51. ALTERED GABA TRANSPORTER-1 mRNA EXPRESSION IN PREFRONTAL CORTICAL NEURONS IN SCHIZOPHRENIA

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Within the prefrontal cortex (PFC) of schizophrenic subjects, recent studies suggest that alterations in markers of GABA neurotransmission, including decreased immunoreactivity for the GABA membrane transporter, GAT-1, may be most prominent in the chandelier cell subpopulation of GABA neurons (PNAS 95:5341, 1998). In order to explore one possible mechanism for these findings, we tested the hypothesis that GAT-1 mRNA expression is decreased in a subset of PFC GABA neurons in schizophrenia. Tissue sections containing PFC area 9 from 10 schizophrenic subjects, each matched to one control subject for sex, age, and postmortem interval, were processed for in situ hybridization histochemistry with 35 S-labeled oligonucleotide probes for GAT-1 mRNA and exposed to nuclear emulsion. The density of labeled neurons was decreased in the schizophrenic subjects by 21–32% in layers 1–5 but was unchanged in layer 6. In contrast, mean grain density per labeled neuron, a relative measure of the cellular level of GAT-1 mRNA expression, did not differ between schizophrenic and control subjects. These findings indicate that GAT-1 mRNA expression is relatively unaltered in the majority of PFC GABA neurons in schizophrenic subjects, but is reduced below a detectable level in a subset of GABA neurons. Furthermore, the magnitude and laminar pattern of these results were strikingly similar to our previous study of GAD67 mRNA expression in the same subjects (Arch Gen Psych, in press). Thus, markers of both GABA synthesis and uptake appear to be altered at the level of gene expression in a subset of GABA neurons, and the resulting changes in GABA neurotransmission may contribute to PFC dysfunction in schizophrenia.

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52. REVERSE PHARMACOGENETICS: A NEW APPROACH TO RAPID RELAPSE IN SCHIZOPHRENIA?

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A significant subgroup of patients with schizophrenia experience rapid exacerbations in clinical symptoms following antipsychotic drug discontinuation. There are limited clinical or biological data with which to predict which patients are at increased risk for rapid relapse. New assessment tools that provide more accurate risk-benefit profiles for individual patients may be of use in determining clinical management strategies of patients at high risk for medication discontinuation. Previously, we have examined the role of a functional polymorphism (5-HTTLPR) in the serotonin transporter gene in antipsychotic drug-free patients participating in a placebo-controlled clinical trial. In this study, the clinical profile of 50 schizophrenia patients was assessed with the Brief Psychiatric Rating Scale (BPRS) after 4 weeks of placebo administration. Analysis by genotype revealed that the 5-HTTLPR ll genotype was markedly over-represented in the group of patients with increased BPRS ratings of positive symptoms (p = 0.0003). Patients with the 5-HTTLPR ll genotype were also observed to experience greater negative symptoms, anxiety and depression BPRS ratings. Although these data are preliminary, they suggest that studies of genetic variation may provide a means to identify schizophrenia patients at high risk for rapid relapse following drug discontinuation. New studies are underway to assess the merits of this reverse pharmacogenetics approach.

The choice of dosing in animal studies of antipsychotics often follows convention without much reference to the brain receptor occupancy of the chosen doses. However, studies in patients show that receptor occupancy is a powerful predictor of antipsychotic response as well as side-effects. The intent of this study was to measure the relationship between the dose/occupancy of haloperidol in animals and to compare it to studies in patients where it is known that the appropriate range of dopamine D2 receptor occupancy with haloperidol is a) 60–80% and b) remains relatively unchanged through the day. We developed and validated a method to measure D2 occupancy in rats using [3H]-raclopride which is similar in principle to the [11C]-raclopride PET method in humans. Using this, we find that a 0.02 mg/kg/sc dose of haloperidol, which corresponds to a plasma level of 1.18 nM, gives 50% D2 occupancy. Even doses 10 times ED50 have little occupancy after 24 hours due to the very short half-life of haloperidol in rat (2.5 hours vs. 24 hours in man). As in humans, the drug shows effects in an antipsychotic screening test (conditioned-avoidance response) when D2 occupancy >70–75%, and leads to effects in an EPS model (catalepsy) when D2 occupancy is >80%. Therefore, we conclude that a large number of animal studies of antipsychotics have used dosing schedules that give rise to inappropriately high D2 occupancy acutely, and, inappropriately low D2 occupancy between doses. The presentation will focus on how our data lead to a reinterpretation of several previous animal studies.

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