Gene polymorphisms of serotonin receptors and drug-induced hyperprolactinemia in patients with schizophrenia

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BACKGROUND

Antipsychotic drug-induced hyperprolactinemia is an increasingly prevalent problem in current psychiatric practice and responsible for troublesome side effects like loss of libido and impotence. The chance to develop hyperprolactinemia depends upon the pharmacological properties of antipsychotic medication used, of its dosage and treatment duration, as well as from the genetic make-up and other characteristics which determine the individual sensitivity of the individual patient.

Second generation antipsychotics are (often) more potent antagonists of 5HT2 than of D2-receptors. Serotonin receptor agonists stimulate prolactin secretion by the anterior pituitary, while the blockade of postsynaptic serotonin receptors leads to a decrease in prolactin levels.

Genes coding for serotonin receptors might have variants which are associated with abnormal intensity of certain antipsychotic drug effects.

OBJECTIVE

The present study aimed to investigate the role of polymorphisms of the serotonin receptors genes (HTR1A, HTR1B, HTR2A, HTR2C, HTR3A, HTR3B, HTR6) in the pathogenesis of antipsychotic-induced hyperprolactinemia in patients with schizophrenia.

METHODS

- 446 Russian patients with schizophrenia were examined, including 225 women and 221 men. The average age of these patients was 42.1±1.4 years.
- Serum prolactin levels were measured using AccuBind ELISA Microwells kit (Monobind Inc., USA)). The upper limits for normal PRL concentration were set at ≤20 ng/ml for men and ≤25 ng/ml for non-pregnant, non-nursing women.
- Genotyping was carried out of 29 polymorphic variants of the serotonin receptor genes HTR1A, HTR1B, HTR2A, HTR2C, HTR3A, HTR3B and HTR6, with the use of MassARRAY Analyzer 4 (Agena Bioscience™).
- SPSS software was used for statistical analysis. The Hardy-Weinberg equilibrium (HWE) of genotypic frequencies was tested by the chi-square test.

RESULTS

All patients with schizophrenia were divided into two groups: those with and without hyperprolactinemia. Patients from both groups were genotyped for HTR1A variants: rs6295, rs1364043, rs10042486, rs1800042, rs749099; for HTR1B: rs6298, rs6296, rs130058; for HTR2A: rs6311, rs6313, rs6314, rs7997012, rs1928040, rs9316233, rs2224721, rs6312; for HTR2C: rs6318, rs5946189, rs569959, rs17326429, rs4911871, rs3813929, rs1801412, rs12858300; for HTR3A: rs1062613, rs33940208, rs1176713; for HTR3B: rs1176744 and for HTR6: rs1805054.

After separation of all patients by gender, statistically significant results were obtained for polymorphic variants of the genes HTR2A (rs6312), HTR2C (rs12858300) in the female group, and HTR2C (rs569959) in males, which suggests the participation of these polymorphic variants in the development of hyperprolactinemia in schizophrenic patients.

Table 1 – Comparison of genotype frequencies of polymorphic variants genes HTR2A and HTR2C between patients with hyperprolactinemia (HPRL), and with normal levels of prolactin

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotypes</th>
<th>Patients with HPRL</th>
<th>Patients without HPRL</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR2A  (rs6312)</td>
<td>GG</td>
<td>16(12.5%)</td>
<td>0(0%)</td>
<td>4,685</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>112(87.5%)</td>
<td>92(95.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTR2C  (rs12858300)</td>
<td>GG</td>
<td>113(88.3%)</td>
<td>95(99.0%)</td>
<td>9,429</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td>15(11.7%)</td>
<td>1(1.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTR2C  (rs569959)</td>
<td>G</td>
<td>35(36.5%)</td>
<td>27(22.3%)</td>
<td>6,284</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>60(63.5%)</td>
<td>95(77.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

Our results indicate that genetic variants of HTR2A and HTR2C may have functional consequences on the modulation of prolactin secretion. Further search for genetic markers associated with the development of side effects of neuroleptic therapy, will contribute to the development of effective methods of diagnosis, correction and treatment of disease, as well as of adherence of patients with mental disorders to psychotropic therapy.