Four naturally occurring, lipid-soluble compounds are used in pharmacological tests to probe the mechanism of the passage of sodium ions across membranes in electrically excitable nerve and muscle cells. These four neurotoxins, acoline, veratridine, grayamoxin and batrachotoxin, come from different plant or animal sources; yet, all exhibit the same effect on sodium channels. These toxins affect the activation or opening step in the overall ion transport process causing the membrane to remain depolarized. Structure-activity studies on the toxins have shown a high degree of specificity. Binding studies with radiolabeled batrachotoxin have shown that the toxins bind competitively at a single receptor site. A comparison of the structural characteristics of the molecular interactions of these molecules with their common receptor may explain some of the molecular events involved in gating ions through channels.

The results of X-ray crystal structure analysis of acoline, grayamoxin III, α-dihydrograyamoxin II, and veratridine have been compared to batrachotoxin (Karle and Karle, Acta Crystallogr. Sect. B (1969) 225, 426-434) to determine the common structural components that enable them to bind to a single polypeptide site. The polycyclic, inflexible backbones of these toxins produce a fixed conformation for each compound type. This characteristic has been used in molecular supersitions to construct a map of the space occupied by these ligands. The model developed by this method explains much of the structure-activity data for the neurotoxins and suggests some of the amino acid residues present in the activation receptor site. This work was supported by the Alberta Heritage Foundation for Medical Research and the Medical Research Council of Canada (MA-8087).

Cardiac steroids represent a major class of medications widely used in the treatment of congestive heart failure. They are also specific inhibitors of Na⁺,K⁺ ATPase, the enzyme which mediates the cellular sodium pump and has been considered as the putative receptor for these drugs.

The structural and conformational characteristics of a series of cardiac steroid analogs (genins) and their glycoside derivatives have been determined from analysis of crystal structure results and molecular mechanics calculations in order to explore the relationship between their structure and biological activity. The A, B and C ring in the steroid backbone remain essentially conformationally invariant in all the structures, while the D rings show a high degree of flexibility. The conformational characteristics of the C17α side groups on the various analogs do not seem to be significantly affected by the nature of the C3 glycoside substituent. The bonds linking the steroid to the sugar moieties show a surprisingly small range of rotational freedom. The C2–C1–C17α torsion angles range only over 29° in ten crystal structures, while the C1–C2–C3–C4 torsion angles range over 115.6°. A comparison of the structural characteristics of the "active" conformations of these analogs and their derivatives with their potency as hog kidney Na⁺,K⁺ ATPase inhibitors, reveals that the same type of linear relationship observed for the genins exists for the glycoside derivatives. Thus, when the positions of the carbonyl oxygen on the C17α side group of the cardiac steroid analogs relative to that oxygen on digitoxigenin are compared to their strength as Na⁺,K⁺ ATPase inhibitors using regression techniques, a linear correlation with an r² of 0.93 is observed. The addition of the sugar substituent enhances the potency over that of the genins in a structurally specific way. The potencies of those analogs derivatized with a sugar, such as α-D-galactose, containing a 4'-axial hydroxyl group or a blocked 4'-equatorial oxygen sugar, such as α-D-digitoxose acetamide, have their inhibition strength increased systematically by a factor of about 2, while those derivatized with a sugar, such as β-D-digitoxose or β-D-glucose, containing a 4'-equatorial hydroxyl have their activities increased by about a factor of 10. These results indicate that the orientation and nature of the 4' substituent on the sugar moiety of the cardiac glycoside is directly involved in the enhancing process.

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