## REVIEW PAPERS

# Biochemistry and Pharmacology of Reversible Inhibitors of MAO-A Agents: Focus on Moclobemide

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**Moclobemide, p-chloro-N-[morpholinoethyl]benzamide, is a prototype of RIMA (reversible inhibitor of MAO-A) agents. The compound possesses antidepressant efficacy that is comparable to that of tricyclic and polycyclic antidepressants. In humans, moclobemide is rapidly absorbed after a single oral administration and maximum concentration in plasma is reached within an hour. It is moderately to markedly bound to plasma proteins. MAO-A inhibition rises to 80% within two hours; the duration of MAO inhibition is usually between eight and ten hours. The activity of MAO is completely reestablished within 24 hours of the last dose, so that a quick switch to another antidepressant can be safely undertaken if clinical circumstances demand. RIMAs are potent inhibitors of MAO-A in the brain; they increase the free cytosolic concentrations of norepinephrine, serotonin and dopamine in neuronal cells and in synaptic vesicles. Extracellular concentrations of these monoamines also increase. In the case of moclobemide, increase in the level of serotonin is the most pronounced. Moclobemide administration also leads to increased monoamine receptor stimulation, reversal of reserpine induced behavioral effects, selective depression of REM sleep, down regulation of β-adrenoceptors and increases in plasma prolactin and growth hormone levels. It reduces scopolamine-induced performance decrement and alcohol induced performance deficit which suggest a neuroprotective role. Tyramine potentiation with moclobemide and most other RIMA agents is negligeable.**

*Key Words*: monoamine oxidase, reversible inhibitors, moclobemide

## INTRODUCTION

The therapeutic efficacy of currently available antidepressants is well established despite gaps in our understanding of the neurochemical pathology and pathogenesis of mood disorders. Central monoaminergic neurotransmitters, particularly 5-hydroxytryptamine (5-HT) (Heninger et al 1984) and norepinephrine (Schildkraut 1965), are consistently implicated in the pathophysiology of affective disorders. It is believed that a deficit in biogenic amine transmission results in depressive illness (Leonard 1989). The monoamine deficiency hypothesis is based mostly on extrapolations from profound depression observed after treatment with reserpine (Pletscher 1991). The mood-altering action of reserpine was attributed to the depletion of brain vesicular stores of monoaminergic neurotransmitters. The acute pharmacological action of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) also supports the monoamine deficiency hypothesis (Schildkraut 1965; Langer and

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Schoemaker 1988). *In vitro* studies showed that TCAs are potent blockers of nerve terminal 5-HT and norepinephrine reuptake (Richelson 1984; Richelson and Pfenning 1984). The compounds thereby retard inactivation and prolong the synaptic life of monoamines; the availability of neurotransmitters at the post-synaptic site is therefore increased. MAOIs, in contrast, decrease the pre-synaptic intracellular metabolism of neurotransmitters and therefore can increase the availability of amines to be released into the extracellular space. The overall effect is an enhancement of functional neurotransmission involving the parent amines. With a few exceptions, the development of new generation antidepressants has largely been the result of minor modifications in the molecular structures of the established antidepressants (Richelson 1984).

The acute pharmacological effect of antidepressant medications is consistent with the amine hypothesis of the etiology and pathogenesis of depression. There is also accumulating evidence that alterations of neurotransmitter function, especially that of 5-HT, are related to the pathogenesis of depression and the therapeutic response to antidepressant medications (van Praag et al 1987). However, the clinical effects of these drugs, specifically their time-course of action, for example, the time-lag, are not consistent with their proposed mechanisms of action (Oswald et al 1972). Pre-clinical and clinical studies have demonstrated several changes caused by the long-term administration of antidepressants (Charney et al 1981; Blier et al 1990). Thus, in addition to their known roles as re-uptake inhibitors of biogenic amines, TCAs can directly interact and alter the binding of these amines at diverse receptor sites. Electro- physiological, behavioral and binding studies have shown that long-term administration enhances $\alpha_1$ adrenoceptor sensitivity and reduces pre-synaptic $\alpha_2$-adrenergic, ß-adrenergic and 5-$HT_2$ receptor sensitivity (Sugrue 1983; Menkes et al 1983; Mason and Angel 1983). The implication of these alterations in receptor sensitivity in relation to the etiology of depression and the response to treatment needs to be clarified further. However, taking into consideration the time-lag between the initiation of treatment and the onset of therapeutic actions, the chronic effects of antidepressants on post-synaptic receptors appears to be more relevant to the mechanism of antidepressant action.

This review will focus on the biochemistry and pharmacology of a new class of monoamine oxidase inhibitors, the reversible inhibitors of MAO-A (RIMAs). Compared with the TCAs, these compounds have more specific pharmacological properties, in that they act primarily on specific intraneuronal isoenzymes located in the pre-synaptic regions.

