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Invited review

Cardiac ischaemia: possibilities for future drug therapy

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Summary — This review discusses some of the new avenues of research into cardiac ischaemia being explored by the pharmaceutical industry, which is one of the few areas of cardiovascular research where the industry has maintained a high level of interest. Discussion centres on the possibilities of discovering site-specific coronary vasodilator or antivasoconstrictor agents, drugs capable of restoring normal function to a damaged vascular endothelium or protecting it from ischaemia, agents with beneficial local neurohormonal modulating or metabolic effects and compounds able to modify the remodelling processes of the cardiovascular system triggered by ischaemia. The review gives a non-exhaustive list of the types of structures under investigation in each of these domains.

cardiac ischaemia / future drugs / vascular endothelium / remodelling

Introduction

Given that several classes of drugs provide very effective symptomatic relief of angina pectoris, major advances in therapy will come only with novel compounds able to modify underlying causes of the disease. This will not be easy because the aetiology of CAD is complex and the response of the heart to ischaemia multifaceted. Depending on severity, duration and precipitating factor(s), the heart reacts with acute and chronic compensatory responses to ischaemia. Furthermore, as the disease progresses, these initially homeostatic adaptations contribute to a worsening spiral of events leading to arrhythmia and death [1].

However, recent trials of lipid lowering agents in CAD patients [2], in men with hypercholesterolaemia [3] and in patients with average cholesterol levels following MI [4] have shown significant treatment-related reductions in mortality and in the risk of suffering an ischaemic event. The statins have, therefore, become the first members of a new class of causally effective agents. This review will examine other potential targets which may lead to the anti-ischaemic agents of the future but its scope will not cover the interesting approach of inducing angiogenesis to combat ischaemia [5], or the acute emergency treatment of MI with drugs like thrombolytics, thrombin antagonists, heparin derivatives and antiplatelet agents, although certain glycoprotein IIb/IIIa antagonists do hold promise for preventing the delayed ischaemia associated with restenosis following cardiac surgery (PTCA, CABG and stenting).

Pathophysiology

Cardiac ischaemia occurs when there is an imbalance between demand and supply of oxygen via the coronary arteries. The view that associates stable angina

Abbreviations – A1(2)-agonist(antagonist), A1(2)-adenosine receptor agonist(antagonist); α1(2)-agonist(antagonist), α1(2)-adrenoceptor agonist(antagonist); AMP, adenosine monophosphate; AT-II, angiotensin-II; ACE (I), angiotensin converting enzyme (inhibitor); β-blocker, β-adrenoceptor blocking agent; BP, blood pressure; CA, calcium antagonist; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; DHP, 1,4-dihydropyridine; ECG, electrocardiogram; EDRF, endothelium-dependent relaxing factor; ET, endothelin; ELAM-1, endothelial-leucocyte adhesion molecule-1; ETCE(I), endothelin converting enzyme (inhibitor); H_3-receptor, H_3-histamine receptor; HF, heart failure; hOP-1, human osteogenic protein; HR, heart rate; ICAM-1, intercellular adhesion molecule-1; IL-1 (6), interleukin-1 (6); ILGF-1, insulin-like growth factor-1; KATP, ATP sensitive potassium channel; LAD, left anterior descending coronary artery; LDL, low density lipoprotein; 5-LO, 5-lipoxygenase; MI, myocardial infarction; MMP, matrix metalloprotein; MOC, myocardial oxygen consumption; NA, noradrenaline; NHE, Na^+/H^+ exchanger; NO, nitric oxide; VCAM-1, vascular cell adhesion molecule-1; PDE (I), phosphodiesterase (inhibitor); PDGF, platelet derived growth factor; PKC, protein kinase C; PTCA, percutaneous transluminal coronary angioplasty; RAS, renin-angiotensin system; SNS, sympathetic nervous system; TGF, transforming growth factor-β; TNF, tumor necrosis factor-α.

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with fixed atherosclerotic lesions, variant angina with vasospasm and unstable angina with lesions and platelet aggregation/thrombosis, has given way to the concept of mixed ischaemia [6]. Mixed ischaemia may include contributions from all these components some time during the anginal attacks [7]. In the mixed ischaemia hypothesis residual blood flow to the heart is not fixed but fluctuates over the course of the day in response to vasomotor changes and alterations in resistance at the sites of flow-limiting stenoses. Ischaemia may result from exercise when demand exceeds the residual coronary reserve threshold or at rest during episodes of intense vasoconstriction [6].

The stenoses precipitating MI and unstable angina may be relatively minor lesions; (< 50% diameter stenoses [8–11]) and the traditional view that the outcome of CAD is closely linked to stenosis severity is also questioned by results from the recent cholesterol-lowering trials. Drug therapy whilst producing only a small reduction in stenosis severity reduced adverse cardiac events markedly by 40–80% [12]. The most likely mechanisms underlying this beneficial effect of the statins include plaque stabilisation and improvement of endothelial function thus pointing the way to new avenues for future research [12]. Plaque stability is determined by its lipid content and the density of smooth muscle cells and macrophages in the cap. Compounds able to modulate these parameters or having the ability to protect or correct the endothelial dysfunction and impaired release of NO observed in atherosclerosed blood vessels could provide alternative therapeutic strategies for the treatment of CAD.

Current therapy

The treatment of angina pectoris today relies on three drug classes, the β-blockers, the nitrates and the CAs. Whilst all provide symptomatic relief and their efficacy in angina is well established it is only β-blockers lacking intrinsic sympathomimetic activity that have so far been shown to improve prognosis in unstable angina, acute MI and during the immediate post-infarction period. With CAs the effect on prognosis depends on the CA subgroup [13] and on the presence of CHF in the patient population. Monotherapy with nifedipine in patients with unstable angina and acute MI fails to improve prognosis and there may even be a tendency towards adverse effects. Verapamil and diltiazem do improve prognosis in a subset of patients with acute infarction but no signs of CHF [14, 15]. However, in patients with signs of CHF both compounds tend to increase the rate of reinfarction and mortality. With the nitrates a trend towards improved prognosis in acute MI has been shown in some studies but data in patients with CAD is still lacking [16, 17].

One well-accepted concept having an important bearing on future therapeutics has recently been quashed. It has been known for some time that HR is an important independent predictor of adverse cardiovascular events in CAD patients [18–21]. In addition the antianginal effect of the β-blockers has often been attributed to a reduction in HR. The importance placed on HR reduction led recently to the development of a new class of drugs known as specific bradycardic agents or sinus node inhibitors. It was hoped that they would possess the beneficial effects of the β-blockers whilst lacking their untoward negative inotropic effects. The recent surprising results with zatebradine have demonstrated that this is not the case [22].

Zatebradine is a relatively selective blocker of the I_f sarcolemmal current which determines the rate of spontaneous depolarization of the sinoatrial node. Its effect is rate-dependent, reversible and selective since the compound has no effect on cardiac output, vascular resistance or on PR and QRS intervals of the ECG [23–26]. Studies in animals indicated that zatebradine possessed potential antianginal and anti-ischaemic activity [27] which was clearly linked to the bradycardia [28]. However, in a series of placebo-controlled clinical trials in effort angina, zatebradine was found to be no different from placebo and to produce no additional benefit on exercise tolerance in patients receiving nifedipine. This was in spite of a reduction in HR at rest and on exercise equivalent to that observed with a DHP + β-blocker combination, therapy which is known to have additive efficacy [29, 30].

Thus drugs reducing HR alone do not produce therapeutic benefit in patients with chronic stable angina and raise questions on the use of the HR–BP product as an indicator of potential antianginal activity [22]. They also revive questions as to the mechanism of action of β-blockers in angina and the relevance of certain animal models used to detect novel anti-ischaemic drugs.

Alternative therapeutic strategies

Whilst lowering MOC is the mainstay of current therapeutics in chronic stable angina the above clinical findings suggest alternative avenues for future research.

Targeted vasorelaxation

Symptomatic benefit could be obtained with a targeted vasodilator or antivasoconstrictor agent if it prevented the transient increases in vasomotor tone in the affected vessel segment. A generalised, sustained reduction of vascular tone is possible with current

drugs like the nitrates and CAs but this will not be optimal therapy if BP is affected. A selective, site-targeted agent able to counteract enhanced vasoconstrictor responses locally provoked by a variety of stimuli would be an interesting therapeutic target for future research [17].

