



Minireview

## Contribution of monoamine oxidase (MAO) inhibition to tobacco and alcohol addiction

Jan van Amsterdam <sup>\*</sup>, Reinskje Talhout, Wim Vleeming, Antoon Opperhuizen

*Laboratory for Toxicology, Pathology and Genetics, National Institute for Public Health and the Environment (RIVM),  
P.O. Box 1, 3720 BA Bilthoven, The Netherlands*

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### Abstract

Whole-body PET-scan studies in brains of tobacco smokers have shown a decrease in monoamine oxidase (MAO) activity, which reverts to control level when they quit smoking. The observed decrease in MAO activity in smokers is presumably due to their exposure to tobacco constituents that possess MAO-inhibiting properties. The inhibition of MAO activity seems, however, not to be a unique feature of tobacco smoking as subjects with Type II alcoholism have been reported to show a similar decrease in MAO activity that reverses when they cease to use alcohol. The present review summarizes the data on MAO-inhibiting tobacco constituents and explains that the decrease in MAO activity observed in alcoholics is probably due to concomitant tobacco use. It is concluded that the inhibition of MAO by constituents contained in tobacco and tobacco smoke, enhances the addiction induced by tobacco smoking.

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### Introduction

It has been well established that the reinforcing qualities of nicotine are mediated by its ability to raise dopamine levels in the mesolimbic system, particularly in the nucleus accumbens. Repeated exposure to drugs of abuse, like nicotine, results in a repetitive stimulation of dopaminergic neurons and subsequent

desensitization of the dopamine receptors. As such, the reinforcing activity of addictive drugs is due to the continuous stimulation of dopaminergic receptors caused by increased release of dopamine (Koob, 1992).

Via oxidative deamination, the enzyme monoamine oxidase (MAO) degrades biogenic amines, like dopamine, noradrenaline, and serotonin. MAO is likely to be involved in the mechanisms of drug addiction, because its inhibition will increase the dopaminergic tone and facilitate the reinforcing effects of addictive drugs. Whole-body PET-scan studies, recently performed by Fowler et

<sup>\*</sup> Corresponding author. Tel.: +31 30 274.2888; fax: +31 30 274.4446.  
E-mail address: [JGC.van.Amsterdam@rivm.nl](mailto:JGC.van.Amsterdam@rivm.nl) (J. van Amsterdam).

al., clearly showed a decreased activity of MAO in the brain (Fowler et al., 1996a,b, 1998) and peripheral tissues (Fowler et al., 2003a,b,c) of tobacco smokers. In brain, MAO-A is found primarily in catecholaminergic neurons, whereas MAO-B is primarily localized in serotonergic neurons and in glial cells. At functional level, MAO-A is more important, because it is the main catabolizing enzyme of the monoamines noradrenaline, serotonin and dopamine. The reason for the lower MAO activity, in particular that of MAO-B, in tobacco smokers is not known. Certain tobacco constituents, but not nicotine, have been proposed as inhibitors of the MAO enzyme. The present paper reviews the MAO-inhibiting compounds that have been found in tobacco, and discusses the role of MAO in addiction to and withdrawal from nicotine and alcohol.

### Inhibition of MAO in tobacco smokers

Essman (1977) was the first who showed that cigarette smoke inhibited MAO activity in mouse skin. Platelet MAO-B activity (only the B form is present in platelets) is a useful surrogate marker for the MAO-B activity in brain considering the biochemical and pharmacological resemblance of both isoenzymes (Donnelly and Murphy, 1977). Various groups have reported lower MAO-B activity in the blood platelets of tobacco smokers as compared to non-smokers (Berlin and Anthenelli, 2001; von Knorring and Orelund, 1985; Norman et al., 1987; Orelund et al., 1981; Berlin et al., 1995b; Saccone et al., 1999; Simpson et al., 1999; Anthenelli et al., 1998). Using whole-body PET scans, Fowler et al. (1996a, 2003c) first showed that smoking reduced the level of MAO-B in the brain and twelve peripheral organs (33 to 46% lower in smokers). Presumably less relevant, they also reported a 28% reduction in MAO-A in nine different brain regions of sixteen smoking subjects tested (Fowler et al., 1996b). The degree of inhibition of MAO in smokers appeared to be quite variable (17–67%), and unrelated to smoking frequency or duration. Others, however, showed a dose-dependency between tobacco exposure and the decrease in MAO-B (Berlin et al., 2000; Norman et al., 1987; Saccone et al., 1999).

The decrease in MAO activity in smokers appeared to be reversible as its activity slowly recovered following smoking cessation (Berlin et al., 1995b; Norman et al., 1987; Rose et al., 2001). Quitting smoking significantly increased platelet MAO-B activity by 22% within 3 days, with a maximal increase of 50% at day 10 of abstinence (Gilbert et al., 2003). Others showed a full recovery of MAO-B in tobacco smokers after 4 weeks of smoking abstinence (Rose et al., 2001). The slow recovery of the enzymatic activity may be explained by the slow elimination of MAO-inhibiting tobacco constituents from the body, or the slow recovery of the MAO activity from inhibition by the tobacco constituent (low  $k_{\text{off}}$ , i.e. low velocity constant of the dissociation of the inhibitor-enzyme complex).