Monoamine oxidase (MAO) is the enzyme which metabolizes different types of biogenic amines, including 5-HT, norepinephrine and dopamine by oxidative deamination (Fig. 1). It is found in two catalytically distinguishable forms, MAO-A and MAO-B, which are encoded by two different genes (Bach et al 1988). The isoenzymes A and B have distinct differences in their primary structure as well as in their main human organ sources, subcellular localization, tissue distribution and substrate preference (Fowler and Tipton 1984; Denney and Denney 1985). Both isoenzymes have the redox co-enzyme flavin adenine dinucleotide cova-

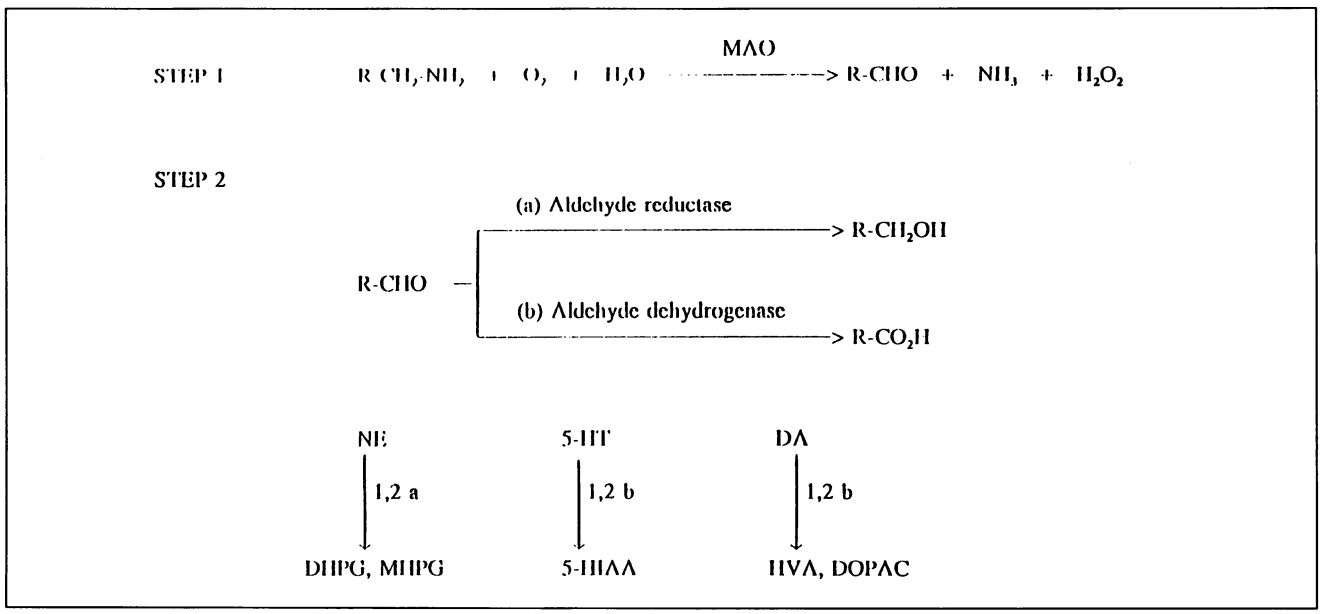


**Fig. 1. Catabolism of monoamines. NE = noradrenaline; 5-HT = serotonin; DA = dopamine; DHPG, 3,4-dihydroxyphenylglycol; MHPG, 3-methoxy-4-hydroxyphenylglycol; 5-HIAA = 5-hydroxyindoleacetic acid; HVA = homovanillic acid; DOPAC = 3,4-dihydroxyphenylacetic acid. The formation of HVA and MxHPG involves an additional enzyme, catechol *O* methyl transferase (COMT).**