One of the consequences of ischaemia is a breakdown of the high energy phosphate compound ATP to ADP, AMP, and finally to adenosine and inorganic phosphate. Adenosine, by stimulating A1-receptors, decreases the activity of adenylyl cyclase and inhibits the exocytotic release of NA. There is evidence that both adenosine and the opening of KATP channels are involved in protecting the myocardium during repeated ischaemic episodes, a phenomenon called preconditioning [31, 32]. Of great interest is the recently described remote preconditioning phenomenon where ischaemia of the gastrointestinal tract or kidney produced by clamping the mesenteric or renal arteries in rats was shown to also protect cardiac tissue from ischaemia [33]. This is a neuronally mediated effect since the ganglion blocking agent hexamethonium prevents remote cardiac preconditioning.

The basis for preconditioning is that short periods of ischaemia do not lead to irreversible cell injury but to adaptive mechanism(s) that result in resistance to a subsequent ischaemic stress. Two distinct phases of protection can be distinguished: the first phase is rapid, within minutes, pronounced and transient, the second phase takes hours to become apparent and can last for days [34, 35]. The mechanisms involved in the two phases are different. However, 10 years after its discovery the precise mechanism of preconditioning is still elusive [36]. The most compelling hypothesis developed by Downey and coworkers [37, 38] suggests that simulation of a variety of G protein-coupled receptors (eg, A1-, α1, bradykinin and ET-1 receptors) results in the activation of PKC. This in turn leads to the physical translocation of PKC from the cytoplasm to the sarcolemma where it phosphorylates a substrate protein (possibly the KATP channel) and thereby confers resistance to ischaemic injury not only to cardiomyocytes but also to the endothelial cells [39]. Support for this hypothesis comes from a wealth of studies with activators and inhibitors of PKC or its translocation process, with receptor agonists and antagonists and with agents that interfere with the signalling pathways between various receptors. Each step of this cascade is a potential target for novel anti-ischaemic agents.

Restoration of normal endothelial function

Recent findings provide evidence of complex functional modifications in the endothelium of diseased coronary arteries [17, 40]. Atherosclerotic coronary arteries lose their ability to dilate upon sympathetic activation provoked by exercise, stress and in response to acetylcholine. This is accounted for by the failure of the endothelium to produce NO and is a hallmark of hypercholesterolaemia and coronary atherosclerotic disease [41, 42]. Restoration of normal endothelial function, therefore, represents a potential target for the symptomatic and long-term treatment and control of cardiac ischaemia.

The endothelial cells of blood vessels are capable of generating several vasoactive substances including prostacyclin and a hyperpolarizing factor but the best characterised of these is NO, also known as EDRF [43, 44]. The absence of this inhibitory signal arriving from the endothelium permits exaggerated expression of vasoconstrictor stimuli and facilitates platelet aggregation [45]. NO also prevents the activation and adherence of leucocytes to damaged vessels and may also scavenge superoxide radicals [46, 47]. The coronary vascular endothelium therefore is not only a sensor of the intravascular environment but also a transducer/effector tissue capable of responding to changes in flow, BP and receptor stimulation in a variety of different ways.

However, the NO-vasodilator system is delicate and easily impaired by hypertension, oxidized LDL uptake and atherosclerotic changes to the vessel wall. Also following ischaemia and reperfusion endothelial dysfunction with reduced production of NO occurs rapidly within 2.5–5 minutes of reperfusion [48]. Coronary arteries with an intact endothelium are resistant to α1-receptor mediated vasoconstriction thus an additional constrictor element is unmasked in atherosclerotic vessels. Exaggerated constrictions to serotonin have been demonstrated angiographically in human coronary arteries at the early stages of coronary disease and evidence from animal studies also show that endothelial dysfunction occurs early in the development of atherosclerosis before evidence of structural changes to the vessel [49].

The vascular endothelium synthesises and releases the vasoconstrictor peptide ET [50]. Only the ET1 isoform of the ET family (ET1, ET2, ET3) is produced by the endothelium and is formed from a prepropolypeptide precursor by ETCE, a membrane-bound metalloendopeptidase. ET1 produces potent, long-lasting vasoconstrictor effects and also acts as a mitogen, stimulating proliferation of smooth muscle [51]. Two ET receptor subtypes, ETA and ETB have been identified and are G-protein coupled [52]. ETA receptors are located mainly on vascular smooth muscle cells and mediate vasoconstrictor responses to ET1 whereas ETB receptors are present on the endothelium and stimulation leads to transient vasodilatation indirectly through the release of NO and

perhaps other mediators. However, ETB receptor stimulation can also lead to vasoconstriction. The ET receptor mediating dilatation has been denoted the ETB1 receptor and that mediating constriction the ETB2 receptor [53].

Endothelial cells also release and are receptive to a variety of other growth regulating factors released from platelets, macrophages and smooth muscle cells [54]. In response to stimuli like PDGF, TGF, IL-1, TNF and oxidised LDL the endothelium secretes growth regulatory factors some of which may induce proliferation of the connective tissue matrix [55]. In this respect it is interesting that ILGF-I, which regulates vascular function by stimulating the release of NO from endothelial cells [56] has recently been reported to reduce myocyte death due to cardiac ischaemia-reperfusion injury in the rat [57].

Local neurohormonal or metabolic effects

Ischaemia excites certain afferent fibres in the heart which then provoke a centrally mediated increase in sympathetic tone to the periphery [58, 59]. During brief (< 10 min) occlusion of the left anterior descending coronary artery levels of NA in coronary sinus blood are not augmented [60]. This is probably because the local exocytotic release of NA is reduced by autoinhibition (negative feedback), via stimulation of prejunctional α2-receptors, and heteroinhibition, by adenosine released during the ischaemia stimulating inhibitory, prejunctional A1-receptors. In addition there is little overspill of NA due to an efficient neuronal uptake (uptake 1) process. Only with prolonged periods of ischaemia are NA levels significantly raised in sinus blood and it appears that NA is then released by a mechanism involving reversal of the uptake 1 carrier. The recent finding in human atrial tissue in vitro showing that during prolonged anoxia the α2-agonist UK 14304 and adenosine were ineffective at modulating NA release [61], whilst the uptake 1 blocker desipramine prevented overspill of NA, is consistent with such an hypothesis [62, 63]. This increase in circulating NA would favour the production of ventricular tachyarrhythmias and could contribute to extension of any myocardial necrosis. In contrast to the adaptation that occurs under normoxia, in acute myocardial ischaemia there is an increase of functionally coupled β-receptors in myocyte membranes despite elevated concentrations of NA. In addition, at least during the early phase of ischaemia, there is sensitisation of adenylate cyclase. Several mechanisms, therefore, contribute to the deleterious effects of sympathetic overstimulation in acute myocardial ischaemia [60].

Since only β-blockers lacking intrinsic sympathomimetic activity improve prognosis following MI it suggests that the mechanism responsible for this favourable effect is linked to β1-receptor blockade. It can also be speculated that the cardioprotective effect is not exclusively mediated by haemodynamic changes and that other mechanisms possibly involving local neurohormonal or metabolic actions may be involved. In this respect the recent identification of functional H_3-receptors in human heart tissue [64] may provide an additional mechanism. These receptors are quiescent under normal conditions but become activated during ischaemia when histamine is released into the coronary circulation [65]. H_3-receptor stimulation is able to modulate both the exocytotic [65] and reverse carrier-mediated NA release from sympathetic nerves associated with acute and protracted myocardial ischaemia [66] and since there is no associated negative chronotropic or dromotropic effects, H_3-agonists may have advantages over other prejunctional agonists.

Vascular and cardiac remodelling

The successful treatment of acute MI and the consequent prolongation of patient survival has led to an increase in morbidity and mortality from CHF such that it has now become a major health problem in Western Europe and the USA (eg [67]). Hypertrophy of the left ventricle is the major risk factor associated with CHF [68] and tissue remodelling, particularly myocardial fibrosis, a key pathological event [69]. Cardiovascular remodelling is an adaptive response of tissues to increased loads and occurs in hypertension and ischaemia 70. The remodelling process generally involves the release of cytokines or other soluble cell mediators and induction of the expression of a variety of genes which affect cell growth and the structure of the cytoskeleton and extracellular matrix [71, 72].

