Fortnightly Review

Ten years of natriuretic peptide research: a new dawn for their diagnostic and therapeutic use?

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In 1981 de Bold *et al* found that atrial extracts contained a substance which caused natriuresis and vasodilatation.¹ Three years later the amino acid structure of atrial natriuretic peptide was identified.² This was followed by a period of fervent research activity to define its role and therapeutic potential. In 1988, just as the initial flush of research activity was wearing off, a second related compound was identified.³ This was called brain natriuretic peptide because it was first identified in porcine brain. It soon became clear, however, that the main source of this peptide was the cardiac ventricle rather than the brain, and brain natriuretic peptide is now sometimes called B type natriuretic peptide. In 1990 a third natriuretic peptide was identified, and in order to maintain the alphabetical nomenclature it was called C type natriuretic peptide.⁴ The amino acid structure of the three peptides is shown in the figure. Though C type natriuretic peptide was, like B type, initially localised to the nervous system, it was later found to be present in high concentration in the vascular tree, especially the endothelium.

The biological effects of atrial natriuretic peptide and B type natriuretic peptide are very similar, both peptides causing natriuresis, vasodilatation, and suppression of the renin-angiotensin-aldosterone system. Indeed, atrial natriuretic peptide suppresses the renin-angiotensin-aldosterone system at three separate sites. It reduces renin release, suppresses angiotensin converting enzyme activity, and blocks aldosterone release. Atrial natriuretic peptide and C type natriuretic peptide are cleared from the body by an enzyme called neutral endopeptidase and by binding to clearance receptors (see below). B type natriuretic peptide is also cleared by neutral endopeptidase, though less so by the clearance receptor mechanism. With C type natriuretic peptide the overall picture is less clear, but probably it has a different function from atrial natriuretic peptide and B type. C type natriuretic peptide is probably part of a "vascular natriuretic peptide system," in contrast with

ABC of natriuretic peptides

Atrial natriuretic peptide

- Stored mainly in right atrium
- Causes natriuresis and vasodilatation

Brain or B type natriuretic peptide

- Stored mainly in cardiac ventricles
- Causes natriuresis and vasodilatation

C type natriuretic peptide

- Stored in vascular endothelial cells
- Causes vasodilatation

atrial natriuretic peptide and B type, which belong more to the cardiac natriuretic peptide system. Not only is C type natriuretic peptide stored in the vascular tree but most of its biological effects occur there. C type natriuretic peptide causes pronounced vasodilatation, especially on the venous side of the circulation. Its renal effects are still being debated. An exciting prospect is to see how this local substance (C type) interacts with the vascular renin-angiotensin-aldosterone system, especially as both atrial natriuretic peptide and B type are potent inhibitors of this system.

It seems probable that more natriuretic peptides will be discovered over the next few years. It also seems probable that more receptors for these peptides will be discovered, as currently the three peptide receptors which exist do not provide a good match to the three peptides. The three natriuretic peptide receptors are A, B, and C. The first two are biologically active, while the third is biologically inactive and acts to clear or mop up excess atrial natriuretic peptide and B and C types. The A receptor preferentially binds atrial natriuretic peptide, while the B receptor preferentially binds C type natriuretic peptide. As yet there is no receptor which preferentially binds B type natriuretic peptide.

This is a very brief summary of the basic facts about the natriuretic peptides. They are reviewed in greater detail elsewhere.⁵⁻⁸ This review is mainly concerned with the clinical use of the natriuretic peptides.

The natriuretic peptides could be of value clinically in two different ways. Firstly, their concentrations in the plasma could give valuable diagnostic information about cardiac function or structure. After all, endocrinologists have for years taken blood samples to tell them about the structure or function of distant glands, and it is possible that cardiologists or physicians could use plasma concentrations of atrial natriuretic peptide or B type natriuretic peptide in the same way for the heart.⁹ Secondly, natriuretic peptides could be used as therapeutic agents.

