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Histaminergic gene polymorphisms associated with sedation in clozapine-treated patients

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Abstract
Sedation is a common adverse effect of clozapine treatment, which may be partly related to clozapine binding to histamine receptors in the central nervous system. The objective of this study was to investigate whether single nucleotide polymorphisms (SNPs) in the histaminergic system are associated with sedation in clozapine-treated patients. The study population comprised 237 clozapine-treated, Finnish, Caucasian patients that were diagnosed with schizophrenia and 176 were genotyped using Illumina HumanCoreExome-12 BeadChip. Sedation levels were assessed using self-rating questions from the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS). The relationships between 55 different SNPs in the histaminergic system and adverse sedation effects were examined. SNPs were analyzed separately, and in groups, to formulate a genetic risk score (GRS). A permutation test was performed to avoid type I errors. Eight linked SNPs ($r^2 = 1$) in the *HNMT* gene were also associated with sedation according to the GLM, adjusted for age, gender and BMI (false-discovery-rate-adjusted $p = 0.013$). An association on a trend level between a GRS of four different SNPs (recessive histamine N-methyltransferase *HNMT* rs2737385, additive histamine receptor H_1 rs1552498, dominant *HRH1* rs17034063 and recessive amine oxidase, copper containing 1 *AOC1* rs6977381) and sedation was found (permuted p-value = 0.066) in a generalized linear model (GLM) incorporating age, gender and body mass index (BMI; adjusted $R^2 = 0.22$). Polymorphisms in genes encoding histamine receptors or enzymes related to histamine metabolism may explain individual variation in sedative effects experienced during clozapine treatment.

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1. Introduction

Sedation is a common side effect of clozapine treatment. It is more prominent at the beginning of clozapine treatment, with some tolerance developing during the first days or weeks of treatment (Safferman et al., 1991). The histaminergic network of the central nervous system (CNS) regulates sleep and wakefulness (Panula and Nuutinen, 2013), with blockade of histamine H_1 and activation of histamine H_3 receptors inducing sedation (Lin, 2000). Histamine N-methyltransferase (HNMT) is a histamine-metabolizing enzyme that inactivates histamine in the CNS (Ogasawara et al., 2006), while diamine oxidase (DAO), encoded by the gene amine oxidase, copper containing 1 (*AOC1*, also called *ABP1*), is another histamine degrading enzyme that functions mostly in peripheral tissues. Under normal conditions, DAO has low activity in the CNS (Haas et al., 2008) but may act as a salvage pathway for histamine degradation when HNMT is blocked (Prell et al., 1997). Histidine decarboxylase (HDC) is required to synthesize histamine from histidine, through oxidative decarboxylation (Haas et al., 2008). Therefore, it is proposed that the sedative properties of clozapine may be related to effects on H_1 histamine receptors (Ashby and Wang, 1996; Richelson and Souder, 2000). Clozapine has a very high affinity for CNS histamine H_1 receptors (Ashby and Wang, 1996) and its metabolite *N*-desmethylclozapine acts as a potent and partial H_1-receptor inverse agonist, a weak, full H_2-receptor inverse agonist, a moderate protean H_3-receptor agonist and a moderate, partial H_4-receptor agonist (Humbert-Claude et al., 2012). The metabolic pathway of histamine and functions of the histamine receptors particularly on behalf of regulating wakefulness are presented in Figure 1.

In this study, single nucleotide polymorphisms (SNPs), or combinations of SNPs, in genes encoding receptors and enzymes of the histaminergic system and their potential association with clozapine related sedation in patients were examined. SNPs in histamine receptor genes (*HRH1*, *HRH2*, *HRH3* and *HRH4*) and histaminergic system, enzyme genes (*HNMT*, *HDC* and *AOC1*) were studied.

2. Experimental procedures

2.1. Patients

The sample was screened from 256 patients, of which 19 declined to participate. The study was conducted in three hospital districts in Western Finland (Satakunta, Pirkanmaa and Seinäjoki Hospital districts). For inclusion, patients had to be current F2-group diagnosed, according to the International Classification of Diseases, Tenth Revision (ICD-10), and stabilized on clozapine treatment. Patients with organic brain diseases were excluded. The study population comprised 237 clozapine-treated patients (136 men, 101 women, mean age 42.5, standard deviation (SD) 11.0 years) diagnosed with schizophrenia (n = 223, 94.1%), schizoaffective disorder or delusional disorder, according to the ICD-10. The mean elapsed time from first hospitalization due to psychotic episode was 17.3 years (SD $\pm$ 10.0 years). All patients were adults ($\geq$ 18 years of age), Caucasian, of Finnish origin and on clozapine treatment. Patients completed a questionnaire, by which we asked about smoking information, estimate of patient's current weight, height and weight change during clozapine treatment, medication and its dosing method (supervised or unsupervised). Psychiatric diagnoses, medication information including the duration of clozapine treatment and dates of the first hospitalization due to psychosis were collected from the medical history entries. Laboratory samples were obtained from 190 patients, and after quality controls, 176 genotyped patients were eligible to remain in the study. Compliance to medication was accounted by measuring clozapine and norclozapine concentrations for this study. Also, as required by the treatment protocol, patients participated in monthly group sessions, where the white cell blood counts were checked and clozapine prescriptions renewed.

Patients gave written, informed consent for participation in this study and agreed to have blood samples taken for the study of adverse effects of clozapine treatment. The study was performed in accordance

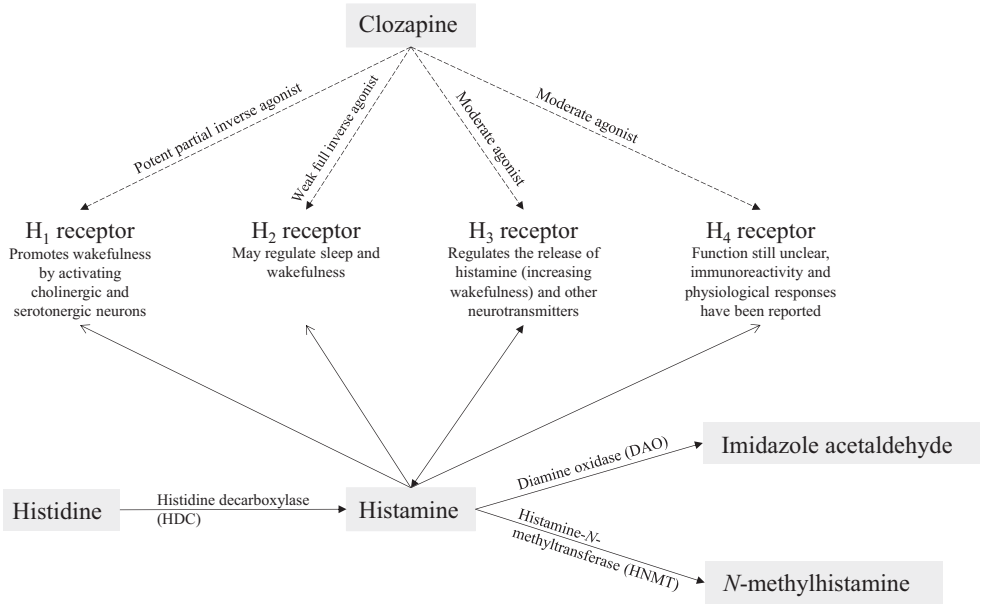

Figure 1 The metabolic pathway of histamine, histamine receptors and their functions particularly on behalf of regulating wakefulness and the affinity of clozapine on histamine receptors.

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