A Peptide Family Being Re-united: the Angiotensins Coming in from the Cold

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SUMMARY

The initial observation that the kidney contains a highly effective pressor substance was made almost a century ago. It was not until 1934, however, when Goldblatt and his colleagues demonstrated that constriction of the renal artery in dogs produced hypertension, that there was an explosion of both scientific and clinical interest in the relevant renin-angiotensin system. The first cure for hypertension by nephrectomy was reported soon after, an event that immediately led to widespread surgical management of renovascular hypertension, as evaluated by Homer Smith in the 1950's. Present day therapeutic approaches in such hypertension have largely been extensively reviewed by Hollenberg with regard to use of drugs designed to inhibit, chemically, angiotensin converting enzyme - ACE (which converts the decapeptide angiotensin II to the octapeptide angiotensin II) and also with surgical intervention and/or angioplasty which produce the best results in terms of both effectiveness and risk— in patients with fibro-muscular dysplasia: the least favourable outcome occurred in cases of widespread advanced atherosclerosis.

There was almost universal agreement until quite recently that RA activity was, to all intents and purposes, entirely mediated by the octapeptide angiotensin II, after its removal from the bloodstream in the systemic circulation, via its vasopressor and other biological effects. In this earlier scenario the decapeptide angiotensin I was regarded as the inactive precursor of the octapeptide with ACE activity being essentially confined to the lungs. The estimation of the plasma concentrations of angiotensin II and of the enzyme renin (which acts on its substrate angiotensinogen—a tetradecapeptide to produce the decapeptide) thus became of overriding interest. As a result other possible modes of action of the RA system received little attention. Such a simplistic viewpoint is, however, no longer tenable so that the relevant homeostatic mechanisms involved in blood pressure control, and water and electrolyte balance, are undergoing a profound reappraisal both regarding RA and RAA (that also involves the steroid aldosterone) activity.

ANGIOTENSIN I: THE LONG NEGLECTED FAMILY MEMBER MAKES A COMEBACK

Until recently most investigators felt that the decapeptide was biologically inactive. However, as suggested in 1987, intra-renal effects of angiotensin I could promote an antidiuresis mediated via the peritubular capillaries, this effect involving complex relationships between angiotensins I and II within the kidney; these importantly concern the distribution of pressures throughout the renal vasculature, and also the intra-renal pattern of sodium chloride levels which strongly influences the ability of the decapptide to promote water reabsorption into the circulating blood. Decreased (NaCl) also stimulates antidiuretic hormone (ADH, vasopressin) secretion by the pituitary and this, coupled with the intra-renal effects of angiotensin I, can profoundly affect renal venous plasma (solute) together with the relative plasma content of blood in the renal vein.

The increased awareness of the possible effects of angiotensin I in blood pressure regulation, combined with the improved availability and acceptability of radioactive iodinated angiotensin derivatives, and the development of more specific radioimmunoassay techniques, will doubtless be the basis of investigations supplementing the kind of clinical study involving the decapptide that has recently been reported.

THE APPARENT CLAIMS OF ANGIOTENSIN III

The loss of asparagine and aspartic acid respectively from the amino-terminals of the widely available synthetic asparaginyl- and asparaginyl-angiotensin II (Hypertensin, Ciba-Geigy) and that of the octapeptide occurring in man (asparyl-isoleucyl-angiotensin II) gives rise to heptapeptide derivatives (ie angiotensin I) designated angiotensin III. Despite the heptapeptides having only about one-third the pressor potency of the octapeptides, both the octa- and the hepta-peptides are equally effective (although the effect of angiotensin II on adrenal steroidogenesis is independent of the heptapeptide as an intermediate) in stimulating aldosterone release from the adrenal zona glomerulosa. (The question of distinct receptors for angiotensins I and III in the zona glomerulosa is of more than academic interest. Goodfird and Peach suggested the possibility of receptors other than those for angiotensin II and this may provide a possible explanation for Bartter's syndrome in which the loss of sensitivity to the pressor effects of angiotensin is not paralleled by a comparable failure of aldosterone secretion. This condition is associated with persistently high circulating plasma renin levels in spite of the lack of aldosterone response and may be due to a defect that is restricted to receptors for the octapeptide).