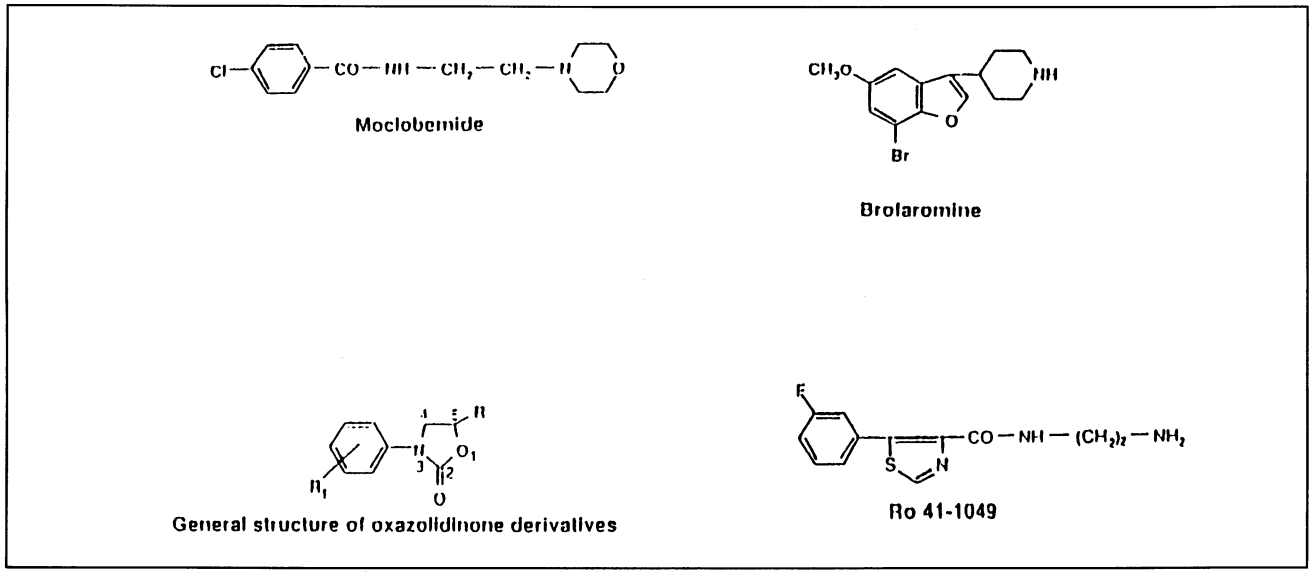


**Fig. 2. Chemical structures of RIMA agents.**

lently bound by a thioether bond to a cysteine moiety. The enzymes are usually present on the outer mitochondrial membrane of both neuronal and non-neuronal cells (Greenwalt 1972). Most human tissues contain both types of MAO. In the periphery, MAO-A is found mostly in the sympathetic terminals, intestinal mucosa and placenta, whereas MAO-B predominates in the liver, lungs and blood platelets (Da Prada et al 1988; Youdim et al 1980). In the human brain, mRNA for MAO-A occurs in the cell bodies of noradrenergic neurones in the locus ceruleus, and mRNA for MAO-B is present in serotonergic cell bodies in the raphe nuclei (Richards et al 1992). MAO-A is responsible for the oxidative deamination of 5-HT, norepinephrine and epinephrine, respectively, in decreasing order of substrate preference for the enzyme, whereas MAO-B preferentially deaminates benzylamine and the trace amine 2-phenylethylamine (Knoll and Magyar 1972). Dopamine and tyramine are common substrates for both types of MAO (Strolin Benedetti and Dostert 1987). It is therefore apparent that MAO-A is the enzyme primarily responsible for the alteration of monoaminergic functions hypothetically related to the etiopathogenesis of mood disorders and should thus be the target isoenzyme in determining therapeutic strategies (Lipper et al 1979).

Although MAO inhibitors were the first chemical compounds to be recognized as true antidepressants after a fortuitous discovery of their efficacy (Crane 1957), they experienced a rapid fall from favor. Such a situation developed mostly because of the recognition of a so-called "cheese reaction," which necessitates a dietary restriction (Blackwell and Marley 1966). These adverse findings were compounded by unfavorable reports of its efficacy (Raskin et al 1974). In light of the development of newer compounds with a higher selectivity and a greatly improved safety profile (Strolin Benedetti and Dostert 1987), the status of MAOIs in the treatment of depression deserves re-evaluation. Compounds which selectively inhibit MAO-A and MAO-B have been developed (Delini-Stula et al 1988). Specific MAO-B inhibitors, such as deprenyl, are being used with some success to treat degenerative diseases, such as Parkinson's disease (Parkinson Study Group 1989a; 1989b; Teravainen 1990), but have a very limited use for treating depression (Mann et al 1989). However, selective inhibitors of MAO-A are found to have antidepressant efficacy with less risk of fatal side-effects, such as hypertensive crisis. Moclobemide, brofaromine, toloxatone, cimoxatone and Ro 41-1049 are among those compounds which selectively and reversibly inhibit MAO-A (Da Prada et al 1990). Together, they form a new class of antidepressants, the reversible inhibitors of MAO-A. Clorgyline also selectively inhibits MAO-A, but only irreversibly.

## Biochemistry

Chemically, the reversible MAO-A inhibitors are derivatives of morpholine (for example, moclobemide), benzofuranyl piperidine (for example, brofaromine), 2-aminoethyl carboxamide (for example, Ro 41-1049) and oxazolidinone (for example, toloxatone, cimoxatone). There are some other compounds of diverse chemical structures which also have an MAO-A inhibiting effect, which are currently undergoing pre-clinical investigations. The chemical structure of moclobemide is p-chloro-*N*-[2-morpholinoethyl]benzamide (Fig. 2). It is a prototype of reversible inhibitors of MAO-A and is the only such compound currently available for clinical use. This paper will refer mainly to moclobemide as a representative of the RIMA agents, and

mention of other compounds of the same class will be made when necessary.

*Selectivity and reversibility*

Based on *in vitro* studies with rat brain homogenates, moclobemide appears to be a weak but specific inhibitor of MAO-A. The concentration of moclobemide producing 50% inhibition of MAO-A *in vitro* ($IC_{50}$) was 6 mmol/L, whereas the *in vitro* $IC_{50}$ of the drug for MAO-B was more than 1,000 mmol/L (Kettler et al 1990). In comparison, *in vitro* $IC_{50}$ value for brofaromine inhibition of MAO-A activity was only 0.013 mmol/L, and for cimoxatone, 0.003 mmol/L. On the other hand, in *ex vivo* experiments, where brain MAO activities were measured two hours after oral administration of moclobemide to rats, the compound was also found to preferentially inhibit MAO-A activity, but was now as potent as brofaromine and clorgyline and twice as potent as cimoxatone (Kettler et al 1990). These experiments also showed that moclobemide was approximately ten times more potent than phenelzine and nearly equipotent to tranylcypromine and isocarboxazide in its enzyme-inhibiting action (Burkard et al 1989a; Da Prada et al 1989b). The last three compounds are irreversible inhibitors.