Whilst the primary target in the pharmacology of cardiovascular remodelling must be normalisation of the deranged physical variables it has been proposed that optimum pharmacotherapy must also take into account the structural abnormalities brought about by the remodelling process (ie, cellular hyperplasia and hypertrophy, extracellular matrix production, deposition and degradation [71, 72]).

Possible future therapeutic agents

Having identified several potential therapeutic drug targets this section elaborates on possible ways in which the desired effect might be achieved.

Targeted vasorelaxation

Short-lived impairments of coronary flow may come from vasoconstriction at a stenotic site in an epicardial coronary artery, from a change in tone of a resistance

vessel, or indirectly from alterations in the transmural distribution of blood flow linked to modifications in cardiac preload, afterload and wall tension. Coronary flow may also be affected by the local release of metabolites and certain neurohormonal mechanisms. There are, therefore, numerous possibilities for therapeutic intervention.

Adenosine modulating agents

Adenosine is of particular interest because it may act as a 'local hormone'. Thus metabolically stable analogues of adenosine and/or maintenance of a local high concentration of adenosine could provide anti-ischaemic agents. Inhibition of the nucleoside transporter located on the endothelium has been proposed to maintain adenosine levels and to achieve cardioprotection. Well known compounds like dipyridamole, dilazep, mioflazine and their analogues are likely to exert their anti-ischaemic effects at least in part via inhibition of the nucleoside transporter [73]. The recent cloning of the human transporter might open new perspectives in this research [74]. Ecto-5'-nucleotidase, mainly located at the endothelial surface, is also a possible target as it is a key enzyme in the production of adenosine in the interstitial compartment. Its possible role in ischaemic tolerance has recently received some experimental support [75, 76].

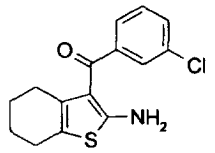
Since adenosine is a natural cardioprotective agent it has become a therapeutic target for drug discovery programmes in many pharmaceutical companies, either aimed directly at relatively selective A1-agonists, or indirectly at agents able to modulate the effects of endogenously released adenosine by blocking its uptake or enzymatic degradation. Amongst the drugs under investigation is PD 81,723 (Warner Lambert-Parke Davis) (table I), an allosteric enhancer of the A1-receptor [77], which acts by stabilising the agonist–A1-receptor–G-protein complex [78] to lower the threshold for ischaemic preconditioning [32]. This effect can be blocked by both the relatively selective A1-antagonist DPCPX (1,3-dipropyl-8-cyclopentyl-xanthine) and the KATP channel antagonist glibenclamide suggesting that these channels may mediate ischaemic preconditioning [31]. Whilst PD 81,723 had no effect on infarct size in these experiments using the dog heart, the highly selective A1-agonist PD 126,280 (Endo(s) norbornyl-adenosine, Warner Lambert-Parke Davis) has been reported to reduce infarct size and preconditioning threshold to similar extents in the micropig [79]. Other A1-agonists under study include SC 44948 (Searle) and the piperidinyl adenosine derivatives of Novo Nordisk (table I). Probably one of the most studied cardioprotective agents in this class is the adenosine regulating drug acadesine (Gensia) where results of a meta-analysis of five clinical trials in patients undergoing CABG surgery has shown that treatment with acadesine before and during surgery can reduce early cardiac death and MI [80]. Gensia also have orally active analogues such as GP-1-531 under clinical investigation and a series of terahydroimidazoldiazepine AMP deaminase inhibitors in preclinical studies (table I). These agents have been shown to improve recovery of contractile function following ischaemia and reperfusion of the heart in vitro and in vivo in a variety of animal models [81]. Cypros have patented a series of hydroxynonyladenines also as adenosine deaminase inhibitors with potent anti-ischaemic activity and Kyowa Hakko has claimed a series of quinazoline-piperazines as nucleoside transport inhibitors (table I).

Paradoxically recent research has shown that pretreatment of cat hearts with the relatively selective A1-antagonists DPCPX and bamifylline is also effective in preventing ischaemia-reperfusion injury [82]. It has been suggested therefore that the protective effects of the A1-agonists described above may be mediated by an uncoupling of the receptor from the signal transduction processes that cause cell injury following prolonged ischaemia and reperfusion [83]. This implicates A1-receptors in the injury process but opposite effects have been reported with another A1-antagonist, KW-3902 (Kyowa Hakko) (table I), which enhanced reperfusion injury [84]. This anomaly may be explained by the lower selectivity of KW-3902 for A1- relative to A2-receptors compared to DPCPX and bamifylline, which would also account for the greater efficacy of DPCPX versus bamifylline reported in the study of Neely et al [83]. Thus the greater the selectivity of the A1-antagonist for the A1-receptor in vivo, the more effective it was in preventing ischaemia-reperfusion injury in the cat heart. If confirmed in other species this opens up a possible alternative approach of adenosine receptor modulation for treating cardiac ischaemia. Since the effect of preconditioning is short-lived blocking this process with an A1-antagonist would not be expected to have significant adverse effects and such an approach would overcome the side-effect problems associated with use of adenosine agonists. As Neely et al [83] suggest such agents may have other potential therapeutic benefits during CABG, angioplasty and in conjunction with other drugs in thrombolysis.

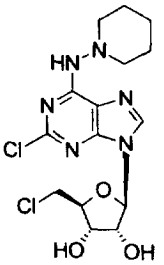
KATP channel openers

K+ channels control the resting membrane potential. The probability of the KATP channel being in the open state increases as ATP concentrations in the cell fall. KATP channels are therefore metabolically gated, blocked by magnesium ions and, as discussed in the previous section, regulated by adenosine receptors [85]. Since KATP channel opening may mediate myocardial preconditioning KATP openers have been dubbed chemical preconditioning agents [86].

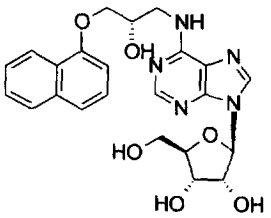
Table I. Some agents modulating the effects of adenosine which are under investigation.



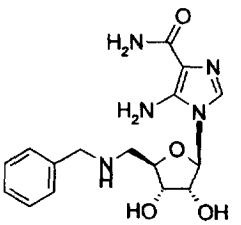
PD-81723 (Parke Davis Warner-Lambert)



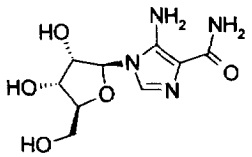
Piperidinyl adenosine (Novo Nordisk)



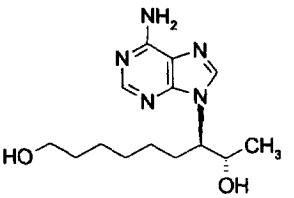
SC-44948 (Searle)



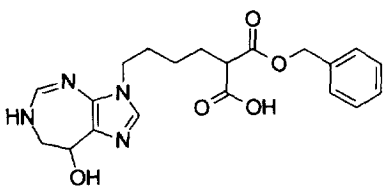
GP-1-531(Gensia)



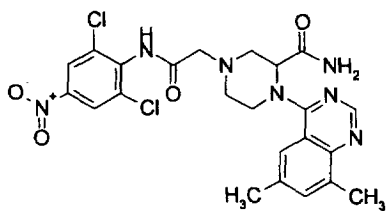
Acadesine(Gensia)



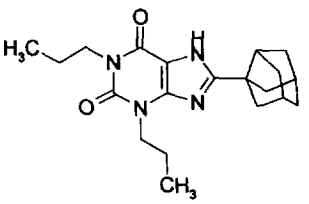
Hydroxynonyladenine (Cypros)



Tetrahydroimidazoldiazepine (Gensia)



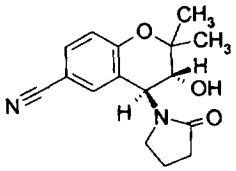
Quiniazoline piperazine (Kyowa Hakko)



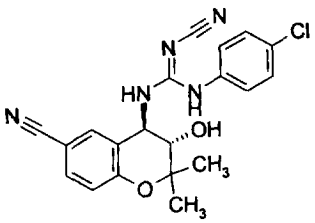
KW-3902 (Kyowa Hakko)

Following up the initial discovery of cromakalim (SK&B) [87, 88] and the therapeutic promise of this new class of drugs many companies started discovery programmes in the area (table II). Results to date suggest that the return on investment of such programmes has been disappointing since first generation drugs have not lived up to expectations. They have not proved to be therapeutic agents of worth and

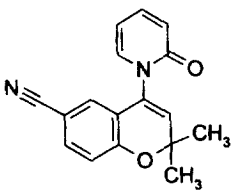
Table II. Selected KATP channel openers under investigation.



