Journal of Medicinal Chemistry

Volume 30, Number 2 February 1987

Perspective

In Search of the Digitalis Replacement

P. W. Erhardt

Department of Medicinal Chemistry, Berlex Laboratories, Cedar Knolls, New Jersey 07927. *Received April 4, 1986*

Congestive heart failure (CHF) occurs when the ventricle is unable to provide an adequate cardiac output to meet the metabolic demands of the body[1] and is characterized by congestion of the pulmonary or systemic circulation due to increases in venous pressure.[2] As CHF progresses to stages III and IV[3] its prognosis is generally poor because the compensatory mechanisms available to the heart are usually exhausted.[4-6] More than 3 million Americans are affected by the disease with approximately 250 000 new cases occurring each year.[7] Recently, it has been suggested that CHF is the most prevalent cause of death in hospitalized patients.[4]

Digitalis and its related cardiac glycosides such as digoxin, and digitoxin, have been employed in the treatment of CHF for nearly 2 centuries.[8] The action of these compounds as positive inotropes (increase the force of contraction of heart muscle) exemplifies the class of therapeutic agents commonly referred to as cardiotonic (CT) drugs. As shown in Figure 1, it is thought that glycosides (a) bind to cell membrane (b) Na,K-ATPase (c) and inhibit the pumping of Na^+ out of the cell. An increased intracellular Na^+ concentration then increases Na^+/Ca^{2+} exchange (d) or, alternatively, increases the displacement of Ca^{2+} from membrane-associated Ca^{2+} pools (e).[9] Increased intracellular Ca^{2+} concentration is directly associated with increased contraction[10] as shown in Figure 2 and described in its related text. Unfortunately, the toxicity of the cardiac glycosides limits their utility as CT drugs.[11,12] Most[13] investigators engaged in Na,K-ATPase research agree that the toxic effects of the glycosides, like their positive inotropic actions, are intimately related to their binding to the Na pump.[9] This situation has led to an arduous search, on the part of the pharmaceutical industry, to find a non-glycoside "digitalis replacement". Finally, this search may be coming to an end since there are now several new CT drugs undergoing clinical study for the treatment of CHF. However, it appears that in most cases the initially desired target, a selective positive inotropic agent similar to digitalis, has been replaced by drugs that have a mixed inotropic-vasodilator profile. This Perspective examines how this search has led to the present drug candidates and briefly discusses possible new approaches for the design of CT agents based upon recent biochemical and mechanistic considerations. It will not discuss the use of diuretics and pure vasodilators, both of which modify the vascular complications of the disease, and although increases in cardiac output may also be obtained through the use of these latter drugs, by strict definition they should not be regarded as CT agents.

The cAMP Cascade and Cardiac Muscle Contraction

Since the initial[14] designation of adenosine 3′,5′-monophosphate (cAMP) as a second messenger,[15] details of its various intracellular actions have been extensively characterized. Several reviews dealing with cAMP in the heart are available.[16-19] The cascade or sequence of events

(1) Wood, P. W. *Diseases of the Heart and Circulation*, 2nd ed.; Lippincott: Philadelphia, 1956.
(2) Killip, T. *Am. J. Cardiol.* **1985**, *56*, 2A.
(3) Classification of the degree of heart failure advocated by the New York Heart Association and commonly used by physicians.
(4) Braunwald, E.; Mock, M. B.; Watson, J. T., Eds. *Congestive Heart Failure: Current Research and Clinical Applications*; Grune and Stratton: New York, 1982.
(5) Braunwald, E.; Sonnenblick, E. H.; Chakrin, L. W.; Schwartz, R. P. Eds. *Milrinone: Investigation of New Inotropic Therapy for Congestive Heart Failure*; Raven: New York, 1984.
(6) Braunwald, E., Ed. *Heart Disease: A Textbook of Cardiovascular Medicine*, 2nd ed.; W. B. Saunders: Philadelphia, 1984.
(7) Braunwald, E. *Am. J. Cardiol.* **1985**, *56*, 1B.
(8) Withering, W. *An Account of the Foxglove and Some of its Medical Uses: With Practical Remarks on Dropsy and Other Diseases*, In *Cardiac Classics*; C. C. Mosby: St. Louis, 1941 (original publication, 1785). For a recent review, see the October issue of *J. Clin. Pharmacol.* (**1985**, 25).
(9) Hansen, O. *Pharmacol. Rev.* **1984**, *36*, 143.
(10) Allen, D. G.; Blinks, J. R. *Nature (London)* **1978**, *273*, 509.
(11) Bowman, W. C.; Breckenridge, A. M.; Sartorelli, A. S., Eds. *Pharmacology and Therapeutics*, Pergamon: Elmsford, NY, 1982; Vol. 18.
(12) Storstein, L.; Taylor, S. H. *Herz* **1983**, *8*, 1.
(13) Of interest is the recent report where dramatic improvements in therapeutic index were obtained for certain methyl derivatives of digitoxigenin: Wiesner, K.; Tsai, T. Y. R.; Kumar, R.; Sivaramakrishnan, H. *Helv. Chim. Acta* **1984**, *67*, 1128.
(14) Sutherland, E. W.; Rall, T. W. *Pharmacol. Rev.* **1960**, *12*, 265.
(15) Robison, G. A.; Butcher, R. W.; Sutherland, E. W. *Cyclic AMP*; Academic: New York, 1971.
(16) Langer, G. *Ann. Rev. Physiol.* **1973**, *35*, 55.
(17) Tsien, R. H. *Adv. Cyclic Nucleotide Res.* **1977**, *8*, 363.
(18) Katz, A. M. *Physiology of the Heart*; Raven: New York, 1977.
(19) England, P. J.; Pask, H. T.; Mills, D. *Adv. Cyclic Nucleotide Res.* **1984**, *17*, 383.