In *ex vivo* animal experiments, moclobemide was found to produce an inhibition of up to 80% in the brain and liver 30 minutes after drug treatment, and enzyme activity recovered more than 100% after 16 hours (Da Prada et al 1989b). Extrapolating from these results, Amrein et al (1989) suggested that, in clinical practice, the carry-over effect caused by moclobemide inhibition would be only short-lasting, in contrast to the irreversible inhibitor tranylcypromine (see below). For brofaromine, the time-course of reversibility was between 24 and 48 hours, whereas for cimoxatone, it was approximately 24 hours (Kan and Strolin Benedetti 1980). In contrast, for the irreversible inhibitor tranylcypromine, there was only a partial recovery of the MAO-A activity (approximately 50%), which took approximately 48 hours. Complete recovery of MAO-A activity took much longer, causing a long-lasting carry-over effect (Amrein et al 1989). In addition, the time-lag for peak inhibition of MAO-A activity in the brains of rats was much longer — four to eight hours (Burkard et al 1989a; Da Prada et al 1989b).

*Pharmacokinetics*

A full biochemical effect is present after the first dose of moclobemide, and there is a distinct relationship between the plasma concentration of the drug and its pharmacological effect (Amrein et al 1989). The differential results obtained from *in vitro* and *ex vivo* experiments suggest that the full expression of MAO inhibition requires a prior biotransformation of the moclobemide molecule (Burton et al 1984). An additional finding in animal experiments is its lack of selectivity of enzyme inhibition in the periphery, a phenomenon probably attributable to the production of metabolites possessing MAO-B inhibitory activity (Da Prada et al 1990). The central effect of moclobemide is not altered by long-term administration, thereby excluding the possibility of any significant cumulative effect (Da Prada et al 1981).

Brofaromine and most of the other compounds of the RIMA class behave in a similar fashion (Hengen et al 1984).

*Mechanism of inhibitions*

*In vitro* investigations of the kinetics of inhibition of MAO-A by reversible inhibitors in general have shown that the characteristic mechanism of inhibition, especially that exhibited by moclobemide, is time-dependant. Initially, the inhibition is competitive in nature, changing gradually to a mixed competitive/non-competitive mode to finally become non-competitive (Callingham 1989; Da Prada et al 1989b; Waldmeier 1985). This type of kinetic behavior is characteristically exhibited by mechanism-based enzyme activated inhibitors and is also shown by irreversible inhibitors. However, in the case of reversible inhibitors, such as moclobemide, the adduct formed between the enzyme and inhibitor is unstable. The nature of the binding is likely to be non-covalent, possibly involving different active sites on the enzyme, when compared with the irreversible inhibitors (Cesura et al 1992). The reversible inhibitors therefore have a shorter duration of action.

Differences in the action of various reversible inhibitors have been observed experimentally. Thus, in *in vitro* studies, pre-incubation of enzyme-inhibitor complex under physiological conditions was found to abolish the enzyme inhibition in the case of moclobemide but not brofaromine (Burton et al 1984). There are two possible explanations for this. As described above, moclobemide acts as a mechanism-based and enzyme-activated inhibitor to initially form an unstable adduct. After dissociating from the activated complex, the moclobemide may be further metabolized to an inactive inhibitor (Da Prada et al 1989b). Alternately, it has been suggested (Cesura et al 1992) that moclobemide may act as a slow-binding inhibitor (Williams and Morrison 1979). Thus, after rapid initial binding between the inhibitor and enzyme, conformational changes to either moclobemide or the enzyme gradually form a more tightly bound complex. This would account for the non-competitive inhibition observed experimentally.

The binding sites for moclobemide on the enzyme have yet to be determined, although the cysteine residue as well as some hydrophobic regions of the peptide moiety at the active site of the enzyme are probable candidates. In contrast, for irreversible MAO inhibitors, highly stable covalent adducts are formed between the enzyme-activated inhibitors and the reactive nucleophillic centres C(4a) and N(5) of the flavin cofactor molecule (Fig. 3) (Singer and Salach 1981).

With the exception of *N*-oxide derivatives, all the metabolites of moclobemide identified in humans or animals are less potent as inhibitors of MAO-A. There is little doubt that inhibition is caused solely by moclobemide itself and its *N*-oxide derivatives. As mentioned earlier, one of the metab-

