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Serotonin Transporter Gene Polymorphism and Myocardial Infarction
Etude Cas-Témoins de l’Infarctus du Myocarde (ECTIM)

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Background—Depression is a risk factor for myocardial infarction (MI). Selective serotonin reuptake inhibitors reduce this risk. The site of action is the serotonin transporter (SLC6A4), which is expressed in brain and blood cells. A functional polymorphism in the promoter region of the SLC6A4 gene has been described. This polymorphism may be associated with the risk of MI.

Methods and Results—The SLC6A4 polymorphism has been investigated by polymerase chain reaction in 671 male patients with MI and in 688 controls from the Etude Cas-Témoins de l’Infarctus du Myocarde (ECTIM) multicentric study. Percentages for LL, LS, and SS genotypes were 35.5%, 45.4%, and 19.1%, respectively, for cases versus 28.1%, 49.1%, and 22.8%, respectively, for controls. S allele frequency was 41.8% and 47.4% for cases and controls, respectively. After adjustment for age and center by using multivariable logistic regression, the odds ratio for MI associated with the LL genotype was 1.40 (95% CI 1.11 to 1.76, \( P = 0.0047 \)).

Conclusions—The LL genotype of the SLC6A4 polymorphism is associated with a higher risk of MI. This could be attributable to the effect of the polymorphism on serotonin-mediated platelet activation or smooth muscle cell proliferation or on other risk factors, such as depression or response to stress. (Circulation. 2002;105:2943-2945.)

Key Words: serotonin transporter \( \rightarrow \) genes \( \rightarrow \) myocardial infarction \( \rightarrow \) risk factors

Serotonin (5-HT) is a neuromediator involved centrally in the regulation of mood and psychological traits but also peripherally in platelet homeostasis. Mood disturbances are a risk factor for heart disease.\(^1\) Selective 5-HT reuptake inhibitors (SSRIs) are effective in the treatment of depression and are associated with fewer cardiovascular side effects than are other antidepressants. A recent case-control study has shown that the use of SSRIs is associated with a protection against myocardial infarction (MI).\(^2\) The site of initial action of the SSRIs is the 5-HT transporter (SLC6A4), which is expressed in brain and blood cells.

A polymorphism in the promoter region of the SLC6A4 gene has been described.\(^3\) This polymorphism is located \( \approx 1 \) kb upstream from the transcription initiation site and consists of a 44-bp insertion or deletion. This polymorphism has been demonstrated to be functional in vitro.\(^3,4\) The transcriptional activity of the long variant is more than twice that of the short variant. At the protein level, membrane preparations from LL lymphoblasts bind 30% to 40% more of a labeled marker than do membranes from LS or SS cells. Uptake of labeled 5-HT in LL cells is \( \approx 2 \) times that in cells carrying the S variant. The research of associations between this polymorphism and personality traits or psychiatric diseases has yielded conflicting results.\(^5,6\) However, we have found an association between the S allele and anorexia nervosa and lower food intake in normal or overweight subjects.\(^6\) Thus, the effect of the S allele appears to be quite similar to that of serotonergic anorectic drugs inhibiting the reuptake of 5-HT.

We hypothesized that this polymorphism involved in the 5-HT pathway could be a good candidate in the predisposition to MI, and the aim of the present study was to test this hypothesis in Etude Cas-Témoins de l’Infarctus du Myocarde (ECTIM), a case-control study of MI.

Methods

The aim of ECTIM is to identify variants of candidate genes predisposing an individual to MI. The population of the ECTIM study has already been described in detail.\(^7\) Briefly, cases were recruited from World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) registers in Belfast (Northern Ireland), Lille (Northern France), Strasbourg (Eastern France), and Toulouse (Southwestern France). Men aged 25 to 64 years who had survived an MI (MONICA category I)\(^8\) were eligible. Male age-matched controls were randomly recruited from the same populations without selection for health status and were thus representative of the general population. To be included,
participants and their parents had to be born in the area of recruitment, and the grandparents had to be born in Europe to ensure homogeneity in ethnic origin. Informed consent was obtained from all participants. A set of questionnaires that included details of medical history, drug intake, cigarette smoking, and alcohol consumption were completed. The assays for measuring lipoprotein parameters in the ECTIM study have been reported previously.7

Genomic DNA was prepared from white blood cells by phenol extraction. The polymorphism of the promoter of the SLC6A4 gene was analyzed by polymerase chain reaction amplification.9

Effects of genotypes on the risk of MI adjusted for age and center were analyzed by multiple logistic regression. The first model tested was an effect of LL by reference to LS and SS genotypes combined, according to the in vitro functional data. In a second model, LL and LS were tested by reference to SS to estimate a possible gene-dosage effect. Effects of genotypes on continuous parameters were analyzed by ANOVA.

