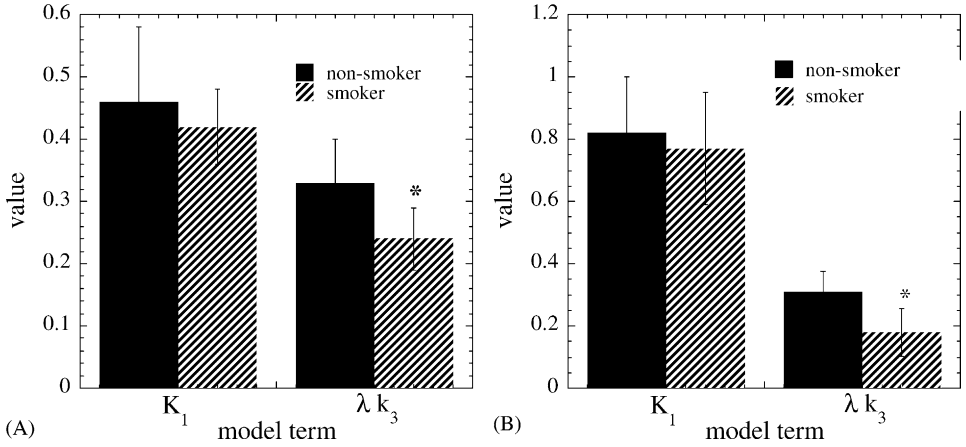

Fig. 1. Bar graphs comparing K_1 (plasma to brain transfer constant which is related to blood flow) and λk_3 (MAO A) (panel A) and MAO B (panel B) in non-smokers and in smokers. Note that there were no significant differences in K_1 while λk_3 (MAO A and B) were significantly reduced in the smoker's brain (Fowler et al., 1996a,b).

whether the degree of MAO inhibition is related to the plasma concentration of cotinine, a metabolite of nicotine which is a reliable and stable measure of exposure to nicotine and presumably other chemical compounds in tobacco smoke. However, we did not find a relationship between plasma cotinine concentration and degree of MAO B inhibition in this small number of subjects.

In contrast to the PET study measuring *brain* MAO B and plasma cotinine levels in smokers, a recent study of the relationship between *platelet* MAO activity and plasma cotinine levels in 85 current smokers (Berlin et al., 2000) reported that platelet MAO levels correlated inversely with plasma cotinine concentration but not with number of cigarettes smoked. Factors which may account for why there is a correlation between plasma cotinine and platelet MAO but no correlation between plasma cotinine and brain MAO B include the small sample size in the PET study ($n = 6$) and the possibility that brain and platelet MAO may not be correlated in some cases. In one PET study (Bench et al., 1991) where both platelet and brain MAO were measured, there was a correlation between platelet MAO and brain MAO B levels. However, there may be circumstances in which the two measures may not be correlated for example in the case of irreversible MAO B inhibition where the rate of synthesis of MAO B in brain would be slower than the rate of platelet turnover (Fowler et al., 1994). In addition, since there was no control for brand of cigarette, it is possible that the concentration of MAO B inhibitory substances (see discussion further) varies with the brand of cigarette. It is also important to consider that the patterns of smoking and the consequences of smoking are highly different in different populations as are biologic differences in how nicotine and other chemical compounds in smoke are distributed and metabolized (Sellers, 1998).

PHARMACODYNAMIC EFFECTS

Limited information on the stability of MAO B levels in the smokers brain has also been determined using PET. For example, the question of whether brain MAO B inhibition can be detected after a single cigarette and also whether MAO B levels increase after an overnight smoke-free interval were investigated in two recent PET studies. Eight normal healthy non-smokers each received two PET studies 2 h apart with [^{11}C]L-deprenyl-D2, one at baseline and the second 5–10 min after the subject had smoked a single cigarette (Fowler et al., 1999). Plasma nicotine and expired carbon monoxide (CO) which were measured prior to smoking and 10 min after smoking completion verified that the smoke was inhaled and provided an index of tobacco smoke exposure. The average MAO B activity for 11 different brain regions did not differ significantly between baseline and smoking (Fig. 2A showing results for 4 brain regions).