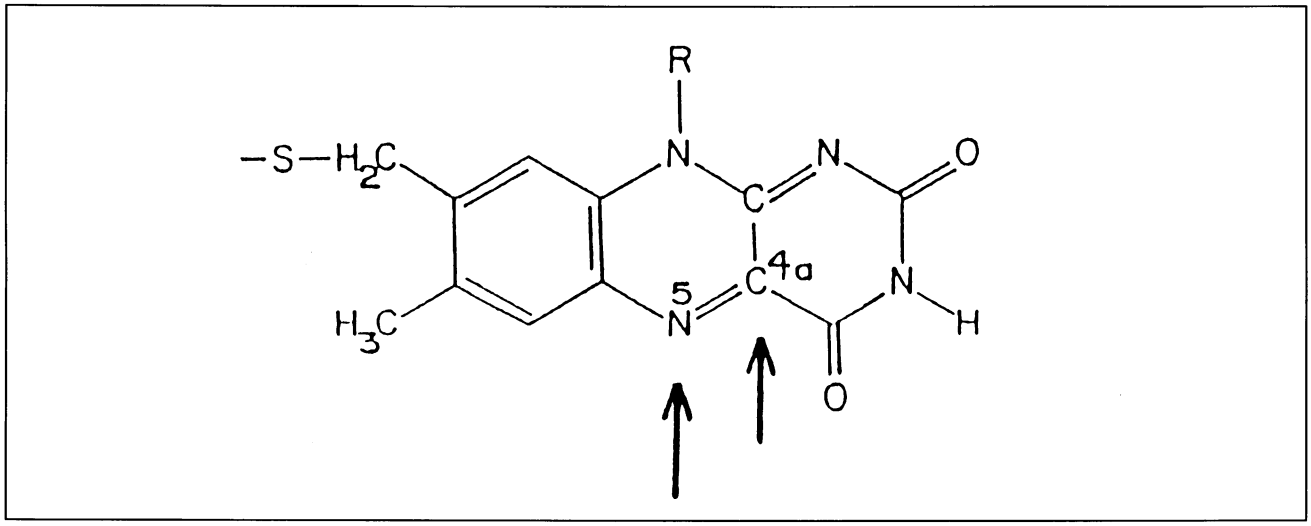


**Fig. 3. Structure of the flavin moiety. Arrows indicate the reactive sites N(5) and C(4a) for covalent bond formation.**

olites (Ro 16-6491) exhibits MAO-B inhibition in rats. However, this biotransformation is not significant in humans (Schoerlin and Da Prada 1990), which would account for the rather specific MAO-A inhibiting property of the drug.

### Effect on central neurotransmitters

MAOIs increase the free cytosolic monoamine concentration in neuronal cells and also in synaptic vesicles, but it has not been demonstrated unequivocally how these drugs affect extracellular monoamine concentrations (Da Prada et al 1989a; 1989b). Indirect evidence, however, indicates that moclobemide and other RIMA agents do increase the extracellular concentrations of monoamines (Burkard et al 1989b). A single oral dose of moclobemide causes a moderate increase in 5-HT, norepinephrine and dopamine in the central nervous system of rats. The levels of normetanephrine and 3-methoxytyramine (3-MT) also increase. However, there is a dose-related reduction in the deaminated metabolites, such as 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid and 3-methoxy-4-hydroxyphenylglycol (MHPG) (Da Prada et al 1989b; Kumagae et al 1991). Compared with the other amines, the increase in serotonin level is the most pronounced and is temporally related to the time course of *ex vivo* MAO-A inhibition (Da Prada et al 1989b). This may be because oxidative deamination is the main catabolic pathway for 5-HT, whereas the catecholamines may be alternatively metabolized by the enzyme catechol *O*-methyl transferase (COMT) in the *O*-methylating pathway to form such compounds as normetanephrine, 3-MT, homovanillic acid and MHPG (see Fig. 1). There is evidence from both *in vitro* and *ex vivo* animal experiments that moderate doses of moclobemide do not significantly inhibit the reuptake of norepinephrine, dopamine or 5-HT (Da Prada et al 1989b). Similarly, the release of norepinephrine and dopamine is not adversely affected by moclobemide. In contrast, brofaromine was found to inhibit 5-HT uptake into rat brain synaptosomes both *in vitro* and *ex vivo*, but only at doses 30 times higher than those needed to inhibit MAO-A. It has also been shown that this inhibition in 5-HT uptake was the result of direct interference with the 5-HT carrier system, and not the result of a rise in synaptic 5-HT concentrations (Waldmeier and Stocklin 1989). Finally, moclobemide does not appear to affect the enzymes involved in monoamine biosynthesis (Keller et al 1978). However, it has yet to be confirmed whether the increase in extracellular monoamine level by selective MAO-A inhibitors is the result of increased quantal release, reduced reuptake or to neuronal activity independent of spill-over of cytosolic amines.

### Effect on receptors

The long-term administration of high doses of moclobemide results in the down-regulation of ß-adrenoceptors and an insignificant increase in the agonist binding affinity of $\alpha_1$-adrenoceptors (Klimek et al 1990). The latter effect is also exhibited during the long-term administration of other antidepressants (Charney et al 1981). However, the long-term administration of moclobemide did not result in any change in the antagonist binding affinity or in density (Bmax) of dopamine (D1 and D2) or $\alpha_1$-adrenergic receptors in the striatum and limbic forebrain of rats (Klimek et al 1990). Subchronic treatment with brofaromine for five days also caused the down-regulation of ß-adrenoceptors in the cerebral cortex of rats (Da Prada et al 1989b).

