Review of: "Discovery and synthesis of hydroxy-L-proline based blockers of the neutral amino acid transporters SLC1A4 (ASCT1) and SLC1A5 (ASCT2)"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

The manuscript by Lyda et al. concerns the synthesis and preliminary characterization of compounds, based on the structure of hydroxy-L-proline, behaving as high-affinity inhibitors of ASCT1 and ASCT2 neutral amino acid transporters. Authors report the synthesis of a series of derivatives ('prolinols') some of which act as high-affinity inhibitors of SLC1A4 and SLC1A5. Active and inactive prolinols were computationally analyzed as far as interaction with models and pharmacological activity are concerned.

Authors conclude that prolinols provide a new group of SLC1A4 and SLC1A5 inhibitors.

Given the relevance of ASCT5-mediated transport, in particular of glutamine, in several pathophysiological processes, the subject of the study is of great interest. The availability of a new class of compounds is therefore of marked interest and may provide the basis for further investigations. I have some issues on the data presented.

1. Substrate specificity of rodent and human SLC1 transporters are similar but not completely overlapping. Therefore, the choice to use mSLC1A5 for experiments shown in Figs. 1, 3 and 4 B should be justified. If possible, key experiments (i.e. Fig. 4B) should be repeated with hSLC1A5.
2. BPOHP pharmacology is mostly studied on SLC1A4 while, from a translational point of view, SLC1A5 would be obviously much more interesting. Can the authors assess if the inhibitor behaves competitively also on SLC1A5 (at least on the murine form)? The sentence at p. 14 (Discussion) in which authors claim that BPOHB “marks an advancement in SLC1A4/5 pharmacology with a Ki of 120 nM” is therefore slightly overreaching.
3. Cross reactivity on SLC38 transporters is tested with 3 microM BPOHP (p. 12). Given the low affinity exhibited by these transporters, higher inhibitor concentrations should be used.

Minor

Some typos are present. For instance, “dnoted” (p. 3), “confomraitnal” (p. 13), “preicted” (p. 15), “Expermientals” (p. 16).

Panels are not identified with letters in Fig. 4. In the same Figure, inhibitor concentrations should be expressed in the same unit marked.

“micromolar” should be expressed with Greek “mu” instead of “u” throughout the manuscript.