MAO B levels were also compared in six smokers who were scanned twice, once at 11.3 h (baseline) after last cigarette and once at 10 min after smoking to determine if MAO B levels increase after an oversight smoke-free interval (Fowler et al., 2000). MAO B levels in this group of smokers were similar to the prior study (Fowler et al., 1996b) and averaged 42% lower than a comparison group. Brain MAO B levels were not significantly different 10 min or 11 h after the cigarette (Fig. 2B). Lack of recovery is consistent with preclinical studies showing that MAO B inhibitory

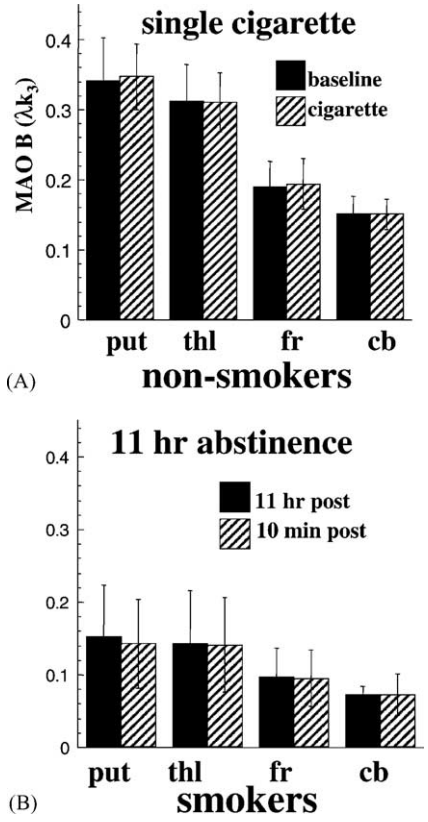

Fig. 2. Bar graphs comparing λk_3 (model term proportional to MAO B) in four brain regions (putamen (put), thalamus (thl), frontal cortex (fr) and cerebellum (cb). In (panel A) MAO B values are compared in a non-smoker at baseline and after smoking a single cigarette and in (panel B) smokers are compared at 11 h and at 10 min after the last cigarette. Note that there are no significant differences in either comparison indicating that MAO inhibition by smoke requires long term exposure and is not rapidly reversible.

substance cannot be removed by dialysis (Yu and Boulton, 1987) and by recent studies of platelet MAO in human smokers showing no recovery of MAO during the first week of abstinence but full recovery by 4 weeks (Rose et al., 2001). Taken together, these studies provide evidence that: (1) reduced MAO B levels in smokers requires chronic exposure to tobacco smoke; (2) MAO B levels are not rapidly reversible and (3) that the PET measure of brain and MAO B activity appears to be relatively invariant for a given individual. Further evidence of MAO B stability is provided by similar MAO B levels for the same smoker measured 4 years apart (Fowler et al., 2000).

MAO INHIBITION AND SMOKING EPIDEMIOLOGY

Low brain MAO B in smokers raises important questions as to whether MAO inhibition by smoke may contribute to some of the behavioral and epidemiological features of smoking including the decreased risk of Parkinson's disease in smokers (Morens et al., 1995), an increased rate of smoking in depression (Glassman et al., 1990) and in addictions to alcohol and other substances (Henningfield et al., 1990) and a general greater prevalence of smoking in psychiatric illnesses (Hughes et al., 1986).

Many epidemiological studies have established an inverse association between smoking and Parkinson's disease (reviewed in Morens et al., 1995) and there have been a number of studies investigating this neuroprotective effect (for example, see Yong and Perry, 1986). An alternative to the neuroprotection hypothesis is that predestined Parkinson's disease patients may be less prone to addiction (Hellenbrand et al., 1997). In 1984, it was reported that 1-methyl-4-phenyl-1,2,3,5-tetrahydropyridine (MPTP), an impurity in a street drug caused an initially puzzling outbreak of Parkinson's disease in a number of young people (Heikkila et al., 1984). It was soon learned that the MAO B inhibition prevented MPTP induced neurotoxicity by inhibiting the conversion of MPTP to 1-methyl-4-phenylpyridinium (MPP+) which is toxic to dopamine neurons (Langston et al., 1983, 1984). This led to the hypothesis that Parkinson's disease may be associated with MAO B catalyzed activation of an environmental toxin and to clinical studies reporting that MAO B inhibitors slow the progression of symptoms in Parkinson's disease (Tetrud and Langston, 1989).