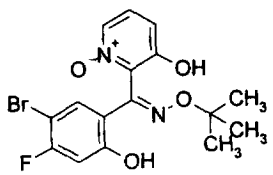
Chromokalim (Smith Kline Beechams)



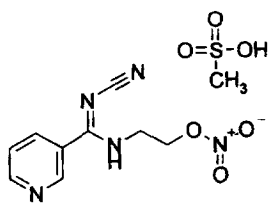
BMS-180448 (Bristol-Myers Squibb)



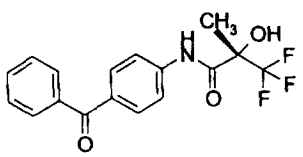
Bimakalim (Merck)



TAK-636 (Takeda)



KRN-2391 (Kirin)



ZD-6169 (Zeneca)

their mechanism of action is linked to potentially serious side-effects. Nevertheless some companies have persevered with projects aimed at second generation drugs with improved tissue selectivity. Indeed the group at Bristol Meyers Squibb [89] have identified tissue selective KATP openers which possess potent anti-ischaemic effects on the heart whilst having much reduced vasorelaxant activity compared to cromakalim. BMS-180448 [90] (table II), for example, is equiactive to cromakalim as an anti-ischaemic agent but some 40 times less potent than the reference drug as a vasodilator. The compound also reduces infarct size in dogs subjected to 90 minutes LAD occlusion and 5 hours reperfusion [91] and, by chance, its action potential shortening effect was less than that of cromakalim. Similarly with bimakalim (Merck) cardioprotective effects in dogs occur at doses that do not affect the cardiac action potential [92]. This suggests that the site of action of these drugs may not be the sarcolemmal KATP channel and its mitochondrial counterpart has been proposed as an alternative possibility [93]. Other agents under investigation include TAK 636 (Takeda), the carboximidamide derivative KRN-2391 (Kirin) and ZD6169 (Zeneca) [94], although the latter is being studied in urinary incontinence rather than ischaemia. As highlighted by Nielsen-Kudsk et al [85] these second generation drugs may not only prevent and relieve symptoms of ischaemia but also reduce important associated events such as stunning and MI. KATP openers may therefore have potential as adjuvant anti-ischaemic therapy during coronary angioplasty, CABG and in inhibiting postoperative myocardial stunning.

Restoration of normal endothelial function

This section includes a discussion of novel NO donors, ET antagonists, CAs and various agents able to modulate cell adhesion/migration processes through the compromised endothelium via antioxidant or receptor-mediated effects.

Compounds acting via nitric oxide

Since a key early event in reperfusion injury and in the atherosclerotic process is a reduced generation of NO by the endothelium an interesting therapeutic possibility would be to supply the deficient NO to those parts of the vessel wall at risk [40]. Indeed the precursor compound L-arginine has been reported to possess anti-ischaemic effects [95] and infusion of gaseous NO exerts significant protection in a cardiac ischaemia-reperfusion model in the cat [96]. Results from these experiments indicate that NO does not have to be delivered as free NO to the myocardium and that its uptake by circulating neutrophils and platelets prevents their activation and adherence as they flow through the injured coronary bed. However the use of NO under these conditions is difficult to control and we are still some way from having organic molecules able to release NO under physiological conditions and deliver it effectively and precisely to the risk zone. It also remains to be seen whether nitrate therapy can replace EDRF in disease states where there is a chronic deficiency although in a preliminary publication dietary L-arginine has been reported to restore NO formation and slow progression of lesions in hypercholesterolemic rabbits [97].

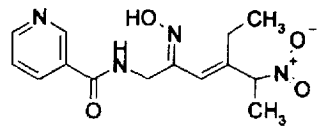
The major problem with current nitrate therapy is the development of tolerence upon prolonged administration [98, 99]. Tolerence to nitrates is most likely linked to a decrease in the availability of sulfhydryl (SH) groups which are obligatory cofactors in their enzymatic conversion to NO [100]. Some of the new NO-releasing compounds appear to evoke less tachyphylaxis either because different pathways are involved in NO release, or release is slower from these compounds, or the fact that some contain SH moieties within their structure [101].

Some of the nitrate-like molecules currently undergoing biological evaluation are shown in table III. FR 144420 (Fujisawa) is a new compound related to FK 409 and although it is some 7 times less potent than the latter in terms of vasodilator activity it has a much longer duration of action since it liberates NO at a much slower rate and this may retard tolerance development [102]. Other compounds include the novel sydnonimine CAS 936 (persidomine, Cassella/Hoechst) [103] which also is claimed to be less likely to induce tolerance since it does not require cellular metabolism to release the NO moiety. A metabolite of this structure, CAS 754 (marsidomine), is also under study. SPM-5185 (Schwarz) is another compound which liberates NO and less readily induces tolerance [104] perhaps because it is a cysteine-containing structure [105]. Both SPM-5185 and CAS 936 reduce the extent of myocardial necrosis in animal models of ischaemia-reperfusion injury [48, 106]. Furthermore protective effects were coincident with an inhibition of neutrophil adhesion to the endothelium. Another compound for which similar claims have been made is ITF 296 (sinitrodil, Italfarmaco) [107]. CHF 2363 (Chiesi) is a member of a series of novel furoxan derivatives possessing potent antiaggregant and vasorelaxant effects mediated via release of NO and to which no cross tolerance to glyceryltrinitrate has been observed [108]. Finally, the nitro-compound GEA-3175 (Gea/Novartis) is being developed specifically for use in counteracting hypertensive crises occurring during general surgery [109].

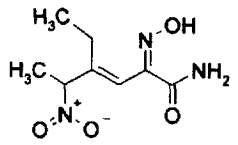
Endothelin receptor antagonists and converting enzyme inhibitors

Since an imbalance in the production of ET and NO may contribute to abnormalities in vessel tone much

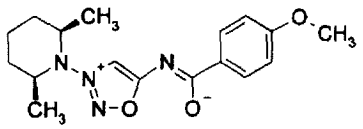
Table III. Certain nitrate-like derivatives under investigation.



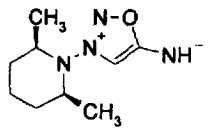
FR-144420 (Fujisawa)



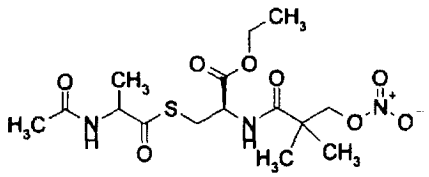
FK-409 (Fujisawa)



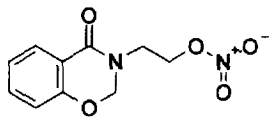
CAS-936 (Cassella / Hoechst)



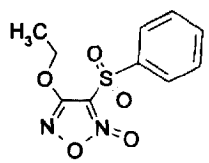
CAS-754 (Cassela / Riedel)



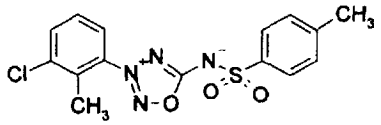
SPM-5185 (Schwarz)



ITF-296 (Italfarmaco)



CHF-2363 (Chiesi)



GEA-3175 (Gea / Novartis)

effort has been invested in the discovery of low molecular weight antagonists of this peptide [53]. There has been much speculation as to the precise physiological role of ET but this remains unclear at the present time and the debate as to whether it is involved in the general control of vascular reactivity

or has a more local, paracrine sphere of activity is still ongoing. Relatively selective antagonists of ET receptors are becoming available which should clarify the situation in man [110] but at the moment they are still agents searching for precise therapeutic applications [40]. The fact that there are at least two receptor subtypes for ET and not knowing if its actions should be regarded as widespread or local makes it difficult to predict the potential therapeutic uses of ET antagonists. The situation has become even more complex recently since research has shown that the relative contributions of ETA and ETB receptors to vasoconstrictor responses varies between and within vascular beds [111]. For example, in man proximal coronary arteries contain constrictor ETB receptors whereas in distal arteries vasoconstriction is mediated via ETA receptors. These findings have important implications concerning the development of antagonists since increases in coronary blood flow would depend on a balanced action of the antagonist on both receptor subtypes [40].