0022-2623/87/1830-0231$01.50/0

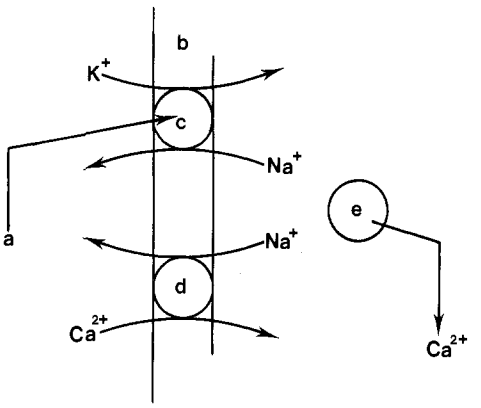


Figure 1. The Na,K-ATPase and Na/Ca exchange systems and the mechanism of the digitalis glycosides: (a) digitalis glycoside inhibits, (b) sarcolemma, (c) Na,K-ATPase, (d) Na/Ca exchanger acting in a reverse direction to reduce rising intracellular Na^+ concentration, and (e) sarcoplasmic reticulum releasing Ca^{2+} as a result of a rising intracellular Na^+ concentration.

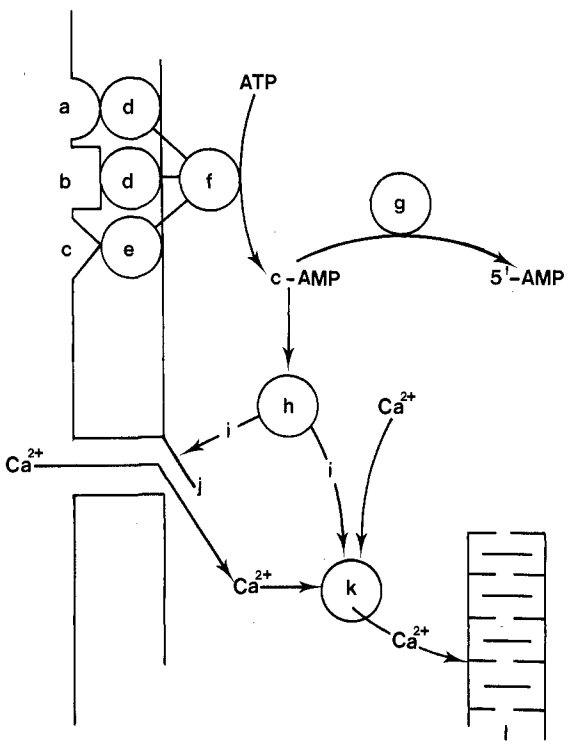


Figure 2. The cAMP cascade in a cardiac muscle cell: (a) β_1-adrenergic receptor, (b) H_2-histaminergic receptor, (c) muscarinic cholinergic receptor, (d) regulatory component, (e) inhibitory unit, (f) catalytic component (d–f comprise the adenylate cyclase complex), (g) phosphodiesterase, (h) protein kinase, (i) phosphorylation of various proteins, (j) Ca^{2+} channel gate, (k) sarcoplasmic reticulum, (l) contractile proteins.

between extracellular stimulation and contraction of a cardiac muscle cell are depicted in Figure 2. Stimulation of either β_1-adrenergic receptors (a) or H_2-histaminergic receptors (b) activates the catalytic component (f) of the adenylate cyclase complex through close association of these cell surface receptors with the cell membrane bound adenylate cyclase regulatory component (d). Since this enzyme system is responsible for the conversion of ATP to cAMP, its activation results in increased cellular concentrations of cAMP. Higher intracellular cAMP concentrations leads to greater interaction of cAMP with the regulatory subunit of protein kinase (h), which, in turn, increases its catalytic activity and causes enhanced phosphorylation (i) of various cellular proteins. Two of these proteins are of particular importance for cardiac muscle contraction. Phosphorylation of specific proteins associated with the Ca^{2+} channel in the sarcolemma[20] enhances the slow channels responsiveness to voltage activation (prolongs the gates (j) open time), which results in a greater influx of Ca^{2+}.[21] The entering Ca^{2+} is thought to act as a trigger[22] for release of intracellular Ca^{2+} stored in the sarcoplasmic reticulum (k). This released Ca^{2+} subsequently causes contraction through direct interaction with the contractile proteins (l). Phosphorylation (i) of specific proteins associated with the sarcoplasmic reticulum (k) allows for a more rapid and increased re-uptake of Ca^{2+} after a contractile event has occurred. Thus, when intracellular cAMP levels are raised, both the rate of contraction (df/dt) and the rate of relaxation ($-df/dt$) are increased and the shape of the resulting contractile force/time curve retains its symmetry. The latter is useful for characterizing the mechanism of compounds suspected to act on the cAMP cascade. Two important regulatory systems are also depicted in Figure 2. At least one consequence of stimulating muscarinic cholinergic receptors (c) is to decrease the conversion of ATP to cAMP[23] through association of these receptors with an inhibitory component (e) of the adenylate cyclase complex. Similarly, the degradative enzyme phosphodiesterase (g; PDE III) decreases intracellular cAMP by converting it to 5′-AMP. A recent Perspective has discussed the various PDE isozymes.[24]

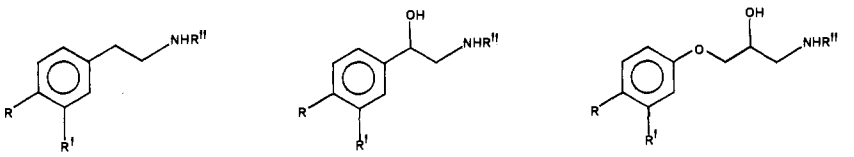
From this cascade there are several points of access for which increases in the end product, cardiac muscle contraction, can be attempted. As these pathways have become elaborated, attention has shifted from approaches involving interaction with cell surface receptor systems to mechanisms involving specific interaction with the various intracellular components.