The mechanism(s) underlying the decreased risk of Parkinson's disease in smokers is of particular interest in light of reduced brain MAO in the smoker. Reductions in MAO A and B, in principle, could spare neurotransmitters from oxidation and reduce the production of hydrogen peroxide, a by-product of MAO catalyzed oxidation which may contribute to the defect in mitochondrial respiration associated with Parkinson's disease (Cohen et al., 1997). Though it is not known whether a 40% inhibition of MAO A and B is of physiological significance, a 40% reduction in MAO B is sufficient to inhibit MPTP-induced Parkinson's disease in animals (Jossan et al., 1987). Moreover, the fact that both MAO A and B are inhibited may have effects beyond the inhibition of a single subtype. In addition, MPTP-induced neurotoxicity in animals has been reported to be attenuated by tobacco smoke (Carr and Rowell, 1990; Shahi et al., 1991). There is also evidence that nicotine and other compounds in tobacco are neuroprotective (Ryan et al., 2001; Soto-Otero et al., 1998). A recent investigation of whether a polymorphism in the MAO B gene may modify the risk of

idiopathic PD concluded that MAO B intron 13 polymorphism does not play a major role in the development of PD, either by itself or by interacting with smoking (Hernan et al., 2002).

MAO inhibition may act synergistically with the dopamine-enhancing activity of dopamine agonists by protecting dopamine from metabolism and it also may spare dopamine produced from remaining dopamine cells. Supporting this is a recent report that comparing presynaptic DA activity in non-smokers and in smokers using PET and [^{18}F]fluoroDOPA (Salokangas et al., 2000). Significantly higher [^{18}F]-fluoroDOPA uptake was observed in both putamen and caudate in smokers than in non-smokers. The authors suggest that in smokers, more DA may be directed toward synthesis rather than to metabolism by intracellular MAO.

The possible enhancement of brain dopamine and other neurotransmitters may be a contributing factor to the co-morbidity of smoking with addiction to other substances including alcoholism and to the high rate of smoking in psychiatric disorders such as depression and schizophrenia. Indeed the nicotine-induced release of dopamine and other neurotransmitters such as norepinephrine and serotonin and the simultaneous inhibition of MAO A and B by other chemical compounds in smoke may contribute to the biochemical framework for the "self-medication" hypothesis. Of special importance is the risk of a major episode of depression in depressed individuals who attempt to stop smoking (Glassman et al., 2001; Berlin et al., 1997). It is noteworthy that the MAO inhibitors are used in the treatment of depression though higher levels of MAO inhibition than occur normally in smokers have been reported to be required for anti-depressant efficacy (McDaniel, 1986).

MAO INHIBITORS IN TOBACCO LEAVES AND SMOKE

Nicotine does not inhibit platelet MAO when it is present in the concentrations normally achieved during smoking (Oreland et al., 1981). Nicotine also does not inhibit MAO B in the living baboon brain when administered intravenously at a dose to achieve plasma nicotine concentrations similar to those achieved in the human smoker (Fowler et al., 1998). Recently the fractionation of extracts from flue-cured tobacco leaves led to the isolation of a competitive inhibitor of human MAO A ($K_i = 3$ μM) and MAO B ($K_i = 6$ μM). The chemical structure was determined to be 2,3,6-trimethyl-benzoquinone by classical spectroscopic analysis and was confirmed by synthesis (Khalil et al., 2000). Interestingly, 2,3,6-trimethyl-benzoquinone has been reported to have protective properties against MPTP toxicity in mice (Castagnoli et al., 2001). Following this report, another MAO inhibitor, 2-naphthylamine, which is present in tobacco smoke, was identified (Hauptmann and Shih, 2001). It also inhibits both MAO A and B but is 10-fold less potent than the benzoquinone. Studies of these compounds may provide insight into some aspects of the pharmacological and toxicological properties of tobacco smoke.