Many pharmaceutical companies have drug discovery programmes in the ET area either directed at receptor antagonists or at inhibitors of the ETCE [112] and some of the structures are shown in table IV. Evidence from pathophysiological models indicate several potential therapeutic applications including infarct size limitation following myocardial ischaemia and prevention of vasospasm and arterial restenosis [40]. Bosentan (Roche) [113] was the first orally active receptor antagonist but can inhibit both subtypes of ET receptors. However, relatively selective, non-peptide antagonists of ETA and ETB receptors are now becoming available. The Roche group in recent patents claim antihypertensive activity with potent ETA receptor antagonists (pA_2 = 10 against ET-induced contraction in rat aorta) in a series of aryl and hetaryl sulfonamides (table IV) and BASF (Knoll) also have found potent, selective ETA antagonists with LU-127043, a member of a novel series of carboxylic acid derivatives having a K_i value at the human receptor in the low nanomolar range. L-754142 (Merck) is a phenoxyphenylacetic acid derivative which possesses a K_i at the cloned human ETA receptor of 0.06 nM and a K_i of 2.25 nM at the ETB receptor (table IV). Relatively selective, extremely potent (IC_{50} = 0.3 nM on the human ETA receptor) ETA antagonists are also claimed by Parke-Davis with PD156707 [114]. Since there is evidence for an upregulation of ETB receptors in some pathological states [115] some companies are also studying the potential therapeutic effects of relatively selective ETB receptor antagonists such as Ro46-8443 (Roche) and IRL-2500 (Novartis).

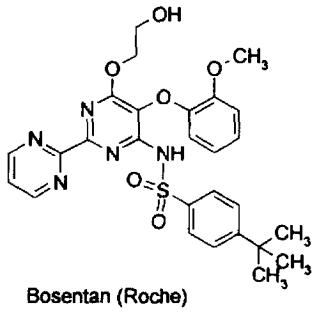
Another related target of many drug discovery programmes involves ETCEIs (see table IV). Since this enzyme has high substrate selectivity this could lead to agents with relatively few side effects. SCH-54470 (Schering) is a phosphinic acid derivative with multi-enzyme inhibitory effects upon ETCE, ACE and neutral endopeptidase. Warner Lambert–Parke-Davis with a series of quinazoline derivatives (PD069185) and Novartis with certain tetrazoles, also claim to have potent inhibitors of the ETCE (table IV). Finally ET may be important in the maintenance of resting vascular tone in man since antagonists produce additional vasodilatation in the forearm bed of CHF patients receiving ACEIs and diuretics [114]. However until these agents are tested in man their therapeutic potential remains highly speculative as is evident from the many and varied claims made in patents and in the literature.

Compounds acting via calcium antagonism

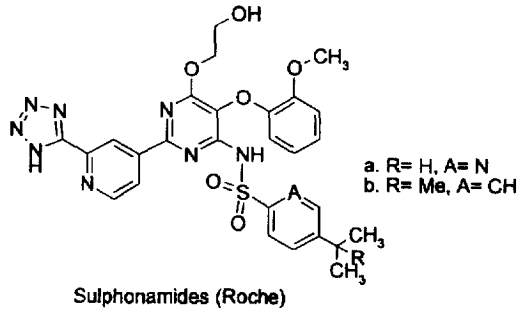
It is well known that there are important pharmacological differences between the various classes of structures possessing CA activity [116]. Recent interest in these compounds has focused more on their potential ancillary properties such as antiatherosclerotic activity, effects upon smooth muscle migration and proliferation and the restoration of normal endothelial function rather than on their vasodilator activity [54]. Nearly 50 studies have been conducted with CAs in the hypercholesterolaemic rabbit model with just about twice as many studies showing positive as opposed to negative effects [117, 118]. Positive effects have been reported with nifedipine, isradipine, nicardipine, nisoldipine, verapamil, diltiazem, and amlodipine but negative results have also been reported with nifedipine, nicardipine, and diltiazem in other studies. Possible reasons for these discrepancies include the time of administration, CA treatment has to begin early to be effective, the dose of CA used, the amount of cholesterol fed in the diet, and the great variability in lesion development in the rabbit model. It should be noted that usually the oral dosage regimes of the CAs are several times higher than the equivalent human doses so extrapolation of results to man is difficult. The consensus view of all these studies is that CA treatment can result in a decline in the rate of atherosclerosis progression in animals but not in complete arrest of the process. With respect to clinical studies, at least 7 trials have been conceived to study the effect of CAs on the development, regression and progression of atherosclerosis in man. The overall conclusions from these studies are that CAs prevent the development of new lesions but it is still controversial whether they stop progression or induce regression of existing atherosclerotic lesions. Therefore there is certainly a need for more effective agents.

With respect to novel CA structures in development some of the more interesting derivatives are shown in

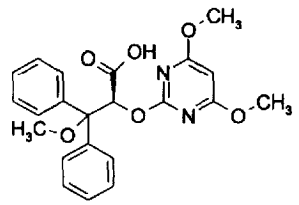
Table IV. Certain ETA and ETB receptor antagonists and ET converting enzyme inhibitors under investigation.



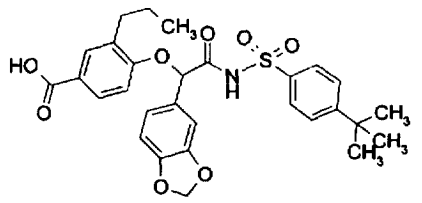
Bosentan (Roche)



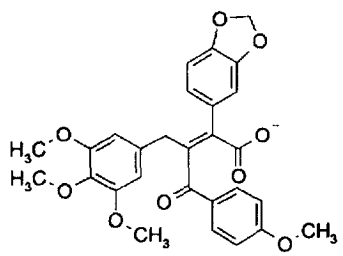
Sulphonamides (Roche)



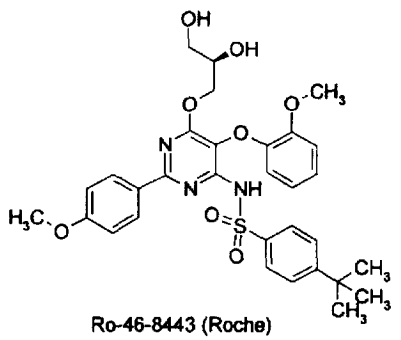
LU-127043 (BASF)



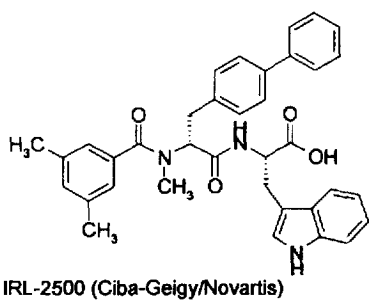
L-754142 (Merck)



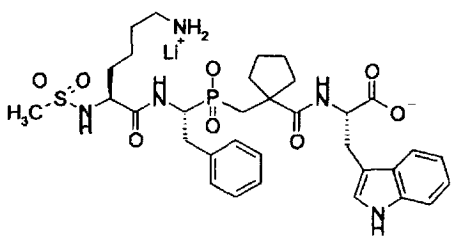
PD-156707 (Warner-Lambert)



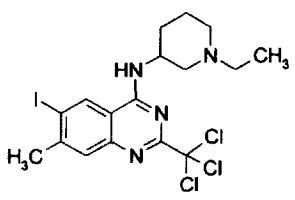
Ro-46-8443 (Roche)



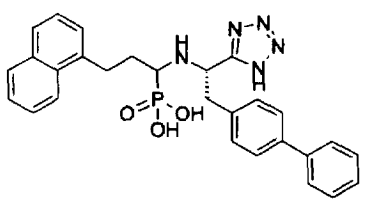
IRL-2500 (Ciba-Geigy/Novartis)



SCH-54470 (Schering)



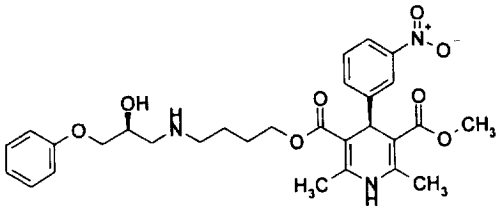
PD-069185 (Parke Davis Warner-Lambert)



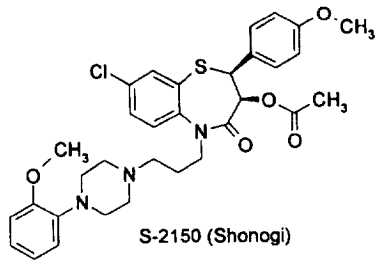
Tetrazoles (Novartis)

table V. In previous publications CAs have been subdivided into three classes; calcium entry blockers, those acting relatively selectively at the slow, L-type calcium channel, calcium overload blockers, and intracellular calcium antagonists [119, 120]. Several of the newer calcium entry blockers possess dual acti-

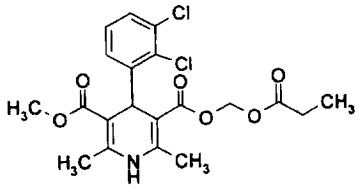
Table V. Some calcium antagonist structures under investigation.



