Conclusion: Based on these findings, Olanzapine was considered a very effective and well-tolerated medication also for this young population. Change in body weight under Olanzapine was comparable to that during pre-treatment. Additionally, based on clinical impression, onset of action was perceived as 'fast'. Once-daily dosing and low AE rates appeared to support good patient compliance.

P.2.050 Is there an association of response to haloperidol treatment with polymorphisms in the DRD2 or in the DRD3 receptor genes?

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Introduction: Reasons for interindividual differences in the response to haloperidol treatment are largely unknown. No clear dosis-response relationship could be yet demonstrated. We tested the hypothesis, that genetic variations in the DRD2 and DRD3 receptor gene may influence clinical response to haloperidol treatment.

Method: A sample of 56 patients with acute exacerbation of psychotic disorders as diagnosed by SKID were treated with haloperidol monotherapy for at least 14 days. Only patients without prior oral neuroleptic treatment for at least 14 days and 2 months in case of treatment with depot antipsychotics respectively were included. Response was measured using the Positive And Negative Syndrome Scale (PANSS) at baseline and at day 14 during haloperidol treatment. Response was defined as 40% improvement of the positive respectively the negative subscale. DNA was extracted from lymphocytes and the distribution of genetic polymorphisms in the DRD2 (Taq I 'A') and in the DRD3 receptor genes (Bal I) were examined. Response was compared between the three possible genotypes for each polymorphism.

Results: The three possible groups for each polymorphism did not differ significantly in age, sex, age of onset and number of prior hospitalisations. The average daily dose of haloperidol was 10 mg in each group and 1 mg biperiden respectively without significant differences.

Only one patient had the DRD2 A1/A1 genotyp, according to the expected low rate (<3%) described in other collectives. From 39 Patients homozygote for the A2/A2 genotype 22 (56%) responded to haloperidol treatment whereas in 13 of 16 (81%) carrier of the A1/A2 alleles responded ($p < 0.05$) in the positive subscale. Furthermore the mean improvement of positive symptoms (50% reduction in the positive subcale) was significantly higher ($p < 0.01$) for the heterozygote compared to the homozygote group (40%). No differences were observed with regard to changes of the negative subscale. For the three possible genotyps of the DRD3 receptor gene no association to treatment response could be found.

Conclusions: This is the first study to show an association between the DRD2 genotype and response to haloperidol treatment. In future genetic testing before neuroleptic treatment with regard to the DRD2 and possibly other genes may help to find individually the most successful treatment.

P.2.051 Alterations of interneuronal subpopulations in rat hippocampus after chronic low dose exposition to a NMDA receptor antagonist; implications for schizophrenia

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GABAergic interneurons of the hippocampus are heterogeneous in respect to distribution and function. Interneurons containing the calcium binding protein parvalbumin are believed to play a crucial role in local feedback circuits. They receive glutamatergic input, by part via the activation of excitatory NMDA receptors which might be essential for their proposed function - the maintenance and modulation of a permanent inhibitory drive on pyramidal neurons. In contrast, calretinin positive interneurons establish predominantly synaptic contacts with other interneurons thereby exerting a synchronizing effect on neuronal networks. We examined the effects of chronic low dose exposure to the non-competitive NMDA receptor antagonist MK-801, a substance with psychotomimetic proprieties, on the relative distribution of the two interneuronal subpopulations mentioned above. MK-801 (0.02 mg/kg body weight) was injected i.p. in 52 d old Long Evans rats for 2 weeks (MK-801: $n = 6$; saline controls: $n = 6$) in a dosage that had previously been shown to neither elicit any neurological symptoms nor structural changes in rat brain when applied acutely. We did not observe any behavioral changes in these rats. 15 µm cyostat slices were double stained with anti-parvalbumin and anti-calretinin. Comparative cell counts were performed and the ratio of the two interneuron subpopulations was calculated for different areas of the hippocampal formation.

Results: In the MK-801 group the portion of parvalbumin positive interneurons was significantly reduced in CA 1 ($p < 0.01$) and the dentate gyms ($p < 0.05$). This alteration was even more marked when calculated for the whole hippocampus ($p < 0.001$). No changes were observed for calretinin positive interneurons.

Conclusions: Chronic NMDA receptor antagonism selectively impairs parvalbumin positive hippocampal interneurons which might play an important role in the control of surplus excitatory drive and the associated excitotoxic damage as seen in this animal model for schizophrenia.

P.2.052 Extrapyramidal symptoms during haloperidol treatment are not associated with polymorphisms in the DRD2 and DRD3 receptor genes

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Introduction: A major reason for the discontinuation of antipsychotics is the occurrence of extrapyramidal symptoms (EPS) during treatment. Interindividual differences are poorly understood and may be partially caused by genetic factors. Interestingly, there is first evidence that tardive dyksinesia might be associated with variations in the DRD2 and DRD3 receptor genes. We tested the hypothesis, that genetic variations in these genes may influence acute side effects during haloperidol treatment.

Method: A sample of 56 patients with acute exacerbation of psychotic disorders as diagnosed by SKID were treated with haloperidol monotherapy for at least 14 days. Patients without prior oral neuroleptic treatment for at least 14 days and 2 months in case of treatment with depot antipsychotics respectively participated. Patients with movement disorders of any ethiology were excluded. EPS was assessed with the Extrapyramidal Symptoms Rating Scale (ESRS) and the Barnes Akathisia Scale (BAS) at baseline and at day 14 during haloperidol treatment. DNA was extracted from lymphocytes and the distribution of genetic polymorphisms in the DRD2 receptor gene (Taq I 'A') and in the DRD3 receptor gene (Bal I) were examined. The occurrence of acute dyskinesia, parkinsonoid and akathisia was compared between the three possible genotypes for each polymorphism.

Results: For each polymorphism the three groups did not differ significantly in age, sex, age of onset and number of prior hospitalisations. The average daily dose of haloperidol was 10 mg in each group and 1 mg biperiden respectively without significant differences. No association with acute dyskinesia, parkinsonoid or akathisia could be found. Furthermore, no combination of the genotypes was related to EPS.

Conclusions: To our knowledge this is the first study which investigates the contribution of genetic polymorphisms in dopamine receptor genes to the development of EPS during acute treatment with haloperidol. No association with the DRD2 and/or the DRD3 genotype could be found. Further candidate genes have to be tested in order to find predictors for a safer neuroleptic treatment which is more acceptable for the patients.