### MAO inhibitors found in tobacco

Certain tobacco constituents, but not nicotine (Orelund et al., 1981), have modest MAO-inhibitory activity. The beta-carboline compound norharman is a prominent candidate as inhibitor of

MAO-B in tobacco smoking. High concentrations of norharman are found in tobacco smoke condensate (12  $\mu\text{g/g}$  tobacco) (Poindexter and Carpenter, 1962; Totsuka et al., 1999). Norharman readily passes the blood brain barrier and accumulates in brain (Fekkes and Bode, 1993), where it effectively inhibits both MAO-A ( $K_i$  of 2.2  $\mu\text{M}$ ) (Herraiz and Chaparro, 2005) and MAO-B ( $K_i$  of 0.73 to 1.1  $\mu\text{M}$ ) (Herraiz and Chaparro, 2005; May et al., 1991). In smokers, increased plasma and urine levels of norharman have been reported (Breyer-Pfaff et al., 1996; Rommelspacher et al., 2002) that were related to the number of cigarettes smoked per day (Spijkerman et al., 2002). Following smoking of a cigarette, norharman serum levels increased from 20 pg/ml to 70–560 pg/ml (Breyer-Pfaff et al., 1996). After one cigarette, the median plasma levels of norharman (0.87 nM; 116 pg/ml) are high enough (Rommelspacher et al., 2002; Spies et al., 1996) to inhibit MAO in vivo by some 50%, though the duration of their effects is relatively short due to the short elimination half-life ( $t_{1/2}$  of approximately 1 h) (Rommelspacher et al., 2002). In contrast to norharman, the beta-carboline harman is no potent inhibitor of MAO-B, but effectively inhibits MAO-A, with reported  $K_i$  values of 55 nM (Herraiz and Chaparro, 2005) and 220 nM (Rommelspacher et al., 2002).

A benzoquinone with weak MAO-inhibiting activity ( $K_i$  of 3–6  $\mu\text{M}$ ) (Khalil et al., 2000) and 2-naphthylamine, with a 10-fold lower potency, have also been isolated from tobacco leaves (Hauptmann and Shih, 2001). Other compounds isolated from cigarette smoke that inhibited MAO-B with low potency ( $K_i$  of 15–40  $\mu\text{M}$ ) were cyano-adducts of 1,2,3,4-tetrahydroisoquinoline (Mendez-Alvarez et al., 1997) and 2,3,6-trimethyl-1,4-naphthoquinone (Castagnoli et al., 2001). Finally, nitric mono-oxide (NO), a major component of cigarette smoke (reaching ppm levels in smoke), possesses MAO-inhibiting activity as indicated by the observation that the NO-donor *S*-nitroso-*N*-acetylpenicillamine (SNAP) could effectively inhibit MAO activity in the range of 0.4 to 40  $\mu\text{M}$  (Muriel and Perez-Rojas, 2003). NO in tobacco smoke is, however, not involved in the inhibition of (brain) MAO activity of tobacco smokers since this radical is rapidly bound in the circulation by hemoglobin and degraded to nitrite.

### Inhibition of MAO in alcohol abusers

With respect to the relation between alcoholism and MAO-B activity, a large and confusing body of literature has developed. According to the Cloninger concept (Cloninger et al., 1981), Type I alcoholism is characterized by a low genetic susceptibility for alcoholism and adult-onset alcohol dependence in men and women, whereas Type II alcoholism appears to be highly heritable, shows an early onset, and is seen only in males. Like tobacco smokers, Type II, and to a lesser extent Type I alcoholics, have been reported to show a lower platelet MAO activity as compared to control subjects (Demir et al., 2002; Snell et al., 2002; Alexopoulos et al., 1983; Major and Murphy, 1978; Rommelspacher et al., 1994; Sullivan et al., 1979, 1990; von Knorring et al., 1985, 1991; Hallman et al., 1996; Lykouras et al., 1987). Others, however, did not observe such an association (Yates et al., 1990; Anthenelli et al., 1998; Farren et al., 1998; Parsian et al., 1995).

Personality traits, gender and race (Robinson and Nies, 1980), psychiatric disorders (Fowler et al., 1982), metabolic factors (Sullivan et al., 1980), medication (Fowler et al., 1982) and drug misuse (Faraj et al., 1994b) may bias the relation between MAO activity and alcoholism, and likely contribute to the mixed results obtained in these studies. Moreover, certain personality characteristics typically linked to Type II alcoholism, like impulsive, seeking and disinhibited behavior have been found to be associated with a decreased activity of MAO-B (for reviews see Orelund, 2004; Shih et al., 1999). This suggests that the low MAO-B activity found in Type II alcoholism may be due to personality traits of alcohol abusers and would explain why normal MAO-B levels are found in Type I alcoholism.