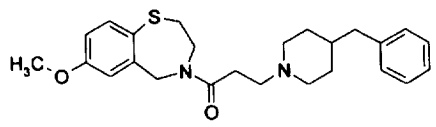
YM-15430-1(Yamanouchi)



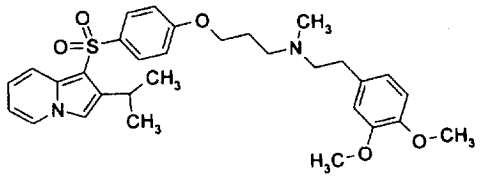
S-2150 (Shonogi)



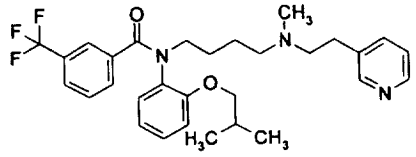
H-324/38 (Astra)



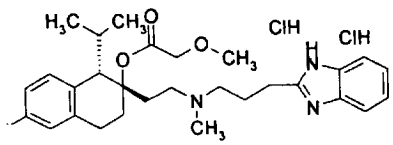
K-201 (Kirin)



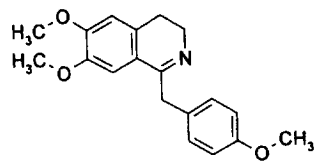
SR-33557 (Sanofi)



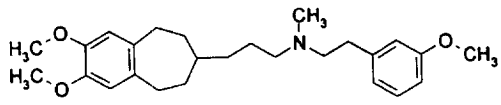
SL-870495 (Synthélabo)



U88999 (Pharmacia / Upjohn)



GS-386 (Gyeonsang National University)



Zatebradine (Knoll)

vities. For example, YM-15430-1 (Yamanouchi) is a DHP structure possessing both calcium entry blocking and β-blocking activity [102]. S-2150 (Shonogi), is a combined calcium entry blocker and α1-antagonist which possesses antihypertensive properties [121]. H324/38 (Astra) is another DHP calcium entry blocker but with an ultrashort duration of action that is being developed to treat perioperative hypertension [122]. K201 (Kirin) is a novel benzothiazepine which unlike diltiazem may have an intracellular locus of action since it inhibits annexin binding to F-actin and prevents over-contraction of the myocardium to excessive catecholamine stimulation [123]. SR-33557 (fantofarone, Sanofi) is claimed to act at a novel site in the L-type calcium channel [124, 125] and SL 870495 (Synthélabo), as having little effect upon cardiac conduction [126]. U88999 [127] is a CA with antioxidant activity and GS 386 (Gyeongsang National University) is an isoquinoline derivative claimed to possess effects upon calcium movements intracellularly [128]. Several structures for which specific bradycardic effects are claimed are to be found in the patent literature but the continued development of such agents must be in doubt following the negative results of recent clinical trials with zatebradine (Knoll).

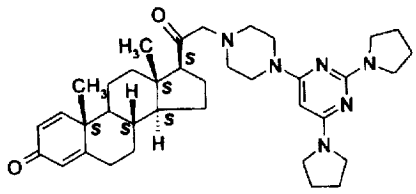
A meta-analysis of secondary prevention trials with nifedipine suggests that high dose, short-acting preparations may be associated with an increased total mortality in patients with CAD [129]. It is now recommended that the use of short-acting agents should be avoided because they induce reflex activation of the SNS. Such reports have elicited much controversy and although the data on individual agents does not allow definitive conclusions they clearly have implications as to whether the pharmaceutical industry will continue to invest valuable resources into the research and development of new CA drugs.

Compounds acting directly on inflammatory or cell adhesion pathways

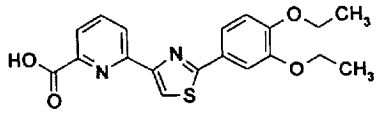
The protective effects of oestradiol against atherosclerosis has been well documented [130] with lipoprotein changes and antioxidant activity being implicated in this effect [131]. However, oestradiol prevents the adhesion of monocytes to endothelial cells [132] and since this is thought to be one of the earliest events in atherosclerosis, it may also provide part of the explanation for the beneficial effects of this hormone. Two other compounds have also recently been claimed to protect the endothelium from ischaemic injury. hOP-1, a member of the TGF β family, has been studied for its anti-ischaemic effects in a rat model of reversible cardiac ischaemia [133]. hOP-1 was found to preserve coronary endothelial function (release of EDRF) following global ischaemia and reperfusion and was observed to significantly inhibit the adherence of neutrophils to the endothelium. Similarly U-74389G (Upjohn) is claimed to improve survival and reverse endothelial dysfunction caused by ischaemia and reperfusion in the splanchnic bed of the rat [134]. Whether similar effects occur at the level of the coronary arteries remains to be determined. The beneficial actions of these agents may be linked to effects upon cell adhesion or inflammatory/oxidant events within the vessel wall. Indeed antioxidant compounds like the thiazole, OPC-6535 (Otsuka) and dithiol-thione compounds from Mitsui-Toatsu (see table VI) are claimed to be useful for the treatment of ischaemic heart disease and a series of membrane bound benzenesulphonamide phospholipase A_2 inhibitors from Eisai have also been reported to reduce the size of occlusion-induced infarcts in the rat when administered before ligation of the coronary artery [135].

From the literature and patents it is evident that many companies have an active interest in the area of adhesion molecule antagonists. Adhesion receptors are expressed following ischaemic injury and reperfusion and are involved in the mediation of leucocyte rolling, adhesion and migration responses through the damaged endothelium [136–138]. Compounds described in the literature (table VI) include a series of dithiocarbamate derivatives (Emory University) claimed to selectively block the expression of VCAM-1 without significant effects upon ICAM-1 and ELAM-1 thus avoiding general immunosuppression. E. Merck also has series of linear and cyclic peptides under investigation which are claimed to act as inhibitors of cell adhesion. Similarly Corvas-Pfizer are studying a neutrophil inhibitory factor which binds to the CDIIb/CD18 integrin cell-surface receptor to prevent neutrophil adhesion and Ligand-Sankyo are working on a series of sialyl Lewis X glycomimetics to prevent P-selectin-induced leucocyte adhesion to the endothelium. LEX032 (Lexin) is a recombinant human protease inhibitor derived from α1-antichymotrypsin in which six amino acids in the centre of the active loop domain have been replaced with those of the α1-protease inhibitor [139]. LEX032 inhibits both neutrophil elastase and cathepsin G, suppresses superoxide generation and attenuates ischaemia and reperfusion-induced injury in the rat, it is claimed through inhibition of neutrophil accumulation in the reperfused zone [140]. Positive results in a similar rat model have been reported with the IL-6 antagonist, KC-12849 (Kalie-Chemie) [141]. However in a canine model of ischaemia and reperfusion the relatively selective 5-LO inhibitor, LY233569 (Lilly) [142], was found to have no significant effect on infarct size or leucocyte recruitment suggesting that leukotrienes do not mediate reperfusion injury in the heart. The

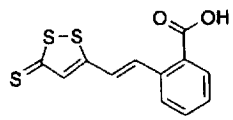
Table VI. Compounds affecting cell adhesion and migration under investigation.



