

## 17. Therapeutics, Pharmacologic Probes

### GLYCINE TRANSPORT INHIBITORS: A NEW CLASS OF ANTIPSYCHOTICS?

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While most extant antipsychotics are antagonists of dopamine receptors, recent evidence suggests that a hypofunction of NMDA receptor (NMDA-R)-mediated glutamate neurotransmission may underlie the pathophysiology of schizophrenia. Glycine is an obligatory co-agonist at NMDA-R, and recent clinical studies have demonstrated efficacy of exogenous glycine in treating negative symptoms. As extracellular glycine is regulated by high-affinity glycine transporters, pharmacological inhibition of such transporters represents a novel mechanism for increasing glycine within the brain. Molecular cloning has identified two classes of glycine transporters: GlyT1 is present in the forebrain and colocalizes with NMDA-R, whereas GlyT2 is present in the spinal cord and brainstem, and colocalizes with inhibitory glycine receptors (Gly-R). Further, three isoforms of GlyT1 (a,b, and c) have been identified in the human brain. We now describe the identification of novel glycine transport inhibitors, from three related chemical series, with potency and selectivity for GlyT1.

A number of compounds in all 3 series display  $pIC_{50}$  values  $>6$  at human GlyT1. The most potent compound at GlyT1c is  $T \times R \times 5311$  ( $pIC_{50} \approx 8$ ).  $T \times R \times 5311$  is 10 000-fold less potent at GlyT2, NMDA-R, Gly-R, and at transporters for GABA, 5-HT, DA, glutamate, and proline. When tested in vivo in the rat (1 & 10 mg/kg i.p.), a number of the GlyT1 inhibitors inhibit PCP-induced locomotion; oral activity is also observed. In contrast, they are ineffective against amphetamine-induced locomotion, indicating their selectivity for NMDA-R function. Further, the transport inhibitors increase extracellular glycine in the rat brain (as determined by in vivo dialysis), and enhance synaptic plasticity in the hippocampal slice. These data suggest that inhibitors of GlyT1 may be beneficial in the treatment of schizophrenia.

### CNS CATECHOLAMINES AND COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

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In the revised dopamine hypothesis of schizophrenia cognitive dysfunction is proposed to reflect reduced dopamine effects

in the cortex. This is supported by findings in non-human primates that dopamine supports prefrontal pyramidal cell function associated with working memory performance. This is mediated by D1 receptors and follows an 'inverted U' function. We tested the hypothesis that augmented catecholamine effects in the CNS would improve cognition in schizophrenia by administering 0.25 mg/kg of d-amphetamine to stable patients medicated with low dose D2 antagonists, and normal controls. Preliminary results show robust improvement in selective attention and working memory in patients, while normals show minimal effects, even under dual task conditions where performance is clearly not at ceiling. Examination of the range of performance in controls suggests an 'inverted U' function in the amphetamine response. These results suggest that augmenting catecholamine effects in the brain can improve cognitive deficits in schizophrenia. Increased D-amphetamine sensitivity in schizophrenia suggests that patients are to the left of the 'inverted U' describing optimal cortical dopamine tone.

### PERSISTENT BEHAVIORAL CHANGES AND PROGRESSIVE SENSITIZATION IN AMPHETAMINE SENSITIZED RHESUS MONKEYS

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Amphetamine (AMPH) sensitization, produced by intermittent escalating doses, has been proposed as an animal model of psychosis since it produces pronounced behavioral changes and enhanced dopamine release in response to acute AMPH challenge. In rats, this regimen results in a transient behavioral depression after withdrawal as well as persistent behavioral sensitization to low dose AMPH challenge. We investigated whether AMPH sensitization may induce a long-lasting alteration of dopaminergic responsiveness in the nonhuman primate by sensitizing monkeys with intermittent escalating low doses of AMPH (0.1–1.0 mg/kg; i.m.) over a 3 month period. Low dose AMPH challenges (0.4 mg/kg; i.m.) in sensitized monkeys produced florid 'psychotic' symptoms and significantly altered endogenous motor stereotypies as early as 5–11 days post-withdrawal (PWD). At time points extending out to 6 months, the same challenge dose induced progressively more robust and more prolonged responses. One monkey has continued to exhibit hallucinatory-like behaviors in the absence of drug and at present (9 months PWD) all monkeys remain 'behaviorally depressed' in the absence of drug. Preliminary pharmacological assessments with a D1 agonist, SKF-81297, (0.3 mg/kg; i.m.) transiently exacerbated hallucinatory-like behaviors in the individual rendered 'permanently psychotic' by sensitization. From this we conclude (1) that AMPH sensitization induces enduring behavioral alterations in the non-human primate which manifest as persistent 'psychosis' in individual monkeys; (2) behavioral sensitization in monkeys shows progression beyond six months. Further pharmacological and ultimate postmortem studies are planned to explore the AMPH sensitized primate as a model of psychosis.