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Amino acid structure of the three peptides

Summary points

- Three different natriuretic peptides (atrial, B type, and C type) have been identified
- Plasma B type natriuretic peptide concentrations may be of value in diagnosing early heart failure, in identifying asymptomatic left ventricular dysfunction (especially after myocardial infarction), and in assessing patients with myocardial ischaemia
- Plasma and tissue concentrations of natriuretic peptides can be increased by orally active inhibitors of neutral endopeptidase
- Neutral endopeptidase inhibitors alone have a poor effect on blood pressure in hypertension but have favourable effects at preventing atherosclerosis and left ventricular hypertrophy and fibrosis
- Potentially, neutral endopeptidase inhibitors combine the natriuretic effect of frusemide with the anti-ischaemic effect of nitrates and the favourable hormonal effects of angiotensin converting enzyme inhibitors
- Neutral endopeptidase inhibitors along with angiotensin converting enzyme inhibitors may well achieve complete suppression of the renin-angiotensin system
- By virtue of their antiatherosclerotic, anti-ischaemic, anti-left ventricular hypertrophy, and neuroendocrine suppressor activity, neutral endopeptidase inhibitors have great potential in cardiovascular medicine

Diagnostic use of natriuretic peptides

Diagnosing moderate or severe heart failure by clinical examination is easy, but diagnosing mild heart failure by clinical examination is very difficult. In one study 1.6% of the population were taking diuretics for heart failure but only 0.84% of the population actually had systolic dysfunction on echocardiography.¹⁰ As all heart failure patients should be taking an angiotensin converting enzyme inhibitor, it seems appropriate to use echocardiography in the 1.6% of the population in order to identify correctly the 0.84% who should receive angiotensin converting enzyme inhibitors. Performing this number of extra echo studies may be feasible in a teaching hospital but is likely to overstretch available resources in district general hospitals. This raises the possibility that measuring plasma natriuretic peptide concentrations may be a cheaper and more available way of identifying mild heart failure. Lerman *et al* have found that concentrations of the N-terminal fragment (1-98) next to atrial natriuretic peptide (99-126) have high sensitivity in detecting asymptomatic left ventricular dysfunction.¹¹ Debate continues on which natriuretic peptide to actually measure.

Allied to this use is the possibility that measuring one of the plasma natriuretic peptides could replace the use of radionuclide ventriculography, as the hormone concentrations may equate to left ventricular ejection fraction. If so, the patient could be spared a hefty dose of radioactivity and the hormone assay would be much cheaper.

The decision whether to give all postmyocardial infarction patients an angiotensin converting enzyme inhibitor or not is contentious. One trial—the SAVE study—suggested that patients with a left ventricular ejection fraction of less than 40% should be identified and that all should receive an angiotensin converting enzyme inhibitor. That trial also showed that 50-60%

of patients with a left ventricular ejection fraction below 40% had no clinical signs of heart failure whatever but that there was still a large mortality benefit from treating these “clinically normal” patients with an angiotensin converting enzyme inhibitor. Screening all postmyocardial infarction patients in order to identify those with a left ventricular ejection fraction of less than 40% can be done by either echo or a nuclear scan. This is easily achieved in a teaching hospital but resources may not stretch to this in district general hospitals. Instead, therefore, it may be that plasma natriuretic peptide concentrations could be used. Motwani *et al* found the plasma B type natriuretic peptide concentration to be a promising means of identifying these patients.¹²

One other intriguing possibility is that the plasma atrial natriuretic peptide (or B type natriuretic peptide) concentration might reflect myocardial ischaemia. The hypothesis is that exercise induced ischaemia leads to exercise induced left ventricular dysfunction of either the systolic or diastolic type. Such left ventricular dysfunction raises the plasma atrial natriuretic peptide or B type natriuretic peptide concentration more in patients with ischaemia than in those without. One study suggested that this is indeed the case, and further work is therefore required to investigate the use of this observation in clinical practice.¹³

Two other possible diagnostic uses relate to the likelihood that increased left ventricular mass will lead to increased plasma B type natriuretic peptide concentrations. A raised plasma concentration of this peptide may therefore identify the presence of left ventricular hypertrophy in hypertension. B type natriuretic peptide concentrations may also be useful in screening for hypertrophic obstructive cardiomyopathy either in a population or in family studies.¹⁴ Whether plasma B type natriuretic peptide concentrations will discriminate sufficiently in these clinical settings remains to be seen.