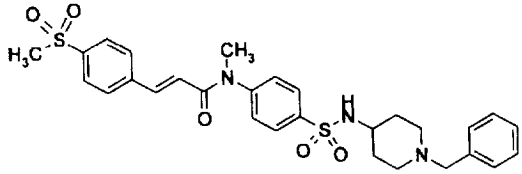
U-74389G (Upjohn)



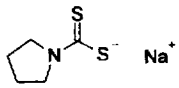
OPC-6535 (Otsuka)



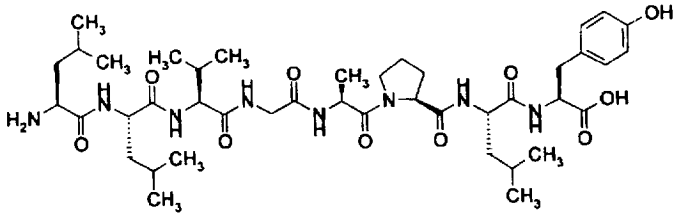
Ditiol-thione compound (MitsuiToatsu)



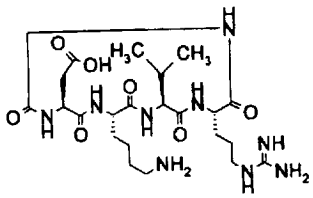
Benzenesulphonamide (Eisai)



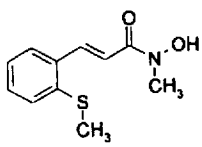
Dithiocarbonate (Emory University)



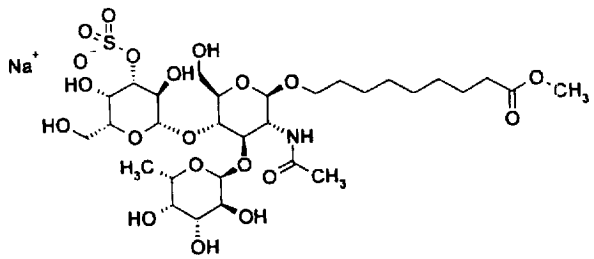
Peptide linear (E.Merck)



Peptide cyclic (E.Merck)



LY-233569 (Lilly)



Sialyl Lewis X glycomimetics (Ligand / Sankyo)

fact that several other 5-LO inhibitors [143–146] have all been reported to salvage ischaemic myocardium and to limit leucocyte accumulation has been attributed to a lack of enzyme selectivity of these agents (eg, inhibition of cyclooxygenase) or additional pharmacological effects (eg, antioxidant activity) [147, 148].

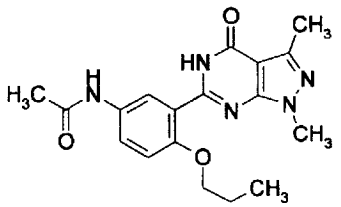
Finally several companies are exploring the anti-ischaemic potential of selective inhibitors of the PDE isoenzymes, especially inhibitors of PDE III and V, probably because of their potential selectivity for vascular smooth muscle and platelets [149]. Glaxo Wellcome is studying a series of pyrazolopyrimidines (table VII) and both Pfizer and SmithKline Beecham are working on calmodulin-insensitive, cyclic GMP-dependent PDE III inhibitors with similar pharmacological profiles (antiaggregant, vasorelaxant activities). In this respect the relatively selective PDE III inhibitor, BMY21190 (Bristol Meyers Squibb) has been reported to reduce infarct size in the canine myocardium following 90 minutes of ischaemia and reperfusion via inhibition of neutrophil infiltration [150]. Following the demise of PDE-I inhibitors in CHF it remains to be seen if any acute improvements in physiological function observed with these drugs will translate into real long-term clinical benefits.

Local neurohormonal or metabolic effects

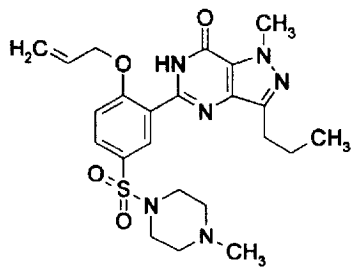
Ischaemia excites certain cardiac afferents which then provoke centrally mediated increases in SNS activity in the periphery. Patients undergoing CABG operations are at risk of myocardial cell injury and several pharmacological approaches have been used in attempts to reduce the incidence of peri- and post-operative myocardial ischaemia. In such situations the α2-agonists clonidine [151], dexmedetomidine [152] and more recently mivazerol [153] have been reported to have beneficial effects (table VIII). Mivazerol, is a relatively selective α2-agonist [154] with little effect on BP, which might be advantageous for this indication [155]. Mivazerol is effective in reducing increases in T-wave amplitude provoked by brief periods of coronary occlusion in anaesthetised rats and dogs [156, 157] and suppresses the tachycardia following emergence from halothane anaesthesia in a rat model [158]. The effect of mivazerol is probably due to a reduction in peripheral SNS activity mediated by α2-receptor stimulation since its effects are abolished by pretreatment with rauwolscine. Studies into the site of action of mivazerol are still ongoing but there is evidence that spinal and ganglionic sites may be involved. Mivazerol is in the final phases of clinical development (Phase III) as a protective agent for use in CAD disease patients undergoing non-cardiac surgery [153].

The therapeutic place of β-blocking drugs possessing additional vasodilator properties like YM-15430-1 is still unclear [120, 159]. Such a combination of activities may be beneficial from a haemodynamic standpoint and with carvedilol [160], for example, this has translated into significant clinical benefits since it

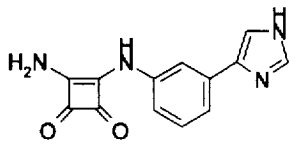
Table VII. Selected phosphodiesterase inhibitors under study.



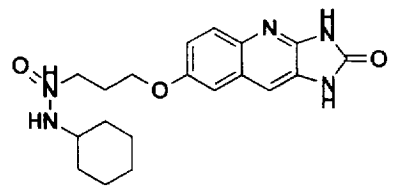
Pyrazolopyrimidine (Glaxo Wellcome)



Pyrazolopyrimidine (Pfizer)

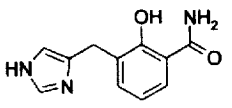


Pyridylamino-cyclobutene dione (Smith Kline Beecham)



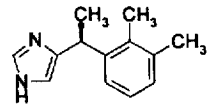
BMY 21190
(Bristol Meyers Squibb)

Table VIII. Compounds affecting β-adrenergic receptors or Na^+/H^+-exchange.

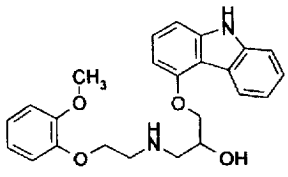


Mivazerol (UCB Pharma)

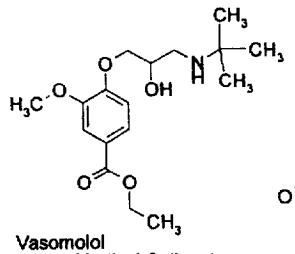
Clonidine (Boehringer-Ingel.)



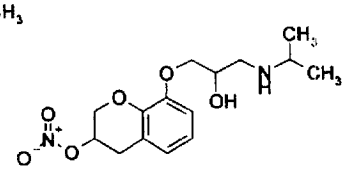
Dexmedetomidine (Orion)



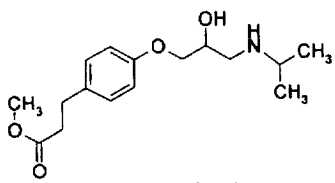
Carvedilol (Boehringer-Mann.)