### Pharmacodynamics

Available data on the pharmacodynamics of RIMA compounds are mostly concerning moclobemide. Only a few published reports are available on brofaromine and other compounds.

### Behavioral effects

Moclobemide, administered alone, does not significantly affect the spontaneous behavior of animals. At very high doses, however, it has behavioral effects predictive of antidepressant activity. These include prevention of Ro 4-1284-induced akinesia and blepharospasm in mice and rats, suppression of REM sleep in cats with no alteration in the sleep-wakefulness cycle, decrease in the immobility score in the behavioral despair test in mice and potentiation of 5-hydroxytryptophan-induced stereotypies in rats (Burkard et al 1989b).

### Neuroendocrine effects

Basal plasma catecholamine levels in normal healthy volunteers remain unaltered after moclobemide. Short-term or long-term administration of moderate doses of moclobemide does not cause any significant change in plasma catecholamine levels in subjects on a tyramine-free or low-tyramine diet, but there may be a rise in conjugated plasma catecholamine level indicating moclobemide-induced inhibition of peripheral MAO (Da Prada et al 1981; Gasic et al 1983; Koulu et al 1989). However, single or multiple oral administrations of 100 mg to 300 mg of moclobemide was found to decrease deaminated metabolites of amines such as 3,4-dihydroxyphenylacetic acid, 3,4-dihydroxyphenylethylglycol and 5-HIAA (Dingemanse et al 1992). The urinary excretion of homovanillic acid and vanillylmandelic acid also decreased (Koulu et al 1989; Berlin et al 1990).

The short-term administration of 100 mg to 300 mg of moclobemide was found to increase plasma prolactin in normal individuals (Koulu et al 1989). This hyperprolactinemia is dose-related and transient and appears to be mediated by central serotonergic pathways (Scheinin et al 1990). The findings about changes in cortisol and growth hormone level however, are less consistent (Koulu et al 1989; Dingemanse et al 1992).

The administration of multiple doses of moclobemide to depressed male patients caused a significant rise in plasma testosterone. This stimulatory effect is unlikely to be mediated by the hypothalamo-hypophyseal axis, since there was no concomitant change in the luteinizing or follicle stimulating hormone level (Markianos et al 1991).

In patients with a depressive illness, especially in those with melancholia, the daytime melatonin level is lower than normal (Nair and Hariharasubramanian 1984; Brown et al 1985). In animal experiments, selective inhibition of MAO-A by clorgyline was found to increase melatonin synthesis in the pineal gland (Oxenkrug et al 1985), but no such effect was observed among healthy volunteers after a single dose of 100 mg to 300 mg of moclobemide (Scheinin et al 1990). The finding is inconsistent with those found in investigations of tranylcypromine and brofaromine. Day-time plasma melatonin levels in humans were higher than normal after single doses of brofaromine (Bieck et al 1988) and tranylcypromine (Oxenkrug et al 1986).

### Tyramine pressor effect

One of the reasons for the reluctance of physicians to prescribe MAOIs is the so-called "cheese reaction" — an acute cardiovascular effect leading to hypertensive crises resulting from the potentiation of indirect sympathomimetic agents ingested in the form of food or medication (Blackwell and Marley 1966). The tyramine content of food is most commonly implicated as a liability factor (Da Prada et al 1988). After ingestion, only an insignificant amount of tyramine reaches the systemic circulation escaping degradation in the intestinal mucosa and liver (Faraj et al 1981). In humans, dietary tyramine is deaminated mostly in the intestinal mucosa. The rest of the degradation occurs in the liver and lungs. Consequently, to cause a pressor effect by itself, tyramine would have to be taken in a very high oral dose (Grind et al 1986; Schulz and Bieck 1987). Once in the systemic circulation, tyramine is taken up into noradrenergic neurones by an active transport system (Bonisch and Trendelenburg 1988). Intracellularly, tyramine reaches the synaptic vesicles and displaces the stored norepinephrine to the cytosol. Free cytosolic norepinephrine leaves the neuronal terminal to exert its vasopressive effect. Under normal circumstances, the release of norepinephrine by this process is not significant. However, when MAO is inhibited, there is a reduction in the deamination of tyramine, leading to increased cytosolic norepinephrine with a consequent rise in blood pressure.

Of the reversible MAO-A inhibitors, moclobemide is perhaps the compound which has been studied most extensively for its pressor effect. In the intravenous tyramine pressure test, therapeutic doses of moclobemide showed an increase in pressor sensitivity by only two to four times the baseline level (Tiller et al 1987; Korn et al 1988a; 1988b). After a single dose, this increase in tyramine sensitivity reached its peak after three hours, but disappeared completely after 24 hours (Korn et al 1988a; 1988b). Higher doses of moclobemide did not cause a major change (Zimmer et al 1990a). However, when tyramine was ingested as an oral solution by fasting subjects, the potentiation of systolic blood pressure was more pronounced. This may be the result of a combination of a lower first-pass metabolism of the sympathomimetic amine and MAO inhibition within adrenergic nerve terminals (Korn et al 1988a; 1988b). However, the pressor effect is less intense when tyramine is taken with food, preferably in solid form (Korn et al 1988a; 1988b). It is therefore recommended that moclobemide be administered post-prandially, thereby delaying absorption of tyramine present in the food. Moreover, it was found that a tyramine dose of at least 150 mg is required concurrently with 600 mg of moclobemide in healthy volunteers to raise their systolic blood pressure by 30 mm of mercury. Normal daily meals

rarely contain such an amount of tyramine (Da Prada et al 1988). Brofaromine also induces the potentiation of tyramine pressor effect, but this is only marginal, comparable to that observed with moclobemide and much lower than that observed with tranylcypromine (Bieck and Antonin 1989). Cimoxatone, however, induces a tyramine pressor effect almost comparable to that caused by the irreversible inhibitor clorgyline (Finberg and Youdim 1988).

