Human three-finger neuromodulator Lynx2 down-regulates cognition-related processes

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Human endogenous three-finger modulators of nicotinic acetylcholine receptors (nAChRs) are proteins from the Ly6/uPAR family with wide functional diversity and can play various roles in the essential processes. These proteins demonstrate structural similarity and share high structural homology with snake α-neurotoxins. Here we investigated structural and functional properties of Lynx2, one of the poorly studied members of the Ly6/uPAR family. It is known that Lynx2 is a membrane-tethered by GPI anchor protein, binds specifically to α4β2-nAChRs and is connected with anxiety-related behavior. The recombinant analog of water-soluble variant of human Lynx2 was produced in E. coli in a form of the cytoplasmic inclusion bodies with subsequent renaturation. The structure and dynamics of Lynx2 were studied by NMR in aqueous solution. Lynx2 adopts the “three-finger” fold, having a compact beta-structural core with three protruding extended loops. Magnetic beads coupled with recombinant Lynx2 specifically extracted from the total rat brain homogenate the α4, α6, and β2 subunits of nAChR and α5 and γ2 (but not β2) subunits of the GABAA-R. Analysis of the Lynx2 binding to the α1, α3, and α7 nAChR subunits did not allow to make an unambiguous conclusion about the interaction of Lynx2 with these subunits. Recombinant Lynx2 inhibited the long-term potentiation (LTP) modeling synaptic plasticity in mouse hippocampal slices. The similarity of α-Bgtx (potent selective inhibitor of a7-nAChR) and Lynx2 effects suggests that the suppression of LTP by Lynx2 can be associated with negative modulation of α7-nAChR. Treatment by recombinant Lynx2 also demonstrated down-regulation of the spine number and mRNA expression of α7, α4 and β2 nAChR subunits, synaptophysin, and synapsin 1 in rat hippocampal neurons. Altogether these data point to the negative Lynx2 influence on cognition-related processes. Study was supported by the Russian Science Foundation (Project № 19-74-20176).