Interaction with Cell Surface Receptors

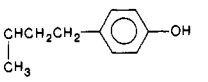
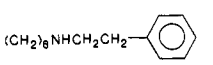
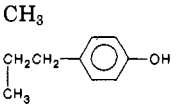
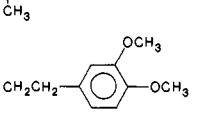
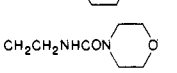
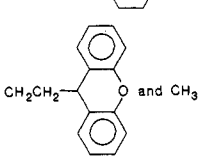
Some of the first attempts to replace the cardiac glycosides involved drugs that were intended to activate β_1-adrenergic receptors.[25] These drugs have shown initial promise when given by the intravenous (iv) route for short durations of infusion and are still useful as inotropes when such therapy is required.[26] However, their use in CHF, which requires long-term oral administration, seems precluded by the tachyphylaxis that generally becomes apparent after their continued iv administration.[27,28] In addition, as CHF progresses, the β-adrenergic receptors appear to down-regulate[29] with the cascade becoming less sensitive to stimulation even from endogenous catecholamines.[30–32] While most of the industry has turned away

(20) Reuter, H.; Scholz, H. *J. Physiol. (London)* **1977**, *264*, 49.
(21) Opie, L. H., Ed. *Calcium Antagonists and Cardiovascular Disease*; Raven: New York, 1984.
(22) Fabiato, A.; Fabiato, F. *Ann. Rev. Physiol.* **1979**, *41*, 473.
(23) Delhaye, M.; De Smet, J. M.; Taton, G.; De Neef, P.; Camus, J. C.; Fontaine, J.; Waelbroeck, M.; Robberecht, P.; Christophe, J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1984**, *325*, 170.
(24) Weishaar, R. E.; Cain, M. H.; Bristol, J. A. *J. Med. Chem.* **1985**, *28*, 537.
(25) Broadley, K. J.; Anton, J. *Pharmacology* **1982**, *2*, 119.
(26) Rae, A. P.; Tweddel, A. C.; Hutton, I. *Herz* **1983**, *8*, 23.
(27) Unverferth, D.; Blanford, M.; Kates, R. E.; Leier, C. V. *Am. J. Med.* **1980**, *69*, 262.
(28) Lambertz, H.; Meyer, J.; Erkel, R. *Circulation* **1984**, *69*, 298.
(29) Galant, S. P.; Duriseti, L.; Underwood, S.; Insel, P. A. *N. Engl. J. Med.* **1978**, *299*, 933.
(30) Bristow, M. R.; Ginsburg, R.; Minobe, W.; Cubicciotti, R. S.; Sageman, W. S.; Lurie, K.; Billingham, M. E.; Harrison, D. C.; Stinson, E. B. *N. Engl. J. Med.* **1982**, *307*, 205.
(31) Bristow, M. *N. Engl. J. Med.* **1984**, *311*, 850.

Table I. Inotropic Drugs That Activate β_1-Adrenergic Receptors[a]



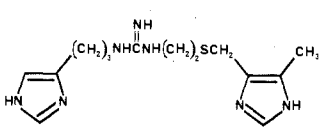
2–5 6, 7 1, 8, 9

drug	R	R′	R″	ref to clinical use in heart failure
1 (prenalterol)	OH	H	$CH(CH_3)_2$	34, 35
2 (dopamine)	OH	OH	H	26
3 (dobutamine)	OH	OH		26
4 (dopexamine)	OH	OH		36
5 (ibopamine)	$OCOCH(CH_3)_2$	$OCOCH(CH_3)_2$	CH_3	37, 38
6 (butopamine)	OH	H		39
7 (denopamine)	OH	H		40, 41
8 (xamoterol)	OH	H		42, 43
9 (doxaminol)[b]	H	H		44, 45

[a] Although most of these agents have actions at several different receptors, their inotropic effect can be attributed to either direct and/or indirect activation of β-adrenergic receptors. For example, **2** and **5** are probably inotropic selective due to their ability to effect preferential release of norepinephrine over the ventricle.[46] Several β_2-selective adrenergic agonists have also been used to treat heart failure. These are not included in this list because their primary action is likely to be vasodilation and afterload reduction with a lessor degree of direct positive inotropy. Similarly, highly selective dopaminergic compounds, which are thought to lack involvement with β-receptors, have been excluded. [b] This compound is a tertiary rather than secondary amine.

from this approach,[33] some work in this area has continued. These efforts have mostly dealt with attempts to address the poor oral bioavailability associated with the catecholamine nucleus typically present in β-adrenergic agonists. Several β-adrenergic CT compounds under development for use in CHF are listed in Table I.

