Dear Editors,

A recent News and Views comment by Weinberger (2007) was editorially headlined as “Schizophrenia drug says goodbye to dopamine”, based on a report by Patil et al. (2007) of an antipsychotic drug that is a glutamate receptor activator. Weinberger comments that this is the ‘first credible evidence of an effective antipsychotic drug that does not target dopamine’.

Not so fast. In fact, LY404039, the prodrug of which was used by Patil et al. and which gave moderate antipsychotic action, is virtually identical to the more potent glutamate agonists LY354740 and LY379268, as shown in the Table 1. Our laboratory has found (Seeman et al., 2008) that these latter two glutamate agonists have dopamine agonist dissociation constants of 21 to 24 nM at the functional high-affinity state of dopamine D2 receptors, or D2High, when competing vs the selective D2 receptor ligand [3H]domperidone, as summarized in the Table 1. These drugs, moreover, inhibited the release of prolactin from isolated anterior pituitary cells in culture (Seeman et al., 2008) (see Table 1), similar to other dopamine agonists. In addition, these two drugs inhibited the dopamine-stimulated incorporation of [35S]GTP-gamma-S, similar to other dopamine partial agonists that are antipsychotics (Cosi et al., 2006). Overall, the agonist dissociation constants at the D2 receptors of these two glutamate agonists are similar to those at metabotropic glutamate-2 and -3 receptors (Schoepf et al., 1999), as detailed in the Table 1. Although Eli Lilly is not presently releasing LY404039 for extramural study, the potencies of the other two glutamate agonists are greater than LY404039, and their potencies at mGluR2, mGluR3 and D2High receptors are essentially similar (Table 1). These data suggest that LY404039 would have a significant action at dopamine D2High receptors, although this remains to be tested.

Although Patil et al. (2007) stated that LY404039 had no effect on dopamine D2 receptors, there is no evidence that they tested for its possible D2 agonist-like potency using [3H]domperidone, which reveals agonist potency at D2High, in contrast to the customary D2 ligands of [3H] raclopride and [3H]spiperone that do not readily reveal D2High (Seeman et al., 2003).

It appears, therefore, that these glutamate agonists would also contribute clinical dopamine partial agonist action, similar to the antipsychotic action of aripiprazole, a dopamine partial agonist. The dopamine hypothesis of schizophrenia, first stated by Van Rossum (1967) and validated by the discovery of the antipsychotic D2 receptor (Seeman et al., 1975), remains strong. While a selective but non-dopamine antipsychotic medication

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**Glutamate agonists for schizophrenia stimulate dopamine D2High receptors**

<table>
<thead>
<tr>
<th>Name</th>
<th>Ki at mGlu2</th>
<th>Ki at D2</th>
<th>Ki at mGlu3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY354740</td>
<td>75</td>
<td>24</td>
<td>90</td>
</tr>
<tr>
<td>LY379268</td>
<td>14.1</td>
<td>21</td>
<td>5.8</td>
</tr>
<tr>
<td>LY404039</td>
<td>231</td>
<td>20</td>
<td>45</td>
</tr>
</tbody>
</table>

*Using recombinant mGlu receptors and [3H]LY 341495.
**Compound not being released by Eli Lilly for extramural study.

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would be welcome in order to avoid current clinical side-effects of anti-dopamine drugs, we are not there yet.

Competing interests statement: The author is an advisor to Clera Inc., a pharmaceutical company.

References


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