Results

The SLC6A4 genotypes in the whole population as well as in subgroups defined by center and case/control status were in Hardy-Weinberg equilibrium. There was an excess of LL genotype in the case population from each center (Table). The odds ratio (OR) for MI associated with the LL genotype versus combined LS and SS genotypes, adjusted for age and center, was 1.40 (95% CI 1.11–1.76, P=0.0047; for LL by reference to SS genotype, OR 1.52 (95% CI 1.12–2.06), P=0.0067; and for LS by reference to SS genotype, OR 1.14 (95% CI 0.86–1.51), P=0.38 (not significant).

Discussion

In the ECTIM study, we show that the LL genotype of the SLC6A4 polymorphism is associated with an increased risk of MI. This association is independent of other risk factors, such as smoking, BMI, hypertension, and blood lipids. This is in agreement with the results observed in Japan on coronary heart disease risk assessed by angiography,10 except for an interaction between genotype and smoking on CHD risk described in that study, which was not evidenced by our data. However, the Japanese study, in addition to the different recorded phenotype, included only 144 patients and 222 controls who were not really drawn from the general population but were at the hospital for a checkup, and the L frequency is much lower in the Japanese population than in individuals of European origin (19% versus 53% in control populations from Japanese and ECTIM studies, respectively).

The lower transcriptional efficiency of the S allele provokes an inhibition of the uptake of 5-HT in vitro. This is highly concordant with the results indicating a protective effect of the SSRIs against MI.2 The SSRIs could be protective either by an effect on depression or stress as risk factors for MI or by inhibiting 5-HT–mediated platelet activation. As for SSRIs, a question arises about the mechanism involved in the modulation in MI risk by the SLC6A4 polymorphism.

A depression-mediated mechanism is compatible with the effects of this polymorphism observed on personality traits or...
mood disorders in some studies. However, these effects are not always reported. The response to stress has also been inhibited the uptake of 5-HT by platelets. A similar effect of the polymorphism on blood pressure was observed in the ECTIM study, but such an influence could appear only in conditions of stress.

It has already been shown that the S allele of the polymorphism, which decreased the number of 5-HT transporters, inhibited the uptake of 5-HT by platelets. A similar effect has been observed with SSRIs. In elderly depressed patients, the LL genotype has been associated with an increase in platelet activation, which could lead to a greater release of 5-HT in response to subclinical vascular damage. 5-HT has a potent influence on the arterial wall and is associated with coronary artery disease. In normal human coronary arteries, 5-HT induces vasodilatation. In the presence of endothelial dysfunction, 5-HT induces vasoconstriction. 5-HT also induces vascular smooth muscle cell proliferation. Blood 5-HT levels are higher in L carriers and pulmonary artery smooth muscle cells with the LL genotype are more proliferative in response to 5-HT than are those of other genotypes. The proliferation of smooth muscle cells is a part of the atherosclerotic process and could be a deleterious effect of the LL genotype, affecting the risk of MI.

Another potential mechanism could be the effect on food intake. We have previously evidenced an effect on anorexia nervosa and also an effect on food intake in subjects at a normal weight and in obese subjects. The S allele was associated with a lower food intake of all nutrients, including fats, which theoretically could protect an individual from heart disease. However, because the polymorphism did not influence blood lipids or BMI in the ECTIM study, the causal role of this relationship is unlikely.

The ECTIM study allows conclusions to be drawn only for nonfatal MI. A prospective study is required to obtain information with regard to fatal and nonfatal cases.

In summary, the LL genotype of the 5-HT transporter gene promoter polymorphism is associated with a higher risk of MI. Many pathophysiological mechanisms could explain this association and must be explored. These mechanisms are not mutually exclusive and could act in synergy.

References