REINVESTIGATION OF LOW PLATELET MAO IN PSYCHIATRIC DISORDERS

A number of studies have reported a link between low platelet MAO, personality and vulnerability to psychiatric disorders (Buchsbaum et al., 1976; Oreland et al., 1999). Because of the high rate of smoking in psychiatric disorders, a number of studies have re-investigated the association between low platelet MAO and psychiatric disorders controlling for smoking. For example, the association of low platelet MAO and schizophrenia (a disease where the smoking rate is high) was recently re-examined in a group of non-smoking schizophrenics who were found to have normal platelet MAO (Simpson et al., 1999). Similarly, low platelet MAO which had been reported in alcoholics (Wiberg et al., 1977; Soto-Otero et al., 1988; Devor et al., 1993) was recently reinvestigated. Anthenelli et al., 1998 showed that the broad diagnosis of alcohol dependence was not associated with low platelet MAO. The phenotypes of alcoholics (i.e. type A versus type B or type 1 versus type 2) also did not differ in platelet MAO levels. Interestingly, Farren et al. (1998) studied a group of abstinent alcoholics and controls and found no correlation between MAO activity and smoking status in either the alcoholics or the controls. A recent study addressing whether low platelet MAO activity in criminal offenders is an artefact of cigarette smoking reported that low MAO in this population is related to vulnerability to psychiatric disorders and not to an artefact of cigarette smoking (Garpenstrand et al., 2002).

SMOKING CESSATION

Smoking remains a major public health problem. Yet advances in treating smoking addiction hinge on characterizing both the neuropharmacological effects

of tobacco smoke and factors accounting for individual variability in smoking behavior and toxicity. Along this line recent studies reporting the use of the reversible MAO A inhibitor moclobemide (Berlin et al., 1995a,b, 2001) and the combination of nicotine and L-deprenyl (Brauer et al., 2000) as smoking cessation treatments is an important step based on the knowledge that the effects of tobacco smoke go beyond the effects of nicotine. Along this line a recent smoking cessation study, Rose et al. (2001), reported that the intensity of withdrawal symptoms was inversely related to platelet MAO activity (i.e. smokers with the lowest platelet MAO experienced the most intense withdrawal symptoms). The authors speculate that MAO inhibition from non-nicotine constituents in cigarette smoke is relevant to tobacco dependence and that the investigation of the potential use of MAO inhibitors in smoking cessation treatment is warranted.

SUMMARY

The observation that smokers have reduced brain MAO A and B reinforces the importance of controlling for and reporting the smoking status of subjects in clinical studies. It also brings out the importance of reevaluating earlier reports that low platelet MAO B is a biological marker of vulnerability to psychiatric disorders in clinical populations where the rate of smoking is high. Finally, it reinforces the need to look beyond nicotine as the only pharmacologically relevant substance in tobacco smoke in order to fully understand the behavioral and epidemiological characteristics of the human smoker.

ACKNOWLEDGEMENTS

This work was carried out at Brookhaven National Laboratory under contract DE-AC02-98CH10886 with the US Department of Energy and supported by its Office of Health and Environmental Research and by the National Institutes of Health (National Institute of Neurological Disease and Stroke and National Institute on Drug Abuse).

REFERENCES

Anthenelli RM, Tipp J, Li T-K, Magnes L, Schuckit MA, Rice J, et al. Platelet monoamine oxidase activity in subgroups of alcoholics and controls: results from the Collaborative Study on the Genetics of Alcoholism. Alcohol Clin Exp Res 1998; 22:598–604.

Bach AWJ, Lan NC, Johnson DL. cDNA cloning of human liver monoamine oxidase A and B: molecular basis of differences in enzymatic properties. Proc Natl Acad Sci USA 1988;85: 4934–8.

Bench CJ, Price GW, Lammertsma AA, Cremer JC, Luthra SK, Turton D, et al. Measurement of human cerebral monoamine oxidase type B (MAO B) activity with positron emission tomography (PET): a dose ranging study with the reversible inhibitor Ro 19-6327. Eur J Clin Pharmacol 1991;40:169–73.

Benowitz NL. Pharmacologic aspects of cigarette smoking and nicotine addiction. New Engl J Med 1988;319:1318–29.

Berlin I, Anthenelli RM. Monoamine oxidases and tobacco smoking. Int J Neuropsychopharmacol 2001;4:33–42.

Berlin I, Said S, Spreux-Varoquaux O, Olivares R, Launay JM, Puech AJ. Monoamine oxidase A and B activities in heavy smokers. Biol Psychiatry 1995a;38:756–61.