### Effect on sleep pattern

The most common sleep abnormalities found in patients with major depressive disorders are prolonged sleep latency, increased wakefulness, shortened REM sleep latency, redistribution of REM sleep to the first half of the night, diminished slow wave sleep and early morning waking (Gillin et al 1984; Reynolds and Kupfer 1987; Gold et al 1988). Most of the tricyclic antidepressants and MAOIs suppress REM sleep and on discontinuation produce a significant rebound in REM sleep which lasts for days. The effect of moclobemide on sleep pattern in normal individuals was found to be weak (Blois and Gaillard 1990). The number of sleep cycles and latency of REM sleep remain unchanged.

There was a slight increase in stage I and II sleep, but the slow-wave sleep remain unchanged. There was also a moderate reduction of rapid eye movement. Like most of the RIMA agents, moclobemide had no hypnotic effect, and there was no cumulative effect on sleep parameters after repeated use. In depressed patients, moclobemide caused an improvement in sleep continuity with increased stage II non-REM and REM sleep. Increase in REM sleep time was progressive and reached significance during the intermediate and late stage of four weeks' treatment (Monti 1989; Monti et al 1990). Suppression of REM sleep or change in REM sleep latency was not noticed (Hoff et al 1986; Monti et al 1990). Withdrawal of moclobemide caused a further increase in REM sleep. The effect of brofaromine on REM sleep has been found to be of short duration and did not persist after withdrawal of the drug (Steiger et al 1987).

### Effect on cognitive functions

Moclobemide was not found to have any detrimental effect on the cognitive functions of young volunteers (Hindmarch and Kerr 1992). In contrast, elderly volunteers showed some degree of memory improvement after a single oral dose of moclobemide (Wesnes et al 1989a; 1989b). In depressed, demented patients, moclobemide caused an improvement of cognitive impairment (Postma and Vranesic 1983). Clinical evidence showed that this improvement in cognitive functions was independent of the alleviation of symptoms of depression. Moclobemide also reduces scopolamine-induced performance decrement more effectively than the cognitive enhancers and antidepressants, piracetam and its analogues, and also alcohol-induced performance deficit (Anand and Wesnes 1990; Wesnes et al 1989a; 1989b).

Further studies are needed to determine the neuroprotective role of moclobemide in humans. Evidence from animal experiments, however, suggests that inhibitors of MAO-A, including moclobemide, have some neuroprotective role as shown in an animal model of transient global hypoxia or ischemia (Lorez et al 1990). Moclobemide was found to reduce post-hypoxic mortality rate and increase the number of surviving hippocampal pyramidal neurones and [$^3$H] 2-deoxyglucose uptake. However, the compound was found to be effective only if given immediately after or before the insult. Tatton and Greenwood (1991) described a possible neurorescuing role of deprenyl in mice. The MAO-B inhibitor was administered in doses that left the MAO enzyme activity unaffected. Investigations into the possibility of a similar role for selective MAO-A inhibitors would be of interest.

### Effect on psychomotor functions

In normal individuals moderate doses of moclobemide did not have any effect on different psychometric indices (Hindmarch and Kerr 1992). There was no impairment, even after long-term administration. Mild impairment was, however, noticed in elderly volunteers (Wesnes et al 1989a; 1989b). Higher doses (600 mg) of the drug did not result in any impairment in automobile driving performance (Ramaekers et al 1992). Young depressed patients displayed an improvement in vigilance after six weeks of treatment (Allain et al 1992).

### Pharmacokinetics

Of the RIMA class of compounds, moclobemide has been studied the most extensively for its pharmacokinetic properties, in normal volunteers, depressed patients of different ages and in patients with hepatic and renal impairment. The studies were performed following both oral and parenteral administration.

### Absorption and bioavailability

In humans, moclobemide is rapidly and almost completely absorbed after a single oral administration, and the maximum plasma concentration is reached within one hour ($t_{max}$). The mean plasma concentration ($C_{max}$) after short-term administration is approximately 0.3 to 2.7 mg/L. The bioavailability of the compound is approximately 50% after a single administration of 100 mg of moclobemide and increases with prolonged administration of multiple doses to approximately 86% (Schoerlin et al 1987). The presence of food in the stomach slows absorption of the drug but does not interfere with its bioavailability (Schoerlin et al 1988). The steady state plasma level is significantly correlated with dose levels, and there is evidence of some accumulation, although

insignificant, after the administration of multiple doses (Maguire et al 1983; Guntert et al 1990).