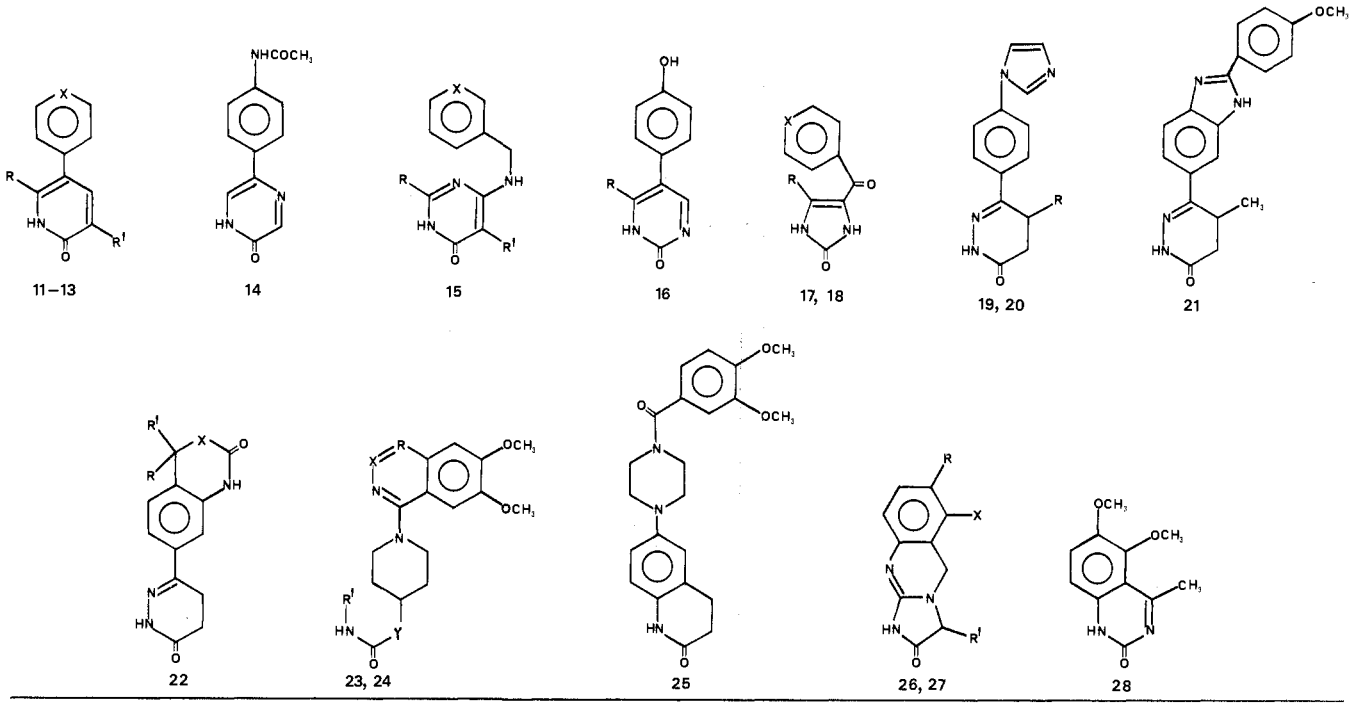
Alternatively, with regard to histaminergic receptors, it appears that they do not down-regulate as CHF progresses.[47-49] This, then, would be a new and possibly more viable cell surface avenue for effecting longer term therapy. Other authors have similarly suggested that "H_2-agonists represent a promising alternative to β-adrenergic stimulation in the medical management of cardiac decompensation".[50] Impromidine, **10**, is a potent and



10 Impromidine

(32) Bristow, M. R. *Int. J. Cardiol.* **1984**, *5*, 648.
(33) It should be noted that there may be a resurgence of interest in this area since preliminary data (results conveyed at the ASPET–ACS MC Meeting in Boston during Aug 1985) suggest that on/off dosing regimens with a β-adrenergic agonist are able to effect week-long periods of therapy between doses. This concept has recently been reviewed: Maskin, C. S. *Heart Failure* **1986**, June/July, 117.
(34) Graffner, C.; Hoffmann, K. J.; Johnsson, G.; Lundborg, D.; Ronn, O. *Eur. J. Clin. Pharmacol.* **1981**, *20*, 91.
(35) Dahlstrom, V.; Graffner, C.; Johnsson, U.; Hoffmann, K. J.; Karlsson, E.; Lagerstrom, P. O. *Eur. J. Clin. Pharmacol.* **1983**, *24*, 495.
(36) Brown, R. A.; Farmer, J. B.; Hall, J. *Br. J. Pharmacol.* **1984**, *81*, 10P.
(37) Dei Cas, L.; Manca, C.; Bernardini, B.; Vasini, G.; Visioli, O. *J. Cardiovasc. Pharmacol.* **1982**, *4*, 436.
(38) Dei Cas, L.; Bolognesi, R.; Cucchini, F.; Fappani, A.; Riva, S.; Visioli, O. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 249.
(39) Nelson, S.; Leider, C. V. *Curr. Ther. Res.* **1981**, *30*, 405.
(40) Kino, M.; Hirota, Y.; Yamamoto, S.; Sawada, K.; Moriguchi, M.; Kotaka, M.; Kubo, S.; Kawamura, K. *Am. J. Cardiol.* **1983**, *51*, 802.
(41) Thormann, J.; Kramer, W.; Kindler, M.; Neuss, H.; Bahawar, H.; Schlepper, M. *Am. Heart J.* **1985**, *110*, 426.
(42) Pouleur, H.; Rousseau, M. F.; Mengeot, P. *Eur. Heart J.* **1982**, *3* (Suppl D), 123.
(43) Snow, H. M.; Nuttall, A.; Marlow, H. F.; Dawes, P. M. *Clin. Sci.* **1983**, *64*, 4P.
(44) Whiting, B.; Kelman, A. W.; Sumner, D. J.; Hillis, W. S.; Ledermann, H. *Br. J. Clin. Pharmacol.* **1982**, *13*, 529.
(45) Bodigheimer, K.; Ischinger, T.; Nowak, F. G.; Delius, W. *Z. Kardiol.* **1983**, *72*, 48.
(46) Gorczynski, R. J.; Anderson, W. G.; Erhardt, P. W.; Stout, D. M. *J. Pharmacol. Exp. Ther.* **1979**, *210*, 252.
(47) Baumann, G.; Mercader, D.; Felix, S. B.; Loher, U.; Ludwig, L.; Sebening, H.; Hagl, S.; Sebening, F.; Blomer, H. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 618.
(48) Baumann, G.; Felix, S. B.; Ries, G.; Loher, U.; Ludwig, L.; Blomer, H. *J. Cardiovasc. Pharmacol.* **1982**, *4*, 542.
(49) Bristow, M. R.; Ginsburg, R.; Minobe, W.; Cubicciotti, R. S.; Sageman, W. S.; Lurie, K.; Billingham, M. E.; Harrison, D. G.; Stinson, E. B. *N. Engl. J. Med.* **1982**, *307*, 205.