Lastly, it is possible that plasma atrial natriuretic peptide measurements could be used to optimise diuretic therapy. For example, in heart failure diuretics gradually reduce intracardiac pressure and so reduce the plasma atrial natriuretic peptide concentration. However, once the patient has undergone excessive diuresis prerenal uraemia may cause a fall in renal atrial natriuretic peptide clearance and lead to an increase in the atrial natriuretic peptide concentration. A trough plasma atrial natriuretic peptide concentration may therefore represent optimal use of diuretic therapy.

Therapeutic use of natriuretic peptides

From a therapeutic standpoint it was plain in 1984 that atrial natriuretic peptide might be of value in hypertension and heart failure but that a large peptide

Possible uses of plasma natriuretic peptide measurements

- Detecting mild heart failure as prelude to treatment with angiotensin converting enzyme inhibitors
- Replacing radionuclide ventriculography
- Identifying postmyocardial infarction left ventricular dysfunction as prelude to treatment with angiotensin converting enzyme inhibitors
- Helping in diagnosing exercise induced myocardial ischaemia
- Detecting left ventricular hypertrophy in hypertension
- Help diagnosing hypertrophic obstructive cardiomyopathy
- Optimising diuretic therapy

Pharmacological properties of neutral endopeptidase inhibitors

- Poor blood pressure lowering effect in hypertension
- Prevent left ventricular hypertrophy and left ventricular fibrosis*
- Prevent atherosclerosis*
- Natriuretic in heart failure
- Vasodilatation in heart failure
- Favourable neuroendocrine profile in heart failure(?)
- Anti-ischæmic effect in angina†
- Counteracts cyclosporin toxicity†
- Dilates pulmonary vasculature†

*Shown only in animals so far.

†Shown only with atrial natriuretic peptide and B type natriuretic peptide in humans. No data yet for neutral endopeptidase inhibitors.

such as this would have to be given parenterally. This problem was overcome by several drug companies which developed orally active neutral endopeptidase inhibitors. These inhibit the breakdown of endogenous natriuretic peptides, and it was hoped that by so doing they could harness the therapeutic potential of atrial natriuretic peptide.¹⁵ Natriuretic peptides, however, are by no means the only substrate for neutral endopeptidase. This enzyme degrades many endogenous peptides, including angiotensin II, bradykinin, and substance P. Neutral endopeptidase inhibitors, therefore, are likely to increase tissue concentrations of several peptides, including atrial and the B type and C type natriuretic peptides. As neutral endopeptidase inhibitors also reduce angiotensin II clearance, it may well be that they will achieve their full therapeutic potential only when used along with an angiotensin converting enzyme inhibitor. This is particularly so in heart failure, in which an angiotensin converting enzyme inhibitor should be part of the treatment anyway.

ESSENTIAL HYPERTENSION

The first therapeutic setting investigated with neutral endopeptidase inhibitors was essential hypertension, but results were disappointing.¹⁶ The blood pressure reducing effect of neutral endopeptidase inhibitors on their own was small. It is tempting to speculate that their blood pressure lowering effect was limited by potentiation of angiotensin II, especially as the combination of a neutral endopeptidase inhibitor and an angiotensin converting enzyme inhibitor is, in fact, a potent blood pressure lowering regimen.

