doi 10.18699/bgrs2024-3.1-36

Neurotrophin receptors: the transmembrane domain as a key player of the receptor activation and a target for antidepressants

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Key words: neurotrophin receptor; Trk; TrkA; TrkB; P75NTR; antidepressants; fluoxetine; NMR

Motivation and Aim: Neurotrophins and their receptors are key players in the development of the vertebrate nervous system and therefore represent a target for the treatment of various neurodegenerative disorders and cancers. The neurotrophins signal through two types of cellular receptors – the Trk family of tyrosine kinases and the p75NTR. To elucidate the mechanism of receptor activation and thus to facilitate rational drug design, the three-dimensional structures are required. To date, the structures of extracellular and intracellular domains of P75 and Trk receptors have been obtained, including ligand-binding state, however, the activation process is still uncovered. The blind spot is the structure of transmembrane domains in different states. Here we present the structures of transmembrane domain of neurotrophin receptors in active and inactive states, and study the interaction of TrkB with antidepressants.
Methods and Algorithms: Cell-free protein synthesis was used to produce the transmembrane domain (TMD) of neurotrophin receptors. The proteins were purified by size-exclusion chromatography and incorporated into detergent micelles or lipid-detergent bicelles for structural studies. To solve the structures of TMD the NMR spectroscopy was employed. Functional assays were used to investigate the biological relevance of these structures.
Results: We solved the structure of TrkA TMD in an inactive state and proposed that the receptor is activated by rotation of the TMD pre-formed dimers upon NGF binding. We show that although extracellular juxtamembrane regions are unstructured, they are likely interact with ligands and thus switch the state of TMD dimer. We also solve the structure of TrkB TMD by NMR in a lipid environment. The biological relevance of this structure was verified by functional assays using mutagenesis. We showed that the conformation found corresponds to an active state of the receptor. We investigated the propensity of TrkB TMD to interact with several antidepressants and found out that drugs stabilize the TrkB TMD dimer.
Conclusion: The spatial structures of Trk TMD presented here make an important branch of the tree of knowledge required to understand the neurotrophin signaling. Our findings on TrkB/drugs interaction confirm that the TrkB TMDs are promising drug targets, and the presented NMR spectroscopy approach can be used to screen new chemical compounds.
Funding: The study was supported by the Russian Science Foundation (project No. 22-14-00130).