Table II. Inotropic Drugs That Inhibit cAMP Phosphodiesterase and Very Closely Related Structures under Preclinical Development



drug	X	R	R′	ref to PDE inhibn (or to general pharmacology)	ref to clinical use in heart failure
11 (amrinone)	N	H	NH_2	24, 56, 57	57
12 (milrinone)	N	CH_3	CN	58	
13 (APP-201533)	CH	CH_3	NH_2	(62)[a]	
14 (SKF-94120)				(63)	
15 (pelrinone)	N	CH_3	CN	64 (65)	66
16 (BDF-8634)		CH_2CH_3		67[b]	67
17 (piroximone)	N	CH_2CH_3		68 (69)	70, 71
18 (enoximone)	$CHSCH_3$	CH_3		72 (69)	73–75
19 (imazodan)		H		76 (77)	78
20 (CI-930)		CH_3		76 (77, 79)	
21 (pimobendan)[c]				80, 81	82
22 (LY-195562)[d]	CH_2	H	H	83	
23 (buquineran)[e]	CH	N	$(CH_2)_3CH_3$	84	85
24 (carbazeran)[e]	N	CH	CH_2CH_3	86	86
25 (OPC-8212)				87	
26 (quazinone)	Cl	H	CH_3	88	89
27 (RS-82856)	H	R[f]	H	90	
28 (ORF-16600)				91	

[a] This compound is thought to increase intracellular Ca^{2+} sensitivity (see separate discussion of this topic). [b] This compound is also claimed to have selective α_1-blocking properties (vasodilation). [c] The O-demethylated analogue (UD-CG-212) is also a PDE inhibitor[81] and is under preclinical development. [d] Several related analogues (LY-181512, X absent and R = R′ = H; LY-195114, X = CH_2CH_2 and R = R′ = H; and LY-195115, X absent and R = R′ = CH_3) form a family from which at least one compound is likely to be developed for the clinic. [e] In buquineran, Y = –NH–, and in carbazeran, Y = –O–. [f] $O(CH_2)_3CON(CH_3)C_6H_{11}$.

selective H_2-agonist which has been studied for its cardiovascular effects in man. Even in catecholamine-insensitive congestive cardiomyopathy, significant improvement of myocardial function was attained after treatment with **10**.[51] However, at least three challenges become apparent when considering H_2-agonists as potential new CT drugs: (1) achieving selective cardiovascular actions over H_2-receptor mediated gastric acid secretion; (2) achieving cardiac selectivity over vascular and respiratory actions; and (3) achieving selective positive inotropic activity over heart rate (chronotropic) increases.[52] Of these challenges, the first one is a significant problem for which the literature is surprisingly sparse. Despite the immense interest in the H_2-mediated gastric acid system and literature for H_2-antagonists in that regard, one finds very few studies where differences in structure activity relationships (SAR) for H_2-cardiac receptors vs. H_2-gastric receptors are revealed. Such information would be very important for the design of agonist compounds that might possess the desired selectivity.

(50) Permanetter, B.; Baumann, G.; Dorner, J.; Schunack, W.; Blomer, H. *Agents Actions* **1985**, *16*, 215.

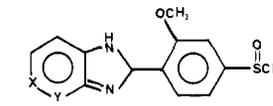
(51) Baumann, G.; Permanetter, B.; Wirtzfeld, A. *Pharmacol. Ther.* **1984**, *24*, 165.

(52) Increasing heart rate as a means of increasing peripheral blood supply in CHF is actually detrimental to therapy for several reasons. Most notable is that increasing heart rate increases the oxygen requirements of the cardiac muscle that is already in an ischemic (local situation of low oxygen supply compared to immediate tissue requirements), sickened state. While increasing inotropy also has this effect, it is less pronounced than when chronotropy is increased.

cAMP PDE Inhibitors

As initial enthusiasm about β-adrenergic approaches diminished, the industry began to search for a "non-glycosidic", "non-catechol" (non-adrenergic) digitalis replacement.[53] The first breakthrough occurred nearly 10 years ago with the finding that amrinone, 11 (Table II), was a positive inotropic agent.[53-55] Although its mechanism of action was at first unknown, it has gradually become linked with inhibition of the low-K_m, cAMP-specific PDE (PDE III).[24,56,57] Accordingly, significant attention and approaches turned toward PDE inhibition and a very large effort in this area ensued. As a result, several related types of heterocyclic compounds that inhibit cAMP PDE are now entering clinical studies for the treatment of CHF. Representative compounds are listed in Table II. Subsequently, amrinone was found to have several side effects (e.g., thrombocytopenia and gastrointestinal disturbances)[57] and it has been replaced by milrinone, **12**,[92] a close structural analogue that has considerably higher therapeutic potency. At this point it is important to emphasize

Table III. Inotropic Drugs That Are Thought To Increase Myofibrillar Ca^{2+} Sensitivity



31, 32

drug	X	Y	mechanistic (or general pharmacology) reference	clinical reference
13[a] (APP-201533)			62	
31 (sulmazole)	CH	N	100	101, 102[b]
32[c] (isomazole)	N	CH	(103)[c]	

[a] Structure shown in Table II. [b] Clinical studies have been discontinued because of tolerance and rapid metabolism after oral administration (Boehringer Ingelheim Co. communication, 1985). [c] Although the mechanism of action for this compound has not been delineated, it is included in this table because of its close structural similarity to **31**.