It might well be, however, that neutral endopeptidase inhibitors have been prematurely dismissed in hypertension. This is because in animal models they have been shown to substantially reduce atherosclerosis.¹⁷ This effect agrees with the well known antiproliferative effect of atrial natriuretic peptide in tissue culture.¹⁸ Clearly this opens up the exciting possibility of using neutral endopeptidase inhibitors as an antiatherosclerotic treatment in many different clinical settings, such as hypercholesterolaemia, hypertension, or even after angioplasty to prevent restenosis.¹⁹

There is, however, another possible benefit for neutral endopeptidase inhibitors in essential hypertension, which relates to left ventricular hypertrophy.²⁰ Part of this hypertrophy is due to increased myocardial fibrosis, which is thought to be harmful because the collagen involved is very stiff and non-compliant. Neutral endopeptidase inhibitors have been shown in animal models to greatly reduce not only left ventricular hypertrophy but also myocardial collagen. Interest-

ingly, these two beneficial effects occurred in the absence of any change in blood pressure. The mechanism of the effect on collagen is uncertain but could be related to reduced aldosterone, as aldosterone increases myocardial collagen formation.

Neutral endopeptidase inhibitors alone therefore produce little change in blood pressure but have the more important prospect for hypertensive patients of being antiatherosclerotic and preventing left ventricular hypertrophy and left ventricular fibrosis. Given these two major benefits it would be unfortunate if neutral endopeptidase inhibitors were dismissed in hypertension because they had little effect on blood pressure. Changes in blood pressure are worth considering only when they reflect target organ damage, and it seems likely that neutral endopeptidase inhibitors dissociate blood pressure changes from target organ damage. Neutral endopeptidase inhibitors highlight the folly of judging antihypertensive drugs purely by their effects on blood pressure.

CHRONIC HEART FAILURE

Heart failure was the next obvious subject for investigation, and in this neutral endopeptidase inhibitors look much more promising.²¹ Neutral endopeptidase inhibitors produce nearly as much natriuresis as frusemide but have the advantage of causing greater falls in pulmonary wedge pressure and having a more favourable neuroendocrine profile.²² Studies are under way in heart failure with the combination of neutral endopeptidase inhibitors and angiotensin converting enzyme inhibitors, and drugs are being developed which can inhibit both enzymes.

An enormous potential advantage of combining neutral endopeptidase and angiotensin converting enzyme inhibition is that both agents should produce a much more suppressed renin-angiotensin-aldosterone system than either agent used alone, and there are at least theoretical benefits to such "augmented neuroendocrine suppression" (see below). Another potential benefit of using a neutral endopeptidase inhibitor and an angiotensin converting enzyme inhibitor over using frusemide and an angiotensin converting enzyme inhibitor relate to the fact that both atrial natriuretic peptide and B type natriuretic peptide have documented anti-ischæmic properties. Many heart failure patients also have coincidental angina, so that a neutral endopeptidase inhibitor could treat both the angina and the heart failure. By contrast, frusemide would tackle only the heart failure. A neutral endo-

Possible therapeutic uses of neutral endopeptidase inhibitors

- Hypertension
 - Antiatherosclerotic
 - Preventing left ventricular hypertrophy and left ventricular fibrosis
- As antiatherosclerotic
- Heart failure
 - Natriuretic
 - Vasodilator
 - Anti-ischæmic
 - Better neuroendocrine profile than frusemide
 - Augmented renin-angiotensin-aldosterone system suppression with angiotensin converting enzyme inhibitors
- Myocardial ischaemia
- Cyclosporin nephrotoxicity/hypertension
- Chronic renal failure
- Cor pulmonale

Therapeutic ways of preventing escape and activation of renin-angiotensin system during long term angiotensin converting enzyme inhibitor therapy

- Angiotensin II receptor antagonists
- Renin inhibitor + angiotensin converting enzyme inhibitor
- Spironolactone + angiotensin converting enzyme inhibitor
- Neutral endopeptidase inhibitor + angiotensin converting enzyme inhibitor

peptidase inhibitor combines the natriuretic effect of frusemide with the anti-ischaemic and vasodilating effect of nitrates and the favourable neuroendocrine profile of angiotensin converting enzyme inhibitors (though in truth, the neutral endopeptidase inhibitor is less potent in each of these aspects). The neuroendocrine effects of neutral endopeptidase inhibitors are, however, fairly complex. Though they decrease angiotensin II clearance, they also substantially reduce aldosterone concentrations. Furthermore, neutral endopeptidase inhibitors lead to lower renin, angiotensin II, and aldosterone values than would be found if frusemide was used instead.

