CHAPTER 20
Monoamine Oxidase: Radiotracer Development and Human Studies* 20
JOANNA S. FOWLER, JEAN LOGAN, NORA D. VOLKOW, GENE-JACK WANG, ROBERT R. MACGREGOR, YU-SHIN DING

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20.1 Introduction

20.1.1 Discovery
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 and coworkers showed that this same enzyme also oxidized catecholamines (Blaschko et al. 1937). To reflect this more general reactivity, Zeller (1938) proposed the general name monoamine oxidase (MAO). In the years that followed its discovery, MAO was further characterized along with its role in the regulation of chemical neurotransmitters and as a target for therapeutic drugs and toxic substances. More recently its genetics have been studied. This chapter will focus on general aspects of MAO, on the development of radiotracers for imaging MAO A and MAO B, and on PET studies of MAO in the human brain.

20.1.2 General Features of MAO

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 peripheral organs. It oxidizes amines from both endogenous and exogenous sources, thereby influencing the concentration of neurotransmitter amines as well as many xenobiotics (eq. 20.1; Singer 1995; Richards et al. 1998). It occurs as two subtypes, MAO A and MAO B which have different inhibitor and substrate specificities (Fig. 20.1). MAO A preferentially oxidizes norepinephrine and serotonin and is selectively inhibited by clorgyline (Johnston 1968) while MAO B preferentially breaks down the trace amine phenylethylamine and is selectively inhibited by L-deprenyl, also called selegiline (Knoll and Magyar 1972). Both forms oxidize dopamine, tyramine,
MAO A Substrates

\[
\text{RCH}_2\text{NH}_2 + \text{O}_2 + \text{H}_2\text{O} \xrightarrow{\text{MAO}} \text{RCHO} + \text{NH}_3 + \text{H}_2\text{O}_2
\]  

(20.1)

MAO B Substrates

MAO A and B Substrates

and octopamine (Youdim and Riederer 1993). Oxidation is accompanied stoichiometrically by the reduction of oxygen to hydrogen peroxide. The relative ratios of MAO A and B are organ and species specific (see Saura et al. 1992, 1994, 1996). For example in the human brain, MAO B predominates whereas in the rat brain, MAO A is the predominant subtype. The two subtypes are also compartmentalized in different cell types in the brain with MAO B occurring predominately in glial cells and in serotonergic neurons while MAO A occurs in catecholaminergic neurons as well as in glia cells. It has been speculated that the compartmentalization of a specific MAO subtype within the neurons prevents the non-specific neuronal accumulation of neurotransmitters.

20.1.3 Genetics

MAO A and B 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). The loss of both MAO A and MAO B genes has been implicated in the severe mental retardation of some patients with Norrie’s disease (Collins et al. 1992). Recently a family has been described in which a point mutation in the gene encoding MAO A abolished MAO A activity and is associated with a recognizable behavioral phenotype, which includes disturbed regulation of impulsive aggression (Brunner et al. 1993). With the development of molecular genetic techniques for the production of knockout animals, mice missing MAO A or MAO B have been produced and studied. MAO A knockout mice have high circulating levels of serotonin and male animals exhibit a distinct behavioral syndrome characterized by enhanced aggression (Cases et al. 1995). MAO B knockout animals have high levels of phenylethylamine, a specific substrate for MAO B, and they are resistant to 1-methyl-4-phenyl-1,2,3,5-tetrahydropyridine (MPTP) neurotoxicity (Grimsby et al. 1997). Studies in MAO B knockout mice also suggest that MAO B may regulate normal blood flow distribution (Scremin et al. 1999). Both MAO A and B knockouts show enhanced reactivity to stress. Transgenic mice overexpressing human MAO B protein have also been described. They express a 4- to 6-fold higher brain MAO B and a higher rate of dopamine metabolism, whereas liver MAO B is equal to that of control littermates (Richards et al. 1998). Transgenic animals have been valuable models for investigating the role of monoamines in psychoses and neurodegeneration and stress-related disorders (Shih et al. 1999).

20.1.4 Medical Importance

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 observation suggested the possibility of treating depression pharmacologically. It was soon learned that iproniazide inhibited MAO (Zeller et al. 1955). This revelation, in part, contributed to the hypothesis that monoamine regulation may be related