Berlin I, Said S, Spreux Varoquaux O, Launay JM, Olivares R, Millet V, et al. A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. Clin Pharmacol Ther 1995;58(4): 444–52.

Berlin I, Spreux-Varoquaux O, Said S, Launay JM. Effects of past history of major depression on smoking characteristics. Drug Alcohol Depend 1997;45:31–7.

Berlin I, Spreux-Varoquaux O, Launay JM. Platelet monoamine oxidase B activity is inversely associated with plasma cotinine concentration. Nicotine Tob Res 2000;2:243–6.

Blaschko H, Richter D, Schlossmann H. The inactivation of adrenaline. J Physiol Lond 1937;90:1–17.

Brauer LH, Paxton DA, Rose JE. Selegiline and transdermal nicotine for smoking cessation. In: Proceedings of the Sixth Annual Meeting of the Society for Research on Nicotine and Tobacco, Feb 18–20, Arlington, VA. 2000.

Buchsbaum MS, Coursey RD, Murphy DL. The biochemical high-risk paradigm: behavioral and familial correlates of low platelet monoamine oxidase activity. Science 1976;194: 339–41.

Carr LA, Basham JK. Effects of tobacco smoke constituents on MPTP-induced toxicity and monoamine oxidase activity in the mouse brain. Life Sci 1991;48:1173–7.

Carr LA, Rowell PP. Attenuation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity by tobacco smoke. Neuropharmacology 1990;29:311–4.

Castagnoli KP, Steyn SJ, Petzer JP, Van der Schyf CJ, Castagnoli Jr, N. Neuroprotection in the MPTP Parkinsonian C57BL/6 mouse model by a compound isolated from tobacco. Chem Res Toxicol 2001;14:523–7.

Cohen G, Farooqui R, Kesler N. Parkinson's disease: a new link between monoamine oxidase and mitochondrial electron flow. Proc Natl Acad Sci USA 1997;94:4890–4.

Coursey RD, Buchsbaum MS, Murphy DL. Platelet MAO activity and evoked potentials in the identification of subjects biologically at risk for psychiatric disorders. Br J Psychiatry 1979; 134:372–81.

Crane GE. Psychiatric side effects of iproniazide. Am J Psychiatry 1956;112:494–7.

Devor EJ, Cloninger CR, Hoffman PL, Tabakoff B. Association of monoamine oxidase (MAO) activity with alcoholism and alcoholic subtypes. Am J Hum Genet 1993;48:209–13.

Essman WB. Serotonin and monoamine oxidase in mouse skin: effects of cigarette smoke exposure. J Med 1977;8:95–101.

Farren CK, Clare AW, Tipton KF, Dinan TG. Platelet MAO activity in subtypes of alcoholics and controls in a homogenous population. J Psychiatry Res 1998;32:49–54.

Fowler JS, MacGregor RR, Wolf AP, Arnett CD, Dewey SL, Schlyer D, et al. Mapping human brain monoamine oxidase A and B with ^{11}C-suicide inactivators and positron emission tomography. Science 1987;235:481–5.

Fowler JS, Volkow ND, Logan J, Wang GJ, MacGregor RR, Schlyer D, et al. Slow recovery of human brain MAO B after L-deprenyl withdrawal. Synapse 1994;18:86–93.

Fowler JS, Wang G-J, Logan J, Xie S, Volkow ND, MacGregor RR, et al. Selective reduction of radiotracer trapping by deuterium substitution: comparison of [^{11}C]L-deprenyl and [^{11}C]L-deprenyl-D2 for MAO B mapping. J Nucl Med 1995;36:1255–62.

Fowler JS, Volkow ND, Wang G-J, Pappas N, Logan J, Shea C, et al. Brain MAO A inhibition in cigarette smokers. Proc Natl Acad Sci USA 1996a;93:14065–9.

Fowler JS, Wang G-J, Volkow ND, Pappas N, Logan J, MacGregor RR, et al. Inhibition of monoamine oxidase B in the brains of smokers. Nature 1996b;379:733–6.

Fowler JS, Volkow ND, Logan J, Pappas N, King P, MacGregor R, et al. An acute dose of nicotine does not inhibit MAO B in baboon brain in vivo. Life Sci 1998;63(2):PL19–23.

