Pharmacological Reports
2012, 64, 449–453
ISSN 1734-1140

Short communication

Serotonin 2A receptor gene (*HTR2A*) polymorphism in alcohol-dependent patients

Małgorzata Wrzosek[1], Andrzej Jakubczyk[2], Michał Wrzosek[3], Halina Matsumoto[2], Jacek Łukaszkiewicz[4], Kirk J. Brower[5], Marcin Wojnar[2,5]

[1]Department of Pharmacogenomics, [2]Department of Psychiatry, [3]Department of Internal Medicine and Diabetology, [4]Department of Biochemistry and Clinical Chemistry, Medical University of Warsaw, Żwirki i Wigury 61, PL 02-091 Warszawa, Poland

[5]Department of Psychiatry, University of Michigan, 4250 Plymouth Rd., Ann Arbor, MI 48109, USA

Correspondence: Marcin Wojnar, e-mail: marcin.wojnar@wum.edu.pl

Abstract:
Background: The serotonergic (5-HT) dysfunction has been frequently described in subjects with alcohol dependence (AD). In the present study, a potential relationship between T102C polymorphism in the 5-HT receptor subtype 2A gene (*HTR2A)* and alcohol dependence was examined.
Methods: Genotypes were analyzed in 150 AD patients diagnosed with DSM-IV criteria and in 80 healthy controls.
Results: The genetic analysis showed that the frequency of 102C allele and C102C genotype in AD subjects was significantly higher than in controls. Moreover, AD patients homozygous for C allele had significantly lower age at onset of alcohol problems than subjects having at least one T allele.
Conclusion: The results suggest a potential role of the T102C *HTR2A* polymorphism in development of alcohol dependence.

Key words:
alcohol dependence, genetic polymorphism, *HTR2A*

Introduction

Alcohol dependence constitutes a serious individual and social problem, which is strongly associated with post-treatment relapse. Although the estimated contribution of genetic factors to alcohol dependence ranges from 40 to 60%, the specific genes and their exact roles have not been identified [4]. In this study selection of a gene that modulates the risk to development of alcohol addiction was based on the premise that serotonergic (5-HT) dysfunction causing depressed mood, anxiety or impulsiveness may predispose to alcohol dependence. Serotonergic neurons of the raphe nuclei affect mood, aggression, sleep, appetite and the development of tolerance to alcohol [3, 8]. There is also evidence that the variations in brain 5-HT synthesis and 5-HT receptor binding are associated with altered neurotransmitter function, plasma cortisol levels, and noradrenergic activity [11, 20]. Furthermore, a number of stress-related psychiatric disorders and alcohol-related disorders are often accompanied by alterations in the serotonergic system [7, 12, 13]. This has been recently confirmed in an animal model by Crawford et al. [3], who found that 5-HT neurons play a unique role in adaptive responses to stress.

The 5-HT receptor subtype 2A gene (*HTR2A*) is located on chromosome 13 (13q14–q21) and contains the T102C (rs6313) single nucleotide polymorphism. Studies in human brain tissue reported that the expression of the 102C allele at both mRNA and protein levels in the temporal cortex is lower than the expression of the T102 allele [17]. Higher frequencies of the 102C alleles of the 5-HT_{2A} receptor polymorphism (T102C) were found among schizophrenics [15]. Moreover, depressed patients carrying 102C allele had significant increased risk for suicidal behavior [2, 5]. However, there have also been several negative studies [15].

Association between gene for serotonin 2A receptor (*HTR2A*) and alcoholism has been reported in prior studies [6, 8, 13, 16] with contradictory results. Nakamura et al. [16] first reported a positive association of alcohol dependence with the *HTR2A* gene. This work referred to the A1438G functional polymorphism in the promoter region of the gene, which is in linkage disequilibrium with T102C polymorphism. The T102C (rs6313) single nucleotide polymorphism has been associated with alcoholism in male alcohol abusers as reported by Hwu and Chen [9] as well as by Lee et al. [13]. However, this association has not been observed by Fehr et al. [6]. The explanation for incongruent results can be small sample size, ethnic stratification problems or heterogeneity of diagnoses. Interestingly, in a postmortem study Underwood et al. [21] found lower 5-HT_{2A} receptor binding in the prefrontal cortex (PFC) of alcoholics with a family history of alcoholism.

The above mentioned data suggest a role of the 5-HT_{2A} receptor gene as a candidate gene for alcohol dependence. Therefore, we aimed to investigate whether *HTR2A* T102C single nucleotide polymorphism is associated with alcohol dependence, with a specific hypothesis that increased prevalence of allele 102C is associated with early onset of alcohol problems. The potential advantage of the current study is well-defined and homogenous group of alcoholic patients, which is representative for a population of alcohol-dependent patients in Poland.

Materials and Methods

The study included a sample of 150 patients (108 males and 42 females) admitted to addiction treatment programs in Warszawa, Poland and diagnosed with alcohol dependence according to the DSM-IV criteria [1]. All subjects were Caucasian adults of a Polish nationality, unrelated to each other. The Michigan Alcoholism Screening Test (MAST) was an instrument quantifying the severity of alcohol dependence. The MAST is a self-administered 25-item questionnaire, originally designed to identify probable cases of alcoholism [18]. Patients were evaluated also with the Mini International Neuropsychiatric Interview (M.I.N.I.) – a short, structured interview for both DSM-IV and ICD-10 psychiatric diagnoses [19]. Demographic data of all the patients are presented in Table 1. Ethnically matched healthy subjects from the general population (healthy blood donors) served as a control group to compare the frequencies of the genotypes. The controls were mostly unrelated young male (75%) volunteers and none of them manifested alcohol problems. Patients were included in the study after a written informed consent. The local bioethics committee of the Medical University of Warsaw and the Institutional Review Board at the University of Michigan approved the study protocol.

Peripheral blood samples were drawn from all subjects and the DNA of white blood cells was extracted using the standard procedure. The genotype of the *HTR2A* T102C (rs6313) single nucleotide polymorphism (SNP) was analyzed in 150 patients and in controls. Real-time PCR (polymerase chain reaction) was performed by the LightCycler® 480 instrument available from Roche Applied Science. Simple Probes,

Tab. 1. Demographic and clinical characteristics of the alcohol-dependent (AD) patients

Characteristics		Participants (n = 150)
Age (years); mean ± SD		43.27 ± 9.7
Gender (males); n (%)		108 (72.0)
Married; n (%)		76 (50.7)
Employed; n (%)		67 (44.7)
Education (years); mean ± SD		11.66 ± 3.14
Family history of alcohol dependence; n (%)		97 (64.7)
Age of onset of drinking (years);	mean ± SD	26.17 ± 9.69
	median (IQR)	23 (19–31)
Michigan Alcoholism Screening Test; mean ± SD		33.43 ± 9.55

SD – standard deviation