03. CRYSTALLOGRAPHY IN BIOCHEMISTRY AND PHARMACOLOGY

03.1-5 STRUCTURE-ACTIVITY RELATIONSHIPS OF BIPSYDINE INOTROPIC CARDIAC AGENTS. Vivian Cody and Joe Luft, Medical Foundation of Buffalo, Inc., 75 High St., Buffalo, NY 14211, USA.

Milrinone [2-methyl-5-amino-(3,4′-bipyridin)-6(1H)-one] (A) and amrinone (B) are members of a new class of oral nonglycosidic, noncatecholamine cardiac positive-inotropic agents developed for the treatment of congestive heart failure. These bipyridine inotropic agents strengthen myocardial contraction by increasing the availability of intracellular calcium. We have reported that milrinone, but not amrinone, shares structural homology with thyroid hormone and like thyroid hormone, stimulates rabbit myocardial membrane Ca2+-ATPase activity as shown by Ca2+-dependent ATP hydrolysis in vitro (Hylotte et al., Proc. Natl. Acad. Sci. USA, 82, 7974 (85)). Comparison of these molecular structures showed that there are structural homologies between the phenolic ring of thyroxine and the substituted ring of milrinone, not shared by amrinone. To further delineate the structural features required for this activity, the crystal structures of a number of milrinone analogues were investigated and are compared with the reported structures of amrinone and milrinone (Cody, Acta Cryst., in press: Robertson et al., J. Med. Chem. 29, 635 (86)). The following inotropic agents (C–P) have been studied to determine the conformational aspects of drug specificity. (C) 2-methyl-(3,4′-bipyridin)-6(1H)-one (C16H11NO, P1, a = 4.3, b = 7.574 (1), c = 11.132 (2), y = 113.47(2), y = 94.90(1)), (D) 2-methyl-5-bromo-(3,4′-bipyridin)-6(1H)-one (C16H11NOBr, P21, a = 4.3, b = 7.269 (2), c = 12.787(4), a = 97.27(3), y = 92.27(4), y = 113.74(2)), (E) 2,3-dimethyl-5-cyano-(3,4′-bipyridin)-6(1H)-one (C16H11NOBr, P21, a = 4.3, b = 7.269 (2), c = 12.955 (3), y = 19.814 (3), a = 97.27(4)), (F) 2,3-dimethyl-5-cyano-(3,4′-bipyridin)-6(1H)-one (C16H11NO, P21, a = 4, b = 7.2993 (8), c = 11.132 0, y = 94.90(1)).

The biochemical data for these compounds show that only the bromo analogue (D) and a 2-methyl analogue (E) are active in this myocardial system. Structural analysis of the N-methyl analogues (R2 = Me) show the largest variation in the twist angle. There is an N-H…O hydrogen bond in D and E. These data show that the presence of the 2-methyl substituent favors the bipyridine rings to adopt a twist conformation which is favorable for Ca2+-ATPase enzyme activity. The nature of the 2-substituent is less critical through these results suggest that a functional group that can mimic iodine in either size or electrochemical properties is preferred. Thus, a 2-methyl for enzyme stabilization include a 2-methyl for a twist conformation, a free 3-N position, and a 5-substituent.

03.1-6 THE SPATIAL ARRANGEMENT OF IMPORTANT MOLECULAR FEATURES IN CLASS I ANTIARRHYTHMIC AGENTS. By Marek L. Glowka and Penelope W. Codding, Departments of Chemistry and Pharmacology and Therapeutics, University of Calgary, Calgary, Alberta, Canada.

Class I antiarrhythmic agents control irregular heart beat in cardiac disorders by binding to sodium channels and slowing conduction velocity. Class I agents are characterized by three structural units: (a) an aromatic ring that can intercalate between the alkyl chains of phospholipids, (b) an amino group that can ionize under biological conditions, and (c) a linkge region between (a) and (b) that contains a hydrogen bonding group. In this work, the optimal three dimensional arrangement of these crucial features has been sought through X-ray crystallography, molecular mechanics calculations and structural correlations. Two series of synthetic antiarrhythmic agents, one based on the 2,6-bis[1-pyrroldinylmethyl]phenol moiety (A) and one based on 2,2,5,5-tetramethyl-3-pyrrolino-3-carboxamide (B) are being characterized. These structures have been compared to those of the traditional local anesthetics like disopyramide (C), quinidine, procainamide, lidocaine and mexiletine to identify the stereochemical requirements for arrhythmia control. These comparisons have been extended by calculating the potential energy surface for both anesthetics (mexiletine) and synthetic compounds (A). Comparisons of the low energy conformers of the active agents thus described indicate that, while flexibility is an important feature of these drugs, there are specific ranges for the distances between the three crucial groups mentioned above. Class I antiarrhythmic drugs have been divided into three subclasses according to the rate of recovery from channel block. We find that the separations between the three molecular features are different for each of these subclasses. Thus, Class I antiarrhythmic activity may be dependent on an induced fit of these flexible agents to a receptor. The similarity in the general three dimensional shape and functionality of these agents suggest that a common receptor mediates the antiarrhythmic action; these findings will be used to propose a model for this receptor site. Crystal data: A: N-[4-hydroxy-3,5-bis[1-pyrroldinylmethyl]phenyl]-2-methyl-benzamide, C23H19NO-HCl, orthorhombic, A = 10.882(2), b = 29.115(3), c = 11.092(1), c = 223K, Z = 8, R = 0.042, Rm = 0.043. B: N-[4-N-ethylaminomethyl)-2,2,5,5-tetramethyl-3-pyrrolino-3-carboxamide, C21H28N3O4HCl•2CH3OH, triclinic, P1, a = 6.995(1), b = 7.692(2), c = 12.154(4), β = 92.27(4). Structural analysis of the three molecular features A, B and C shows that the structural elements of the active agents are shared by amrinone. To further delineate the structural features required for this activity, the crystal structures of a number of milrinone analogues were investigated and are compared with the reported structures of amrinone and milrinone (Cody, Acta Cryst., in press: Robertson et al., J. Med. Chem. 29, 635 (86)).