AUGMENTED NEUROENDOCRINE SUPPRESSION

In chronic heart failure the most successful therapeutic strategy over the past 20 years has been neuroendocrine suppression, as exemplified by the angiotensin converting enzyme inhibitors. What is not so well appreciated is that long term treatment with angiotensin converting enzyme inhibitors is fairly poor at keeping the renin-angiotensin system suppressed. During such long term treatment angiotensin I concentrations build up so that the angiotensin converting enzyme inhibiting drug becomes less able to prevent some of the excess becoming angiotensin II. Angiotensin converting enzyme inhibitors therefore do not keep angiotensin II concentrations fully suppressed during prolonged treatment.²³ Furthermore, the suppressive effect of angiotensin converting enzyme inhibitors on aldosterone values is also gradually lost during chronic treatment. A report from the SOLVD investigators suggested that those chronic heart failure patients taking enalapril who continue to deteriorate are those in whom angiotensin II concentrations have escaped suppression.²⁴

Several solutions are possible. One might be to develop drugs which block angiotensin II receptors rather than blocking the formation of angiotensin II. Many such angiotensin II antagonists are at the clinical trial stage, and it is likely from pharmacological principles that they will block the effects of angiotensin II more efficiently. However, from early aldosterone data in chronic heart failure this is not necessarily so in practice. A second solution would be to use aldosterone antagonists or renin inhibitors either alone or along with angiotensin converting enzyme inhibitors. A third solution would be to use a neutral endopeptidase inhibitor along with the angiotensin converting enzyme inhibitor. As atrial natriuretic peptide reduces renin release, inhibits angiotensin converting enzyme activity, and blocks aldosterone release, neutral endopeptidase inhibitor given along with an angiotensin converting enzyme inhibitor should be a very powerful way of keeping the renin-angiotensin-aldosterone system completely suppressed.

Why should it be desirable, at least theoretically, to keep the renin-angiotensin-aldosterone system completely suppressed rather than partially suppressed? This is still only a theoretical advantage, but it

applies to both atherosclerosis and heart failure. Recent data on the angiotensin converting enzyme gene suggest that people who spontaneously generate more tissue angiotensin II are at greater risk of having a myocardial infarction than those who generate less tissue angiotensin II.²⁵ It has also been shown that the likelihood of developing a myocardial infarction increases with the plasma renin value.²⁶ Two large heart failure studies (SOLVD and SAVE) have also shown that angiotensin converting enzyme inhibitors reduce myocardial infarctions.^{24 27}

The circumstantial evidence quoted above is beginning to link an activated renin-angiotensin-aldosterone system with the risk of a subsequent myocardial infarction as well as the progression of chronic heart failure, and in these circumstances it begins to look sensible to suppress the renin-angiotensin-aldosterone system by as much as possible. In support of this are early if inconclusive data from heart failure studies which suggest that higher doses of angiotensin converting enzyme inhibitors are better than lower doses.²⁸ If future data confirm this, then it will be interesting to see which strategy suppresses the renin-angiotensin-aldosterone system by the most—that is, angiotensin II antagonists, renin inhibitors, aldosterone antagonists, neutral endopeptidase inhibitors along with angiotensin converting enzyme inhibitors, or simply higher doses of angiotensin converting enzyme inhibitors. This kind of discussion is clearly most relevant to heart failure, but it may be that similar considerations will apply to antiatherosclerotic therapy.

