Association analysis of the functional monoamine oxidase A gene promotor polymorphism in migraine

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Summary. Migraine affects about 15% of the adult population. Serotonergic and dopaminergic systems are believed to be involved in its pathophysiology. One of the key enzymes in the degradation of serotonin and to a lesser extent of dopamine is monoamine oxidase A (MAO-A). In this study we investigated a functionally relevant gene-linked polymorphic repetitive sequence (LPR) located approximately 1.2 kb upstream of the ATG codon in the MAO-A-promotor gene. 119 patients with migraine and 229 controls were tested. The allelic distribution of the controls and the migraine patients did not show significant differences with respect to the low- and high-activity alleles. Moreover, effectiveness of the potent serotonergic antimigraine agents, triptans, which are metabolized by MAO-A, was clinically not affected by the MAO-A-LPR in our patients. These findings thus indicate that there is no association between the functional MAO-A-LPR and susceptibility to migraine.

Keywords: Functional MAO-A promotor polymorphism, migraine.

Introduction

Migraine is a common disorder which affects between 14 to 18% of the general population (Breslau and Rasmussen, 2001). The two most frequent varieties are migraine without aura (MO) and migraine with aura (MA). Population based studies and twin studies indicate a significant familial risk of migraine (Montagna, 2000) and the genetic trait appears to differ between MA and MO (Russell et al., 2002). Migraine is nowadays regarded as a polygenic disease, and serotonergic and as well dopaminergic systems seem to play an important
role in its pathophysiology; for a detailed review on the role of serotonin (5-HT) in migraine see (Johnson et al., 1998). Triptans, highly selective 5-HT1B/D agonists, are the most effective drugs in acute migraine (Silberstein, 2000). An association study of the distribution of allelic polymorphisms of the serotonin transporter (5-HTT) gene on chromosome 17q11.2 revealed a higher frequency of the short and less active form in patients with migraine with aura (Marziniak et al., 2001). Dopaminergic hypersensitivity has been proposed to play an important role in migraine by several authors, for review see (Del Zompo, 2000). Nausea, frequently accompanied by vomiting, often precedes the headache and can be suppressed by dopamine D2 receptor antagonists (Dahlof and Hargreaves, 1998). Flunarizine, a calcium channel blocker, is an effective prophylactic agent in migraine and shows significant dopamine antagonist properties and a moderately high affinity for the DRD2 receptor (Ambrosio and Stefanini, 1991).

An ideal candidate linking both neurotransmitters would be the monoamine oxidase (MAO). The two isoforms MAO-A and MAO-B are mitochondrial enzymes which are involved in the degradation of several different biological amines. MAO-A has a high affinity to endogenous neurotransmitters (e.g. serotonin and norepinephrine), and a lesser affinity to dopamine. A complete MAO-A deficiency due to a nonsense mutation in the coding region of the gene on chromosome Xp11.23–p11.4 (Ozelius et al., 1988) is associated with disturbed amine metabolism, borderline mental retardation and impulsive aggressive behavior in affected males (Brunner et al., 1993). In the treatment of migraine, moclobemide, a MAO-A inhibitor, that is frequently used as an antidepressant, showed a positive effect as a prophylactic agent in an open trial (Meienberg and Amsler, 1996). Furthermore MAO-A is one of the most important enzymes for the elimination of the triptans (Bigal et al., 2003).

Recently, a novel functional repeat polymorphism of the MAO-A gene promoter VNTR (variable number tandem repeat) has been described, which consists of a 30 base pair repeated sequence with 2, 3, 3.5, 4 or 5 copies (Sabol et al., 1998). The longer alleles 3.5, 4, and 5 were functionally more active than the short allele 3 in luciferase assays (Deckert et al., 1999).

Thus, the MAO-A gene-linked polymorphic region (LPR) might be involved in disorders that are associated with abnormalities in monoaminergic neurotransmission, like migraine. The present association study was designed to test the hypothesis that length variation of the regulatory MAO-A-LPR is associated with susceptibility to migraine.

**Patients and methods**

**Subjects**

119 patients (94 women, 25 men) with migraine were diagnosed according to the International Headache Society (IHS) criteria and were recruited from our Headache Clinic after informed consent and approval by the local ethics committee. Patients completed a standardized headache questionnaire and were subject to a full neurological examination. The 119 migraine patients received a second standardized questionnaire by mail and were asked to indicate the medication