GlyT1 − Up from the Ashes. The Importance of Not Condemning a Mechanism Based on a Single Chemotype

Clinically utilized antipsychotic agents target a common mechanism: antagonizing the dopamine D_2 receptor and to a lesser extent other biogenic amine receptors, but the D2 inhibition is widely assumed to provide their efficacy against the positive symptoms of schizophrenia (*1*). The efficacy of currently marketed antipsychotic agents on the negative and cognitive symptoms of this disease, however, is not optimal. One alternate hypothesis to the "dopamine hypothesis" of schizophrenia derives from the observation that antagonists of *N*-methyl-D-aspartate (NMDA) receptor activity better mimic the symptomatology of schizophrenia in its entirety than do dopamine agonists. Findings from this line of research have led to the NMDA receptor "hypofunction hypothesis" of schizophrenia, which complements existing research implicating dopamine dysfunction in the disease (*1*−*5*). According to the NMDA receptor hypofunction hypothesis, any treatment that enhances NMDA receptor activity may prove useful for the treatment of the complex symptom clusters (positive, negative, and cognitive) of schizophrenia. This idea is now supported by numerous clinical studies that have reported an efficacious response following treatment with activators of the NMDA receptor coagonist glycine B site. One area of study, aimed at potentiating the NMDA receptor via activation of the glycine B site, is small molecule blockade of the glycine reuptake transporter type 1 (GlyT1) (*1*−*5*).

In the early days of GlyT1 inhibitors, the efforts of most pharmaceutical companies focused on derivatives of the substrate inhibitor, sarcosine, leading to the prototypical GlyT1 inhibitor (*R*)-*N*-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)-propyl]sarcosine ((*R*)-NFPS) (*1*−*5*). Several members of this class were evaluated *in vivo* and demonstrated efficacy similar to clinically useful antipsychotics. Despite these promising characteristics, the sarcosine-derived GlyT1 inhibitors suffer from a range of serious side effects including ataxia, hypoactivity, and decreased respiratory activity, the latter often leading to death in preclinical species upon chronic dosing (*1*−*5*). GlyT1 inhibitors based on sarcosine, like (*R*)-NFPS, increase glycine levels in the prefrontal cortex for >24 h, leading to overstimulation of the inhibitory strychnine-sensitive glycine binding site. Compounds of this chemotype are also tight binders that slowly dissociate from the transporter and are noncompetitive with respect to glycine (*1*−*5*). These observations led to a backlash against the GlyT1 mechanism as a toxic and undruggable target in the early 2000s, all based on data generated by a single chemotype. Importantly, many companies discontinued their GlyT1 programs.

In the mid-2000s, reports began to surface that nonsarcosine-based GlyT1 inhibitors only increase glycine levels in the prefrontal cortex for ∼3−6 h and then return to basal levels. Moreover, both the *in vitro* and *in vivo* pharmacology of the nonsarcosine GlyT1 inhibitors, as well as toxicity profiles, were fundamentally different than the sarcosine-based GlyT1 inhibitors, demonstrating competitive inhibition with respect to glycine (*6*). Finally, Roche reported in January 2010 results from a phase II trial with their nonsarcosine-based GlyT1 inhibitor, RG1678 (*7*). In a 320 patient phase II proof of concept trial, RG1678 demonstrated robust efficacy on the negative symptoms of schizophrenia (personal and social performance), a symptom cluster that the standard D_2 antagonist therapies do not impact.

Finally, validation in humans for the GlyT1 mechanism and efficacy for an unmet medical symptom cluster of schizophrenia. This underscores an important caveat in CNS drug discovery, chemotype matters and mode of inhibition matters. In 2000, the GlyT1 mechanism was virtually dismissed as a viable target. Ten years later, novel GlyT1 chemotypes with a competitive mechanism of inhibition address an unmet medical need for schizophrenic patients. We should all remind ourselves of the GlyT1 story and be vigilant and not so quick to judge with only limited data.

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7. For data on the Roche clinical trial with RG1678, see www.roche.com or www.clinicaltrials.gov.

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