### Distribution

Moclobemide is moderately bound to human plasma protein (approximately 50%), particularly albumin. The volume of distribution during the terminal disposition phase is approximately 2L/kg, suggesting an extensive distribution. Toloxatone was found to have a similar binding affinity, whereas both brofaromine and cimoxatone was found to have a marked binding to plasma protein (about 90% to 95%) (Amrein et al 1989).

### Metabolism and excretion

In humans, moclobemide appears to be metabolized extensively by the liver. The metabolic pathway is relatively complex. Elimination proceeds rapidly, and the elimination half-life is approximately two hours. The elimination half-life values of other RIMA agents, with the exception of tolaxotone, are much higher. It is 12 to 15 hours for brofaromine and nine to 16 hours for cimoxatone. For toloxatone, it is similar to that of moclobemide, i.e., less than three hours (Amrein et al 1989). Renal clearance of the parent drug in the case of moclobemide is very low, and after oral administration, only 0.5% of the parent compound is excreted unchanged in the urine (Jauch et al 1990). In the case of brofaromine, about two percent of the parent drug could be recovered from the urine. The main metabolic processes involved for moclobemide are oxidation of the morpholine ring moiety, aromatic hydroxylation and deamination (Jauch et al 1990). The pattern of plasma metabolites is qualitatively similar to that of urinary metabolites. There are a variety of urinary metabolites, but carboxylic acid derivatives are the major components (Fritze et al 1989). The possibility of *in vivo* formation of an intermediary active product by biotransformation has yet to be explored. As mentioned earlier, elimination is almost exclusively by hepatic metabolism, and in healthy volunteers, 92% and 95% of the radioactivity is eliminated in the urine within 12 hours and four days, respectively, of administration of [$^{14}$C] moclobemide orally (Jauch et al 1990). Metabolism of brofaromine involves *O*—demethylation of aromatic methoxy group followed by *O*-glucuronide formation (Schneider et al 1989). Oxazolidinone derivatives are metabolized by oxidation, hydroxylation, sulfation and glucuronoconjugation (Rovei et al 1984). After repeated administration, the mean plasma concentrations of moclobemide were found to be higher, although the concentration profile remains similar to that obtained after a single dose. The observed reduction in systemic clearance after repeated doses has been ascribed to auto-inhibition or metabolite-induced inhibition (Callingham 1989; Kettler et al 1990).

Breast-fed infants whose mothers are receiving therapeutic doses of moclobemide are probably exposed to only a very insignificant amount of the parent drug and its metabolites, since, in healthy postpartum women, only 0.06% of the parent drug was recovered from the breast milk over 24 hours after a single dose of 300 mg of moclobemide (Pons et al 1990).

### Kinetics in the elderly and medically ill

The absorption and disposition of moclobemide in elderly individuals do not differ significantly from those in young healthy volunteers (Stoeckel et al 1990) and depressed patients (Maguire et al 1991). The absorption and elimination kinetics do not show any difference even after long-term administration. Preliminary reports on brofaromine showed similar results (Degen et al 1989).

In a study of patients with cirrhosis of the liver, moclobemide displayed a significant prolongation of plasma terminal elimination half-life (Stoeckel et al 1990), a decreased systemic clearance, increased oral bioavailability and increased $C_{max}$ value. For such patients, the dose of moclobemide should therefore be reduced to between one-third and one-half. For patients with impaired renal functions, there were no differences in kinetics between patients undergoing hemodialysis and those who did not. The only difference observed was the prolongation of the mean absorption in patients with renal dysfunctions.

### Drug interactions

Interaction studies with moclobemide have been performed on both healthy volunteers and depressed patients. Tricyclic agents can be added to or replace moclobemide without any dose reduction or drug-free wash out period and with no sign of impaired tolerance (Korn et al 1984). Moclobemide did not interact with sympathomimetic agents, such as norepinephrine, isoproterenol or phenylephrine (Zimmer et al 1990a). No postural hypotension was noticed when it was added to antihypertensive agents. The combination of moclobemide with phenprocoumon, glybenclamide, oral contraceptives, digoxin or benzodiazepine did not show any clinically relevant interactions (Amrein et al 1992). However, cimetidine increases the plasma concentration of moclobemide by nearly 100% (Zimmer et al 1990b).

## CONCLUSIONS

RIMA agents, by virtue of their reversible specific-enzyme inhibitory action and unique age-independent pharmacokinetic properties, have opened a new vista on the treatment of depressive illness with MAO inhibitors. The resultant effects of their pharmacodynamic actions do not differ significantly from the currently available tricyclic and polycyclic antidepressants. Meta-analysis of clinical data suggests that, in contrast to traditional MAO inhibitors, moclobemide has a dependable safety profile. It is the only currently available antidepressant of the RIMA class avail-

able for clinical use in North America and is marketed under the trade name Manerix®. Relative freedom from drug-food and drug-drug interactions gives this compound a new place in the pharmacotherapy of mood disorders. Finally, possible improvements in cognitive functions are an added advantage of this compound in the treatment of elderly patients.

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