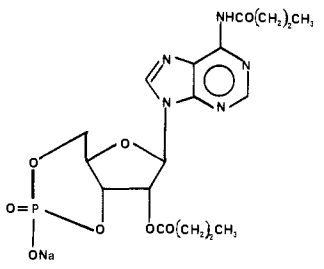
(53) Farah, A. E.; Alousi, A. A. *Life Sci.* **1978**, *22*, 1139.
(54) Benotti, J. R.; Grossman, W.; Braunwald, E.; Davolos, D. D.; Alousi, A. A. *N. Engl. J. Med.* **1978**, *299*, 1373.
(55) Alousi, A. A.; Farah, A. E.; Lesher, G. Y.; Opalka, C. J. *Circ. Res.* **1979**, *45*, 666.
(56) Weishaar, R. E.; Quade, M.; Boyd, D.; Schenden, J.; Marks, S.; Kaplan, H. R. *Drug Dev. Res.* **1983**, *3*, 517.
(57) Perry, R. S. *Drugs Today* **1984**, *20*, 381.
(58) "Milrinone is an inhibitor of c-AMP PDE, with resultant increases in cardiac c-AMP levels. However, the time course for this increase does not seem to correspond to the increase in muscle developed tension, and, therefore, it is unlikely to be responsible for the initiation of the inotropic response." Alousi, A. A.; Canter, J. M.; Montenaro, M. J.; Fort, D. J.; Ferrari, R. A. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 792.
(59) Baim, D. S.; McDowell, A. V.; Cherniles, J.; Monrad, E. S.; Parker, J. A.; Edelson, J.; Braunwald, E.; Grossman, W. *N. Engl. J. Med.* **1983**, *309*, 748.
(60) Monrad, E. S.; McKay, R. G.; Baim, D. S. *Circulation* **1984**, *70*, 1030.
(61) Benotti, J. R.; Lesko, L. J.; McCue, J. E.; Alpert, J. S. *Am. J. Cardiol.* **1985**, *56*, 685. Also: Likoff, M. J.; Weber, K. T.; Andrews, V.; Janicki, J. S.; Wilson, H.; Rocci, M. L. *Am. Heart J.* **1985**, *110*, 1035.
(62) Herzig, J. W.; Bormann, G.; Botelho, L.; Erdmann, E.; Salzmann, R.; Solaro, R. J. *J. Mol. Cell. Cardiol.* **1983**, *15* (Suppl 1), 244.
(63) Coates, W. J.; Eden, R. J.; Emmett, J. C.; Gristwood, R. W.; Owen, D. A.; Slater, R. A.; Taylor, E. M.; Warrington, B. H. *Br. J. Pharmacol.* **1985**, *84*, 22P.
(64) Out data employing homogenized canine cardiac tissue assayed for cAMP PDE inhibition suggests blocking potency comparable to milrinone, fenoximone, and CI-914.
(65) McQuillan, J.; Bagli, J.; Grimes, D.; Lee, D.; Metcalf, G. *Pharmacologist* **1984**, *26*, Abs. 204.
(66) Ayerst company communication, Feb 1984: Oral and iv formulations are in phase II clinical trials.
(67) Beiersdorf company communication, March 1985: PDE inhibitor in phase I clinical trial.
(68) Kariya, T.; Wille, L. J.; Dage, R. C. *J. Cardiovasc. Pharmacol.* **1984**, *6*, 50.
(69) Schnettler, R. A.; Dage, R. C.; Grisar, J. M. *J. Med. Chem.* **1982**, *25*, 1477.
(70) Petein, M.; Levine, T. B.; Weingarten, J.; Cohn, J. N. *Clin. Res.* **1984**, *32*, 198A.
(71) Petein, M.; Levine, T. B.; Garberg, V.; Cohn, J. N. *J. Am. Cell. Cardiol.* **1985**, *5*, 515.
(72) Kariya, T.; Wille, L. J.; Dage, R. C. *J. Cardiovasc. Pharmacol.* **1982**, *4*, 509.
(73) Arbogast, R.; Brandt, C.; Haegele, K. D.; Fincker, J. L.; Schechter, P. J. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 998.
(74) Crawford, M. H.; Richards, K. L.; Sodums, M. T.; Kennedy, G. T. *Am. J. Cardiol.* **1984**, *53*, 1051.
(75) Shah, P. K.; Amin, D. K.; Hulse, S.; Shellock, F.; Swan, H. J. C. *Circulation* **1985**, *71*, 326.
(76) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* **1984**, *27*, 1101.
(77) Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405.
(78) Mancini, D.; Sonnenblick, E. H.; Latts, J. R.; Olson, S.; Chadwick, B.; LeJemtel, T. H. *Circulation* **1984**, 70 (4, Pt. 11), Abstr 1227.
(79) *Drugs Future* **1985**, *10*, 449.
(80) Honerjager, P.; Heiss, A.; Schafer-Korting, J.; Schnosteiner, G.; Reiter, M. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1984**, *325*, 259.
(81) Meyer, W. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1984**, 325 (Suppl), R46.
(82) Thomae/Boehringer Ingelheim company communication, July 1984: Undergoing phase II clinical evaluation.
(83) Robertson, D. W.; Krsushinski, J. H.; Beedle, E. E.; Pollock, G. D.; Wilson, H.; Hayes, J. S. *Abstracts of Papers*, 190th National Meeting of the American Chemical Society, Chicago; American Chemical Society: Washington, DC, 1985; MEDI 68.
(84) Jackson, P. G.; Jackson, G.; Kitson, D.; Jewitt, D. E. *Br. J. Clin. Pharmacol.* **1978**, *5*, 7.
(85) Follath, F.; Kersting, F.; Lewis, G. R. J.; Walden, R. J.; Woolhouse, N. M.; Dollery, C. T. *Clin. Pharmacol. Ther.* **1976**, *20*, 24.
(86) Taylor, C. R.; Baird, J. R. C.; Blackburn, K. J.; Cambridge, D.; Constantine, J. W.; Ghaly, M. S.; Hayden, M. L.; McIlhenny, H. M.; Moore, P. F.; Olukotun, A. Y.; Pullman, L. G.; Salsburg, D. S.; Saxton, C. A.; Shevde, S. *Am. Heart J.* **1981**, 515.
(87) Tiara, N.; Endoh, M.; Ijima, T.; Satoh, K.; Yanagisawa, T.; Yamashita, S.; Maruyama, M.; Kawada, M.; Morita, T.; Wada, Y. *Arzneim.-Forsch.* **1984**, *34*, 347.
(88) Holck, M.; Thorens, S.; Muggli, R.; Eigenmann, R. *J. Cardiovasc. Pharmacol.* **1984**, *6*, 520.
(89) Roche company communication, Dec 1984: phase II clinical trials with quazinone (RO-13-6438) have been discontinued.
(90) Alvarez, R.; Bruno, J. J.; Jones, G. H.; Strosberg, A. M.; Venuti, M. C. *Abstracts of Papers*, 188th National Meeting of the American Chemical Society, Philadelphia; American Chemical Society: Washington, DC, 1982; MEDI 12.
(91) Falotico, R.; Moore, J. B.; Tolman, E. L.; Bandurco, V. T.; Bell, S.; Tobia, A. J. *Pharmacologist* **1985**, *27*, 679 (abstr).
(92) Milrinone is undergoing clinical study for eventual use by the oral route whereas amrinone has been limited to short-term treatment of left ventricular failure by parenteral administration.

