The host/guest interactions of the key protein for the Bipolar Disorder

Schultz, L.G.[1]; Villalta-Romero, F.G. [1]; Borro, L.C. [2]; Jardine, J.G.[2]; Neshich, G.[2]; Tasic, L.[1]

[1] Chemical Biology Laboratory, Institute of Chemistry, Unicamp, Campinas;
[2] Embrapa Agricultural Informatics, Computational Biology Research Group, Campinas, Brazil

One of the key proteins identified as potentially causing bipolar disorder (BD) is the human inositolmonophosphatase 2 (IMPase 2), whose gene (IMPA2) is located in the chromosomal region (18p11.2). Lithium (I) carbonate is administered since 1949 to treat BD and recently other spasmolytics and antipsychotics drugs, such as carbamazepine, sodium valproate and lamotrigine are used. Although these drugs present lower toxicities than lithium (I), they still have unpleasant side effects. Hesperitin is a bioflavonone found in glycoside form in the citrus fruits, which has interesting pharmacological properties, highlighting its anticancer and action against neurodegenerative diseases. Our idea is to use hesperitin as a candidate to inhibit IMPase 2, motivated mainly by its capacity to easily cross the blood-brain barrier and also due to its low or absent toxicity. Our research started with computational biology tools to verify *in silico* hesperetin and IMPase 2 interactions. We have tested some other ligands: inositolmonophosphate, *myo*-inositol, hesperidin and three inhibitors of phosphatases, against IMPase 2 whose 3D structure (PDB code: 2CZH) has been used in all docking analyses. The *in silico* results indicated strong interactions between hesperetin with the active site of IMPase 2, thus proving hesperitin has interesting inhibition properties against BD target enzyme. *In vitro* tests are under way. After successful expression of human IMPase 2 in *E. coli* BL21(DE3) pLysS strain and protein purification by Ni-affinity chromatography, we are going to use biophysical methods for IMPase 2 characterization. Also, the circular dichroism (CD), fluorescence, biochemical method using *p*-nitrophenylphosphate (*p*-NPP) and a Saturation Transfer Difference (STD) NMR experiments are going to be applied as to confirm and map these important host/guest interactions *in vitro*.

Keywords: hesperitin, inositolmonophosphatase 2 (IMPase 2), bipolar disorder, host-guest interactions.

Sponsor: CAPES.