NMDA RECEPTOR: MOLECULAR MODELING OF A POTENTIAL TARGET

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NMDA receptor (NMDAr) is a glutamate receptor composed of NR1 and NR2 (A-D) subunits forming tetramers or pentamers structures. It is involved in several neurodegenerative diseases, thus becoming a potential target for developing high specific antagonists, especially NR2B subunit whose antagonists seems to have less adverse effects. Herein we analyzed the NMDAr structure by constructing the homology models of the NR2B subunit open (NMDAr-O) and closed (NMDAr-C) forms (resulting from binding the antagonist or agonist respectively). Our study revealed a significant conformational change of NMDAR-O compared to NMDAr-C (RMSD = 1,25Å). NR2B was also compared with NR2A subunit of NMDAr and to GluR2 subunit of AMPA receptor showing that all aminoacids that may interact with glutamate (Thr514, Arg519, Ser690 and Thr691) were present in all structures analyzed whereas the Asp732 is only in the NMDArs. The electrostatic potential map of NR2B revealed more negative regions compared to GluR2. The primary sequence alignment of NR2B with NR2A subunits of NMDAr and GluR2 of AMPAr revealed different degrees of similarity (79% and 27% respectively). Cysteines 461, 746 and 801 were conserved in all structures while other cysteines (429, 436, 456 and 457) were present only in NR2B and NR2A. The structural study of NMDA receptor may help on designing more selective drugs to be used in neurodegenerative disorders.

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