that, in general, these compounds also exhibit pronounced vasodilator properties. In fact, it appears that amrinone, the parent or prototype compound responsible for igniting the PDE inhibitor CT area, causes only modest inotropy in CHF patients and that its predominant and principal effect is that of after-load reduction due to vasodilation.[57] While it immediately became fashionable to regard these newer CT representatives as combination inotropes with added beneficial vasodilator properties, it has not been established that the vascular profile obtained from PDE inhibition is ideally suited to effect therapy in CHF. In fact, there are few vascular agents that appear to clearly exhibit sustained therapy in CHF, one example being the angiotensin converting enzyme inhibitor family. In any case, because of their vascular activity, these compounds should not be viewed as pure inotropes, as pure CT drugs, or, in the strict sense, as digitalis replacements. Since many of these compounds are now entering the clinic, the efficacy of the mixed inotropic-vasodilator profile will soon be determined and the wisdom, on the part of the industry, for pursuing so many drug examples with this type of profile can then be evaluated.

Alternatively, it is clear that a compound having selective inotropic activity would represent a novel addition to this large group of PDE inhibitors that show combined inotropic-vasodilator properties. In this sense, it is interesting that a return to the original pharmacological target, while employing this popular biochemical mechanism, could still afford an opportunity for important new research in this area.

Analogues of cAMP

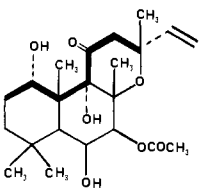
While major attention has focused on PDE inhibition, a small effort[93] has been directed toward preparing cAMP analogues with the thought that they might penetrate the sarcolemma[94] of cardiac cells and simulate the messenger roles played by cAMP. However, because of the fragile nature of cAMP and its susceptibility to PDE, work in this area has initially sought to obtain only injectable agents. At least one such compound, the dibutyryl derivative known as bucladesine, **29**, has shown promise as a combination inotrope and vasodilator after iv administration to man.[95] With this precedent, it would seem that there is now an increased need for research directed toward the poor bioavailability and problems associated with rapid degradation of these systems.



29 Bucladesine

Direct Activation of Adenylate Cyclase

The natural product forskolin, **30**, is thought to interact directly with the regulatory subunit or catalytic subunit of the adenylate cyclase system.[96,97] This compound exhibits both inotropic and pronounced vasodilator properties.[98] There are few compounds that exhibit inotropy via this type of stimulation and it would seem worthwhile to explore the SAR associated with this unique mechanism. In this regard, forskolin uniquely provides a structural template for new research that might define the minimum structural requirements for stimulation of adenylate cyclase. For instance, one approach would be to retain features and stereochemistry located along a single edge of forskolin (see darkened edge of **30**). This is based on a report[99] where binding interactions with adenylate cyclase are apparently still retained when the other edge of the molecule is attached to polymers for use in chromatography.



30 Forskolin

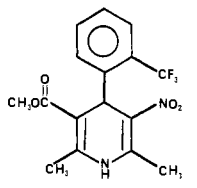
Agents Acting on Systems Closely Linked to the cAMP Cascade

For classification, agents in this category do not increase cAMP levels and the shape of their contraction curves need not retain symmetry. There are several such agents that represent new approaches toward achieving inotropy. One approach involves compounds that are thought to increase myofibrillar Ca^{2+} sensitivity. A few structural representatives for this category are shown in Table III. Sulmazole, **31**, showed initial promise in treating CHF although it has now been dropped from clinical study. Like the PDE inhibitors, the profile generally observed for these agents appears to be that of positive inotropy with significant vasodilation.

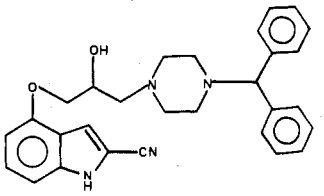
Another new area is represented by the "Ca^{2+} channel partial agonists".[104] Bay K 8644, **33**, is a representative from this category that acts primarily as an agonist.[105] Its positive inotropic activity results from its ability to promote an influx of Ca^{2+} (see Figure 2) via direct interaction with the Ca^{2+} channel. However, this compound, through the same mechanism, also causes vasoconstriction. If such compounds are to be utilized in CHF, it is clear that selectivity for cardiac muscle will be vitally important for

