The effects of lifelong treatment with MAO inhibitors on amino acid levels in rat brain

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Summary. In a previous paper a possible relationship had been suggested to exist between age-induced changes in total MAO activity and amino acid levels in some rat brain areas.

To further investigate the possible involvement of MAO activity in changes of brain amino acid levels with aging, moclobemide and Ro 19-6327, short acting MAO-A and MAO-B inhibitors, respectively, were administered to female Wistar rats for their whole life-span. Brain amino acid levels in animals treated with MAO inhibitors were compared to those of young and old non-treated rats. The age-induced changes in brain amino acid concentrations found in the present study were in good agreement with those previously reported. Treatment with both moclobemide and Ro 19-6327 was found to restore taurine and serine concentrations in cortex and glutamine concentrations in cerebellum, to the same values as in young rats, to decrease cerebellum concentrations of serine and to increase taurine concentrations in hypothalamus. Administration of moclobemide brought aspartate concentrations in accumbens and cortex back to the same values as in young rats. A similar effect was observed on hypothalamus glutamate concentrations in rats treated with Ro 19-6327. Some possible causes and consequences of the correction of age-induced brain amino acid levels by chronic administration of MAO inhibitors are discussed.

Keywords: MAO inhibitors, moclobemide, Ro 19-6327, amino acids, aging.

Introduction

In previous papers (Strolin Benedetti et al., 1986, 1990; Strolin Benedetti and Dostert, 1989 a) it had been pointed out that the ammonia and H$_2$O$_2$ produced both in the extracerebral organs and in situ in the central nervous system during oxidative deamination of primary monoamines by monoamine oxidase (MAO) might be toxic for the brain. Various mechanisms underlying the neurotoxic
effects of ammonia have been exhaustively discussed in a recent paper by Lai et al. (1989). As concerns \(\text{H}_2\text{O}_2\), its neurotoxicity might be related to the Fenton and/or the Haber-Weiss reactions, which generate highly reactive hydroxyl radicals (\(\text{OH}^\cdot\)) producing lipid peroxidation and cell death (Kagan et al., 1983; Strolin Benedetti and Dostert, 1989b). In a clinical trial still in progress, the ability of the MAO-B inhibitor 1-deprenyl and of tocopherol to delay the onset of disability necessitating levodopa therapy in patients with early, untreated Parkinson’s disease has been reported (The Parkinson Study Group, 1989). This study was based on the assumption that the formation of oxygen radicals formed from \(\text{H}_2\text{O}_2\) produced by MAO may contribute to the pathogenesis of nigral degeneration, as previously suggested by Laplante and Tran (1973). Therefore, 1-deprenyl and tocopherol may be expected to slow down the clinical progression of the disease.

In a previous study significant modifications in the concentrations of some amino acids, particularly those involved in \(\text{NH}_3\) detoxication and lipid peroxidation, were observed in brain areas to old rats compared to those of young animals (Strolin Benedetti et al., 1990). The purpose of the present study was to investigate whether or not inhibition of MAO-A and MAO-B during the life-span of the rat could maintain, at least partially, the brain concentrations of those amino acids at values similar to those found in young animals. Since reversible and selective inhibitors of MAO, which should be less likely to cause secondary effects than first-generation MAO inhibitors (Strolin Benedetti and Dostert, 1987), have recently been extensively studied, two of them, moclobemide and Ro 19-6327, short acting MAO-A and MAO-B inhibitors, respectively (Keller et al., 1987; Da Prada et al., 1988), where chosen for this study.

**Materials and methods**

Four groups of female Wistar rats (KFM-HAN), each one consisting of eight animals, were used. One control group (group 1) was composed of young rats aged 2 months, a second control group (group 2) of 28-month-old rats, the third and the fourth group of rats aged 28 months having received moclobemide (group 3) or Ro 19-6327 (group 4) in the diet for their whole life-span. Doses were approximately 13 mg/kg/day of moclobemide and 2 mg/kg/day of Ro 19-6327.

The animals were injected with 3-mercaptopropionic acid (4 mmol/kg, i.p.) 2 min before decapitation, brains were removed, the different brain areas dissected and the analysis of amino acids was carried out as previously described (Strolin Benedetti et al., 1990). D,L-homocysteic acid was used as internal standard, in spite of the presence of endogenous S-(+)-homocysteic acid in rat brain (Kilpatrick and Mozley, 1986). However, it is to note that the endogenous concentrations of homocysteic acid are 2–3 orders of magnitude less than the amino acids measured in this work. Inhibition of MAO activity by moclobemide and Ro 19-6327 at the end of treatment was measured in cerebellum and liver, using serotonin (5-HT) and phenylethylamine (PEA) as substrate for MAO-A and -B respectively, as previously described (Da Prada et al., 1989).

**Statistical analysis**

Old control rats and rats treated with moclobemide or with Ro 19-6327 where compared with young control rats using Dunnett’s test.