More important is, however, the smoking behavior in these subjects. Due to the high concomitant tobacco use of 70 to 90% by alcoholics (National Institute on Alcohol and Alcoholism (NIAAA), 1998; Gulliver et al., 1995; Anthenelli et al., 1998), it is not easy to discriminate between the effects of Type II (and Type I) alcoholism and those induced by tobacco smoking. Most studies into the relation between MAO activity and alcoholism, however, do not correct for smoking behavior (von Knorring et al., 1985, 1991; Hallman et al., 1996; Lykouras et al., 1987; Sullivan et al., 1979, 1990; Alexopoulos et al., 1983; Faraj et al., 1994a; Major and Murphy, 1978; Rommelspacher et al., 1994) or include a high number (>88%) of smokers (Demir et al., 2002). This makes the observed associations highly doubtful. Indeed, in two large studies the association between reduced platelet MAO versus life-time alcohol use (Whitfield et al., 2000) or alcohol dependence (Anthenelli et al., 1998) disappeared after correction for smoking.

### MAO and withdrawal from alcohol

Studies on the activity of MAO-B in chronic alcohol abusers following alcohol abstinence show mixed results. Sullivan et al. (1978) found in alcoholics that platelet MAO activity remained reduced over a period of 9 to 12 months of withdrawal. In contrast, Giller et al. (1984) reported no difference in platelet MAO activity between alcoholics who were abstinent for several years and non-alcoholics. Others (Takahashi et al., 1976; Brown, 1977) reported that the low platelet MAO activity returned to normal levels after episodes of alcoholism had subsided. As observed in smoking cessation, the activity of MAO in platelets of alcohol-dependent subjects (type of alcoholism was not further specified) increased by 40% after 8 days of alcohol withdrawal, and attained control values that remained stable thereafter (15 to 22 days of abstinence) (Coccini et al., 2002). This temporal pattern remained after correction for smoking and gender. In smoking and non-smoking Type I alcoholic subjects, Berggren et al. (2000) observed a transient increase in MAO-B upon alcohol withdrawal. In smoking Type I alcoholics, Esel et al. (2002) even noted during the first week of alcohol withdrawal a 30% lower platelet MAO activity, that approached control values in the fourth week of withdrawal though all subjects persisted in smoking. This observation, that MAO activity increased even though the subjects continued their smoking habit is strange and in contradiction to the outcome reported in

other studies. To the best of our knowledge, studies on the effect of alcohol withdrawal on MAO-B activity in subjects with Type II alcoholism that control for smoking behavior have not been described.

### Discussion

Both tobacco smokers and subjects with alcoholism were reported to show a decrease in the activity of MAO-B, the subtype of the enzyme localized in serotonergic neurons and in glial cells in brain (and in platelets). It now appears that smoking indeed induces a decrease in the activity of MAO in brain and various peripheral tissues. Furthermore, considering (1) the high prevalence of tobacco use in alcoholics, and (2) the low MAO-B levels in both chronic alcohol users and alcohol-dependent subjects (Whitfield et al., 2000; Anthenelli et al., 1998), it is highly probable that the decrease in MAO activity observed in alcoholics is mainly due to tobacco smoking by these subjects (Anthenelli et al., 1998). It can, however, still not be excluded that other factors (confounders) also play a role here. As most of the alcohol studies did not correct for smoking behavior, the validity of the reported association(s) between alcoholism and decreased activity of MAO is doubtful. This does not rule out the possibility that subjects with a low MAO-B activity are more prone to addictive behavior (Orelund, 2004; Orelund et al., 2002), a suggestion underpinned by observations that rhesus monkeys with low platelet MAO activity exhibited excessive alcohol consumption (Fahlke et al., 2002).

Tobacco smoking (and not alcohol use) leads to a non-selective decrease in MAO activity (lower activity of both MAO-A and MAO-B) and withdrawal from tobacco gradually results in a normalization of these activities. Knowing that the antidepressant effects of non-selective MAO-inhibitors are generally attributed to inhibition of MAO-A, it is conceivable that an increase in MAO-A activity (but not that of MAO-B) during smoking cessation will provoke or contribute to depressive symptoms. Indeed, it has been well established that (1) depressed mood is a major withdrawal symptom of quitting smoking and (2) antidepressant drugs like bupropion and nortriptyline (Hughes et al., 2002), but also MAO-inhibitors (Berlin et al., 1995a, b, 2002; George et al., 2003; Houtsmuller et al., 2002), are useful for smokers attempting to quit smoking.

The observation that inhibition of MAO dramatically and specifically increased the motivation of rats to self-administer nicotine (Guillem et al., 2005) and maintained the increased locomotor activity which is otherwise abolished following three periods of withdrawal (Villegier et al., 2003) emphasizes that the inhibition of MAO is more than a biomarker of tobacco use. MAO-inhibitory compounds in tobacco therefore contribute to the reinforcing properties of nicotine in tobacco. Upon withdrawal from tobacco, MAO activity slowly recovers, which would imply that the need to self-administer nicotine decreases. Though this initially seems not to be the case, the former smoker progressively loses the need to self-administer during the subsequent weeks of abstinence.

In the general population, tobacco dependence seems to be stronger than alcohol dependence. That MAO inhibition is

involved in nicotine addiction, but not (or less prominently) in alcohol addiction may explain this difference.

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