Fowler JS, Wang G-J, Volkow ND, Franceschi D, Logan J, Pappas N, et al. Smoking a single cigarette does not produce a measurable reduction in brain MAO B in non-smokers. Nicotine Tob Res 1999;1:325–9.

Fowler JS, Wang G-J, Volkow ND, Franceschi D, Logan J, Pappas N, Shea CS, et al. Maintenance of brain monoamine oxidase B inhibition in smokers after an overnight cigarette abstinence. Am J Psychiatry 2000;157:1864–6.

Garpenstrand H, Longato-Stadler E, af Klinteberg B, Grigorenko E, Damberg M, Oreland L, et al. Low platelet monoamine oxidase activity in Swedish imprisoned criminal offenders. Eur Neuropsychopharmacol 2002;12:135–40.

Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, et al. Smoking, smoking cessation, and major depression. J Am Med Assoc 1990;264:1546–9.

Glassman AH, Covey LS, Stetner F, Rivelli S. Smoking cessation and the course of major depression: a follow-up study. Lancet 2001;357:1929–32.

Hare MLC. Tyramine oxidase. I. A new enzyme system in liver. Biochem J 1928;22:968–79.

Hauptmann N, Shih JC. 2-Naphthylamine, a compound found in cigarette smoke, decreases both monoamine oxidase A and B catalytic activity. Life Sci 2001;68:1231–41.

Heikkila RE, Manzino L, Cabbat FS, Duvoisin RC. Protection against the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine by monoamine oxidase inhibitors. Nature 1984;311:467–74.

Hellenbrand W, Seidler A, Robra B-P, Vieregge P, Oertel WH, Joerg J, et al. Smoking and Parkinson's disease: a case–control study in Germany. Int J Epidemiol 1997;26:328–39.

Henningfield JE, Clayton R, Pollen W. Involvement of tobacco in alcoholism and illicit drug use. Br J Addict 1990;85:279–82.

Hernan MA, Checkoway H, O'Brien R, Costa-Mallen P, De Vivo I, Colditz GA, et al. MAO B intron 13 and COMT codon 158 polymorphisms, cigarette smoking, and the risk. Neurology 2002;58:1381–7.

Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA. Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 1986;143:993–7.

Johnston JP. Some observations upon a new inhibitor of monoamine oxidase in brain tissue. Biochem Pharmacol 1968;17:1285–97.

Jossan SS, Sakurai E, Oreland L. Is monoamine oxidase B activity rate limiting for MPTP neurotoxicity? Biogenic Amines 1987;4:371–9.

Khalil AA, Steyn S, Castagnoli N. Isolation and characterization of a monoamine oxidase inhibitor from tobacco leaves. Chem Res Toxicol 2000;13:31–5.

Knoll J, Magyar K. Some puzzling effects of monoamine oxidase inhibitors. Adv Biochem Psychopharmacol 1972;5:393–408.

Langston JW, Ballard JW, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine analog synthesis. Science 1983;219:979–80.

Langston JW, Irwin I, Langston EB, Forno LS. Pargyline prevents MPTP-induced Parkinsonism in primates. Science 1984;225: 1480–3.

McDaniel K. Clinical pharmacology of monoamine oxidase inhibitors. Clin Neuropharmacol 1986;9:207–34.

Morens DM, Grandinetti A, Reed D, White LR, Ross GW. Cigarette smoking and protection from Parkinson's disease: false association or etiological clue? Neurology 1995;45:1041–51.

Norman TR, Chamberlain KD, French MA, Burrows GD. Platelet monoamine oxidase activity and cigarette smoking. J Affect Disord 1982;4:73–7.

Norman TR, Chamberlain KG, French MA. Platelet monoamine oxidase: low activity in cigarette smokers. Psychiatry Res 1987;20:199–205.

Oreland L, Fowler CJ, Schalling D. Low platelet monoamine oxidase activity in cigarette smokers. Life Sci 1981;29:2511–8.

Oreland L, Garpenstrand H, Damberg M, Alm PO, Thorell LH, af Klinteberg B, et al. The correlation between platelet MAO activity and personality—the effect of smoking and possible mechanisms behind the correlation. Neurobiology (Bp) 1999; 7:191–203.