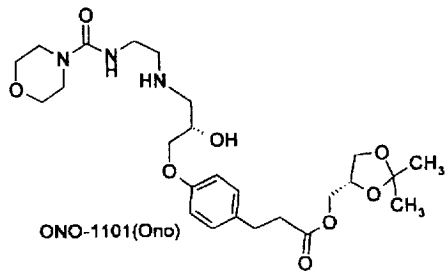
Vasomolol
(Kaohsiung Medical College)



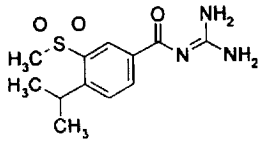
Nipradilol (Kowa)



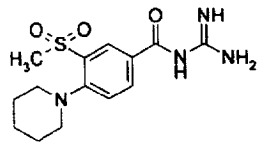
Esmolol (Du Pont)



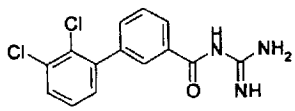
ONO-1101(Ono)



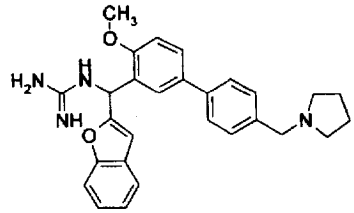
HOE-642 (Hoechst)



HOE-694 (Hoechst)



Benzoylguanidines (Fujisawa)



Methylguanidines (Elf / Sanofi)

reduces the risk of death and hospitalisation due to cardiac causes in patients with CHF [161]. In experimental animals the cardioprotective potential of carvedilol in reducing infarct size has been demonstrated to be greater than that observed with conventional β-blockers [162]. This may be due to antioxidant properties of the molecule [163, 164] and has stimulated several other companies to search for compounds with similar profiles. However, recent results in an ischaemia-reperfusion model with carvedilol suggests that it protects against injury via antiadrenergic rather than antioxidant mechanisms [165]. Thus nipradilol (Kowa) is a β-blocker with vasodilator properties which contains a nitroxy group in the structure (table VIII) and DCC-10255 (Du Pont-Merck) is a catechol containing β-blocker reported to be a potent inhibitor of free-radical induced oxidation of cardiac membranes [166]. The other major direction in which the search for novel β-blockers has evolved in recent years is towards the development of ultra-short acting derivatives like esmolol (Du Pont), ONO-1101 (Ono) [167] and vasomolol (Kaohsiung Medical College) [168] for use in critically ill patients.

It is well established that ischaemia produces intracellular acidosis. Restoration of flow at physiological pH leads to the rapid development of a trans-sarcolemmal pH gradient and activation of the NHE, the most important mechanism for regulating intracellular pH [169]. Amongst the five distinct NHE isoforms discovered to date, isoform 1 (NHE_1) appears to be selectively involved in the regulation of pH in cardiomyocytes [170]. Convincing evidence for NHE involvement in myocardial reperfusion injury has emerged from studies showing beneficial effects with NHE inhibitors, amiloride and some closely related analogues [169]. These prototype molecules suffered, however, from low potency and selectivity. Several new compounds particularly from Hoechst [171, 172], Sanofi (methylguanidine analogues) and Fujisawa (benzoylguanidine derivatives [173]) (table VIII) with improved potency and/or selectivity have been described recently. The guanidine function common to all structures seems to be necessary to interact selectively with the NHE. The best described compounds (Hoe 642, cariporide and Hoe 694) demonstrated marked protective effects against ischaemia-induced myocardial necrosis and reperfusion dysrrhythymias without affecting BP [171, 172].

Vascular and cardiac remodelling

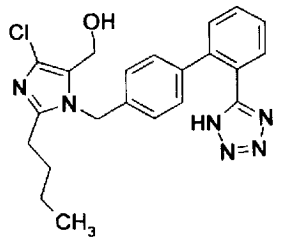
Several existing classes of cardiovascular drugs are known to modulate the remodelling process in both positive and negative ways but it is only recently that additional targets in the remodelling process are being attacked. One reason for interest in remodelling is that results with antihypertensive agents suggest that just reducing BP in hypertensive patients does not always reduce the risk of MI, neither does simply ameliorating the haemodynamic derangements observed in HF influence patient survival in the long term. Clearly other factors are playing important roles in such chronic pathological states and these factors seem to be of neurohormonal origin [174].

Whilst α-blockers and inhibitors of the RAS are inactive in angina pectoris results suggest that they may, by damping neurohormonal activation, have beneficial effects on the remodelling process. In this respect ACEIs have been shown to reduce mortality and prevent progression of CAD in patients more effectively than hydrallazine + isosorbide dinitrate [175, 176]. Trials with the β-blocker carvedilol have reinforced the involvement and the importance of the SNS in CHF [174]. The clinical importance of the ACEIs in hypertension and CHF is undeniable and the hope is that the AT-II receptor antagonists will be similarly successful. Questions still to be resolved are the importance of bradykinin in the beneficial therapeutic effects of ACEIs and whether the AT-II receptor antagonists may be more effective since they antagonise the effects of AT-II elaborated by enzyme sources (eg, chymases) not affected by the ACEIs [177]. AT-II receptor antagonists, therefore, may possess enhanced antiproliferative effects by modulating cell growth and hyperplasia induced by AT-II under pathophysiological conditions [40].

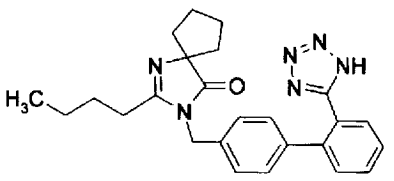
There are many AT-II receptor blocking agents in late-phase clinical trials following on the heels of losartan (Du Pont Merck) and valsartan (Novartis) which have already reached the market. Some of the more advanced structures are shown in table IX but this gives an incomplete picture and it is fair to say that most of the major pharmaceutical companies in the world have antagonist compounds under study. Irbesartan (Sanofi/BMS) is at the pre-registration phase with eprosartan (SK&B), telmisartan (Thomae) and tasosartan (American Home Products) in Phase III clinical trials.

As discussed previously the extracellular matrix is involved in the remodelling of the cardiovascular system in disease with local RASs perhaps playing an important role in the process [178]. There is evidence suggesting that mechanical stress is transmitted into cells from their sites of attachment to the extracellular matrix [179] and that this response may involve a class of integrin receptors [180] thus opening the potential for pharmacological manipulation. Results suggest that the remodelling process is mediated by members of the MMP family of enzymes. There are 4 main MMP families with 14 members currently known. Recent findings suggest that the individual enzymes can be inhibited by relatively selective

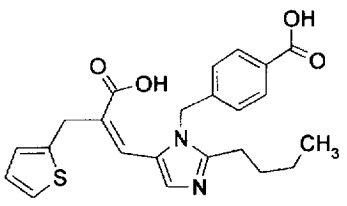
Table IX. Angiotensin-II receptor antagonists under investigation.



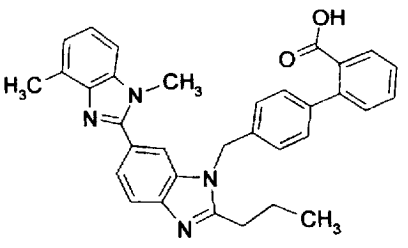
Losartan (Du Pont Merck)



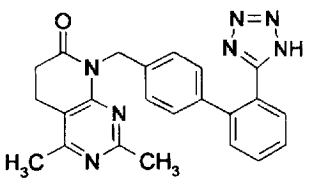
Irbesartan (Sanofi / BMS)



Eprosartan (Smith Kline Beecham)



Telmisartan (Thomae)



Tasosartan (American Home Products)

compounds but it is beyond the scope of this article to go into details on this subject and the reader is referred to the excellent reviews of Cawston [181], Hagmann et al [182] and Cleutjens [70]. In diseases like CHF and atherosclerosis there is degradation of the extracellular matrix and the hope is that relatively selective agents can be found to prevent this but such agents may also find use in a wide range of other diseases [182, 70] and as yet agents with selective applications in cardiac ischaemia do not exist.

Conclusions

Over the last five years our understanding of CAD and the response of the heart to ischaemia has increased exponentially and will continue to do so in the coming years. Despite its complexity there now is a real hope of finding novel, causally effective agents for the treatment of CAD. At the level of the vascular wall the lipid environment of the vessel lumen can be manipulated quite effectively by diet and drugs and there is evidence that the damaged endothelium can be protected by some agents and nursed back to health. Over-stimulation of the SNS and RAS can be attenuated with relatively selective agents and the adhesive processes responsible for platelet aggregation and neurophil infiltration into the vessel wall can also be modulated and new therapeutic entities should become available in the coming years. A major challenge to the pharmaceutical industry is still to find agents capable of preventing the extracellular and cellular remodelling processes that occur in the cardiovascular system after surgical procedures like CABG and in response to hypertension and other pathologies which lead to a loss in organ efficiency and efficacy.

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