MYOCARDIAL ISCHAEMIA

With regard to myocardial ischaemia, it is conceivable that atrial natriuretic peptide, B type natriuretic peptide, C type natriuretic peptide, or neutral endopeptidase inhibitor could be a useful treatment. Atrial natriuretic peptide itself has been shown to be of benefit in exercise induced angina and dilates the coronary microvasculature.²⁹ In addition, both atrial natriuretic peptide and B type natriuretic peptide produce benefit in hyperventilation induced coronary vasospasm.³⁰ Neutral endopeptidase inhibitors produce coronary vasodilatation in animals but I am not aware of any studies with these agents in myocardial ischaemia in humans. This seems to be a subject worthy of urgent investigation, not only because of its potential value in anginal patients but also because heart failure patients inevitably have a lot of coincidental ischaemia, be it overt or silent. It is even possible that intravenous atrial natriuretic peptide or B type natriuretic peptide

A role in human coronary artery disease?

could be of value in unstable angina, where its "nitrate-like" effects might be particularly valuable.

CYCLOSPORIN

A completely different setting in which atrial natriuretic peptide, B type natriuretic peptide, or neutral endopeptidase inhibitors might be of value is in blunting the adverse effects of cyclosporin. Cyclosporin is a potent immunosuppressive which has been shown to be of benefit in virtually every autoimmune disease in which it has been tried, from asthma to diabetes mellitus. Clearly it is little used in these common diseases because of its adverse effects on nephrotoxicity and hypertension. When we examine the intrarenal effects of cyclosporin and atrial natriuretic peptide it almost seems that atrial natriuretic peptide was "tailor made" to blunt the toxic effects of cyclosporin. For example, key effects of cyclosporin are increased cytosolic calcium, constriction of the glomerular afferent arteriole, an increased blood pressure, and in the long term salt retention. Atrial natriuretic peptide does exactly the opposite. We found that intravenous atrial natriuretic peptide increases the glomerular filtration rate dramatically in both cardiac and renal transplant patients receiving long term cyclosporin.^{31 32}

CHRONIC RENAL FAILURE

One other possibility which has been little explored till now is that neutral endopeptidase inhibitors might be of benefit in chronic renal failure in terms of reversing some of the dysfunction or delaying future deterioration. Animal studies have been encouraging. In patients with chronic renal failure the kidneys can respond to neutral endopeptidase inhibitors with a pronounced natriuresis at a stage when loop diuretics would have little effect.³³ Studies are now required in patients to see if neutral endopeptidase inhibitors slow the process of renal deterioration.

COR PULMONALE

Neutral endopeptidase inhibitors may also have a place in respiratory medicine. Atrial natriuretic peptide has beneficial effects in preventing induced bronchospasm in asthma but the overall clinical effects of neutral endopeptidase inhibitors in asthma were disappointing. Investigators have now found that B type natriuretic peptide in particular relaxes the pulmonary vasculature, which might translate into clinical benefit in cor pulmonale.³⁴

Conclusion

In conclusion, 10 years of natriuretic peptides research has raised several possible clinical uses both in helping diagnosis and in treating cardiorenal disease. The next 10 years should establish whether any or all of these potential uses actually bears fruit. A final word of caution is that many of the potential therapeutic benefits have as yet been seen only in animals, and humans have the unfortunate habit of not benefiting from new drugs as much as animals. Only time will tell, but the prospects at this stage are rosy, especially for neutral endopeptidase inhibitor-angiotensin converting enzyme inhibitor combination therapy.

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Corrections

Discrimination against people with HIV and AIDS in Poland

An author's error occurred in this paper by Renée Danziger (30 April, pp 1145-7) concerning the booklet *AIDS and You*. This booklet was published by the BMA in 1987 not by the Health Education Authority. Copyright is held by the BMA.

Invasive cancer of the cervix in women with mild dyskaryosis followed up cytologically

Two printer's errors occurred in this Education and Debate article by W P Soutter and Astrid Fletcher (28 May, pp 1421-3). In the penultimate column of table I, headed No of women with invasive lesions (microinvasive lesions), the first two entries should have been 7 (?) and 5 (?) [not ? (?) and 5 (0) as published].