Pavlin R, Sket D. Effect of cigarette smoke on brain monoamine oxidase activity, Farmacevtski Vestnik 1993;44:185–92.

Richards JG, Saura J, Luque JM, Cesura AM, Gottowik J, Malherbe P, et al. Monoamine oxidases: from brain maps to physiology and transgenics to pathophysiology. J Neural Transm Suppl 1998;52:173–87.

Rose JE, Behm FM, Ramsey C, Ritchie Jr, JC. Platelet monoamine oxidase, smoking cessation, and tobacco withdrawal symptoms. Nicotine Tob Res 2001;3:383–90.

Ryan RE, Ross SA, Drago J, Loiacono RE. Dose-related neuroprotective effects of chronic nicotine in 6-hydroxydopamine treated rats, and loss of neuroprotection in alpha4 nicotinic receptor subunit knockout mice. Br J Pharmacol 2001;132: 1650–6.

Salokangas RK, Vilkman H, Ilonen T, Taiminen T, Bergman J, Haaparanta M, Solin O, Alanen A, Syvalahti E, Hietala J. High levels of dopamine activity in the basal ganglia of cigarette smokers. Am J Psychiatry 2000;157:632–4.

Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965;122:509–22.

Selikoff I, Robitzek E, Ornstein G. Treatment of pulmonary tuberculosis with hydrazide derivatives of isonicotinic acid. J Am Med Assoc 1952;150:973–80.

Sellers EM. Pharmacogenetics and ethnoracial differences in smoking. J Am Med Assoc 1998;280:179–80.

Shahi GS, Das NP, Moochhala SM. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity: partial protection against striato-nigral dopamine depletion in C57BL/6J mice by cigarette smoke exposure and by beta-naphthoflavone-pretreatment. Neurosci Lett 1991;127:247–50.

Shih JC, Chen K, Ridd MJ. Monoamine oxidase: from genes to behavior. Ann Rev Neurosci 1999;22:197–217.

Simpson GM, Shih JC, Chen K, Flowers C, Kumazawa T, Spring B. Schizophrenia, monoamine oxidase activity, and cigarette smoking. Neuropsychopharmacology 1999;20:392–4.

Singer T. Monoamine oxidases: old friends hold many surprises. FASEB J 1995;9:605–10.

Soto-Otero R, Mendez-Alvarez E, Riguera-Vega R, Quinoa-Cabana E, Tabakoff B, Hoffman PL, et al. Differences in platelet enzyme activity between alcoholics and nonalcoholics. N Engl J Med 1988;318:134–9.

Soto-Otero R, Mendez-Alvarez E, Riguera-Vega R, Quinoa-Cabana E, Sanchez-Sellero I, Lopez-Rivadulla, Lamas M. Studies on the interaction between 1,2,3,4-tetrahydro-beta-carboline and cigarette smoke: a potential mechanism of neuroprotection for Parkinson's disease. Brain Res 802;1998:155–62.

Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. Science 1989;245:519–22.

Vindis C, Seguelas MH, Lanier S, Parini A, Cambon C. Dopamine induces ERK activation in renal tubule epithelial cells through H_2O_2 produced by monoamine oxidase. Kidney Int 2001;59: 76–86.

von Knorring L, Oreland L. Personality traits and platelet monoamine oxidase in tobacco smokers. Psychol Med 1985;15:327–34.

Wiberg A, Gottfries CG, Oreland L. Low platelet monoamine oxidase activity in human alcoholics. Med Biol 1977;55:181–6.

Yong VW, Perry TL. Monoamine oxidase B. J Neurol Sci 1986; 72:265–72.

Youdim MDH, Riederer P. Dopamine metabolism and neurotransmission in primate brain in relationship to monoamine oxidase A and B inhibition. J Neural Transm 1993;91:181–95.

Yu PH, Boulton AA. Irreversible inhibition of monoamine oxidase by some components of cigarette smoke. Life Sci 1987;41:675–82.

Zeller EA, Barsky J, R E. Amine oxidases. XI. Inhibition of monoamine oxidase by 1-isonicotinyl-2-isopropylhydrazine. J Biol Chem 1955;214:267–74.

Zeller EA. Uber den enzymatischen abbau von histamin und diaminen. Helv Chim Acta 1938;21:880–90.