(93) For example, see: Miller, J. P.; Boswell, K. H.; Meyer, R. B.; Christensen, L. F.; Robins, R. K. *J. Med. Chem.* **1980**, *23*, 242 and references cited therein.
(94) Heart cells are normally highly impermeable to cAMP: Drummond, G. I.; Severson, D. L. *Circ. Res.* **1979**, *44*, 145.
(95) Reported at the *Gen. Meet. Jpn. Soc. Intensive Care* **1984**, *9*, 59.
(96) Seamon, K. B. *Drug Dev. Res.* **1985**, *6*, 181.
(97) Our biochemical studies also support the notion of a direct action since we observed increases in cAMP with no apparent PDE inhibition.
(98) Bhat, S. V.; Dohadwalla, A. N.; Bajwa, B. S.; Dadkar, N. K.; Dornauer, H.; deSouza, N. J. *J. Med. Chem.* **1983**, *26*, 486.
(99) Pfeuffer, T.; Metzger, H. *FEBS Lett.* **1982**, *146*, 369.
(100) Solaro, R. J.; Ruegg, J. C. *Circ. Res.* **1982**, *51*, 290.
(101) Hauf, G. F.; Bubenheimer, P.; Roskamm, H. *Arzneim.-Forsch.* **1981**, *31*, 253.
(102) Renard, M.; Jacobs, P.; Dechamps, P.; Dresse, A.; Bernard, R. *Chest* **1983**, *84*, 408.
(103) Robertson, D. W.; Beedle, E. E.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Wyss, V. L.; Hayes, J. S. *J. Med. Chem.* **1985**, *28*, 717.
(104) This author prefers this designation for these types of compounds that suffer from a variety of misnomers. For instance, at higher doses the so-called "agonist" Bay K 8644 can be shown to exhibit antagonist activity and lower doses of certain so-called "antagonists" can be shown to exhibit agonist properties: Thomas, G.; Gross, R.; Schramm, M. *J. Cardiovasc. Pharmacol.* **1984**, *6*, 1170.
(105) Schramm, M.; Thomas, G.; Towart, R.; Franckowiak, G. *Arzneim.-Forsch.* **1983**, *33*, 1268.

agents with this mechanism.



33 Bay K 8644



34 DPI-201106

Finally, several new compounds exhibit two or more mechanisms from which their inotropy can be derived. In addition to combinations of the mechanisms already discussed, recent studies suggest that some inotropes may, like the glycosides, increase intracellular Na^+. However, their mechanism for this effect is thought to involve prolongation of the open time for the Na^+ channel gates rather than an inhibition of Na,K-ATPase. Representative structures having this additional property include **25**[106] and **34**.[107] The inotropic polypeptide anthopleurin-A (AP-A)[108] may owe its cardiotonic effects entirely to this mechanism.[109] Compound **34** was initially thought to act by increasing myofibrillar Ca^{2+} sensitivity.[110,111] It has also been reported to have significant vasodilator effects.[112] Although their mechanism for increasing intracellular Na^+ is different from the glycosides, it would seem prudent to establish the arrhythmogenic potential (and therapeutic index) of these representatives before emphasizing major new research in this area.

Summary

There are now several new CT drugs undergoing clinical study for the treatment of CHF. While most of these new agents are like digitalis in that they possess significant inotropic activity, they differ from digitalis in that they tend to also have pronounced vasodilator properties. Such compounds, because they are not pure CT agents, should not be regarded as true digitalis replacements. Despite the increased understanding about the cAMP cascade and about cardiac muscle contraction in general, the long search for a specific digitalis replacement cannot be regarded as having been accomplished. It should also be noted that the initial clinical assessment for any of these new compounds will be complicated by the fact that they are tested in only the latter stages of CHF where prognosis is very poor and the possibility of showing significant improvement in mortality is extremely difficult. It will be unfortunate if the potential for positive inotropic agents (pure CT drugs) is compromised by clinical studies that employ mixed inotropic-vasodilator compounds in extremely sick patient populations. The continued use of the digitalis glycosides for such a long period of history implies that at least some subpopulation of CHF patients should derive benefit[113] from therapy with an appropriately selective CT drug. Neither the appropriate drug nor the appropriate specific patient population, both of which are needed to properly address the eventual role of inotropic therapy in CHF, have, as yet, been identified.

Registry No. cAMP, 60-92-4.

(106) Lathrop, D.; Schwartz, A. *Eur. J. Pharmacol.* **1985**, *117*, 391.
(107) Buggisch, D.; Isenber, G.; Ravens, U.; Scholtysik, G. *Eur. J. Pharmacol.* **1985**, *118*, 303.
(108) (a) Scriabine, A.; Van Arman, C.; Morgan, G.; Morris, A.; Bennett, C.; Bohidar, N. *J. Cardiovasc. Pharmacol.* **1979**, *1*, 571. (b) Norton, T. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1981**, *40*, 21.
(109) Kodama, I.; Shibata, S.; Toyama, J.; Yamada, K. *Br. J. Pharmacol.* **1981**, *74*, 29.
(110) Herzig, J. W.; Quast, U. *J. Mol. Cell. Cardiol.* **1984**, *16* (Suppl 3), 6.
(111) Scholtysik, G.; Salzmann, R.; Berthold, R.; Herzig, J. W.; Quast, U.; Markstein, R. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1985**, *329*, 316.
(112) Hof, R.; Hof, A. *J. Cardiovasc. Pharmacol.* **1985**, *7*, 1188.
(113) As commonly mentioned in clinical reviews, all the current drug therapies for CHF (inotropes, vasodilators, and diuretics) are palliative in that while they may provide some relief from symptoms, they are not aimed at halting the progression of the underlying disease. However, the clinical studies to determine actual reductions in mortality are subject to the same complications mentioned in this Perspective. Recent clinical reviews of drug therapy for CHF include: (a) Zelcer, A. A.; LeJemtel, T. H.; Sonnenblick, E. H. *Heart Failure* **1985**, *1*, 7. (b) Lee, W. K.; Regan, T. J. *Heart Failure* **1985**, *1*, 36. (c) Dipalma, J. R. *Clin. Pharmacol.* **1985**, *31*, 177. (d) Dollery, C. T.; Corr, L. *Br. Heart J.* **1985**, *54*, 234. (e) Lipkin, D. P.; Poole-Wilson, P. A. *Br. Med. J.* **1985**, *291*, 993. (f) Leier, C. V. *Rev. Clin. Basic Pharmacol.* **1985**, *5*, 175.