INVESTIGATIONS OF ACONITUM AND DELPHINIUM ALKALOIDS OF CURARE-LIKE ACTIVITY. QSAR AND COMPUTER MODELING STUDIES OF ALKALOIDS BINDING TO AChBP

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Abstract: Early studies have shown that some of diterpenoid alkaloids, found in highly toxic plants of the genera Aconitum and Delphinium are of curare-like activity and, therefore, act at neuronal nicotinic acetylcholine receptors (nAChRs) and exhibit potent N-cholinolitic activity. N-AChRs are involved in neuropsychiatric disorders such as Parkinson’s and Alzheimer’s diseases, epilepsy and schizophrenia. Recently resolved X-ray structures of Acetylcholine-binding protein (AChBP), homolog of the ligand binding domain (LBD) of nAChR, serve as a good template for modeling new drug molecules of high selectivity. Alkaloids from our collection have been investigated by means of molecular docking and QSAR approaches. The crystal structure of AChBP complexed with methyllycaconitine (MLA) has been used as a model for computational investigations of the ligand-receptor interactions. The alkaloid-AChBP complexes were built and analyzed by docking each alkaloid from the series into the binding site of MLA. QSAR analysis on N-cholinolitic activity of studied alkaloids has been performed applying BuildQSAR program. Molecular docking calculations revealed a good affinity of the curare-like Aconitum and Delphinium alkaloids to the MLA-site. Alkaloid-AChBP complexes are stabilized by formation of H-bonds with some residues (190 Cys, 188 Tyr) located in the binding pocket. The calculated binding energies are in quite good correlation with biological activity data and increase in the following order: OH<OHCH₃<OAc<OAr. However, alkaloids with -OAr substitution at C-1, C-6 and C-14 are shown to acquire different orientation from MLA. Our results show that obtained models are able to provide insight of drug-nAChR interactions. A crucial role of some aminoresidues within the MLA binding pocket has been demonstrated by their ability to form H-bonds with ligand molecules. Different orientation of some diterpenoid alkaloids (with -OAr at C1, C-6, C-14) from the one of MLA can probably explain their lower curare-like activity but increased ability to bind to sodium ion channel. A number of QSAR models with “drug-likeness” descriptors have also been obtained and discussed in terms of their relativity to the mode of toxic action exhibited by the alkaloids.

Key words: Alkaloids, QSAR, toxicity, curare-like activity, N-AChR-binders

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