Infusion of angiotensin II into conscious rabbits, anaesthetised and conscious sheep causes an immediate increase in the plasma concentration of potassium ions with a similiar decrease in that of Na+ and Cl−, a pattern of (electrolyte) response that is reasonably well maintained throughout the 6 minute infusions in the sheep, with a rapid return to preinfusion plasma levels after the infusions ceased. The octapeptide also increases plasma (K+) in humans. Comparable findings to those with use of the octapeptide were also obtained when the decapptide was similarly utilized, either in sheep under general anaesthesia or in the conscious animals. The results clearly demonstrated that the ability of angiotensins I and II to liberate the potassium ions into the bloodstream is dose dependent and unrelated to pressor sensitivity, since the conscious sheep are much more sensitive to the pressor effects of both peptides than are the anaesthetised ones. These findings highlight the possibility that the electrolyte concentration changes are responsible, either partly or wholly, for stimulating adrenal aldosterone secretion (this being associated with increased RA activity as initially advanced by Healy and his co-workers and supported by others. In both rat and dog adrenal cells the lack of any
synergistic effect concerning angiotensin II and potassium suggests "that these factors share a common mode of action on steroidogenesis in zona glomerulosa cells". Their dual role has been further emphasized by Laragh with regard to the direct stimulation of aldosterone secretion. However, Foster, Lobo and Marusic, utilizing adrenal tissue from anaesthetised dogs, concluded that, because angiotensin II augmented aldosterone production without concurrent alteration of either intracellular [K+] or Na,K-ATPase activity, the octapeptide does not stimulate secretion of the steroid via potassium release. It was, however, found that angiotensin II did not promote aldosterone synthesis below a threshold K+ concentration in the zona glomerulosa cells, although the basal aldosterone production was, itself, unaffected by low intracellular potassium concentrations per se.

Whether infusions of angiotensin II and III produce similar patterns of plasma (electrolyte) changes in experimental animals has apparently not yet been considered. The relevant investigations would especially concern the potassium-releasing potency of the two peptides and would doubtless throw further light on relationships between them.

ANOTHER HEPTAPEPTIDE ON THE SCENE

The loss of phenylalanine from the carboxy-terminal of angiotensin II gives rise to the non-pressor heptapeptide des-phenylalanin-angiotensin II (i.e., angiotensin I) and only recently has this molecule been shown to possess biological activity. It's ability to stimulate vasopressin release equals that of the octapeptide and it also modulates the sensitivity of baroreceptors as readily as does angiotensin II, as indicated. This heptapeptide can be formed, either by carboxypeptidase action on angiotensin II, or by endopeptidase action on angiotensin I. A metabolic pathway bypassing angiotensin II formation. ACE inhibition markedly increases the plasma concentration of angiotensin I (1-7) together with that of angiotensin I. This importantly concerns the possibility that the heptapeptide has depressor effects in several possible ways that are augmented by ACE inhibitors as discussed by Goodfriend who states that such a depressor angiotensin would be consistent with the existence of pressor, depressor and pressure-neutral members in other families of hormones.

WHAT THE FUTURE HOLDS

The recently changed scenario regarding RA operation - coupled with doubts concerning the nature of its link-up with aldosterone secretion as outlined in this paper — will undoubtedly stimulate future developments in the relevant fields. These could well involve angiotensinogen in ways other than as a substrate for renin as indicated by Goodfriend ("For that matter, it is probably presumptuous to dismiss angiotensinogen itself, and the large fragment of angiotensinogen that remains after removal of Ang I, as having no function beyond delivering its namesake... Maybe, just maybe, angiotensinogen plus or minus Ang I is a potent protein whose other function presently eludes us"). Other possibilities regarding the tetradecapeptide could also result from the experimental findings of Poulsen and Jacobsen who argued that it was a protease inhibitor restraining renin, resembling serum protease inhibitors such as α-antitrypsin.

Certainly no one would now dispute either Goodfriend's statement "... it is by no means certain that all the biologically active peptides involved in RAA operation have yet been identified" or the conclusion of Samani that "We are there entering a most exciting stage in our understanding of the renin-angiotensin system and in our ability to manipulate it".

CONCLUSIONS

The rapid retreat from previous concepts of RA, RAA operation, that has resulted from investigations focussing on the cellular activity of the systems, has profound physiological and clinical implications. These especially concern the complex inter-relationships of the various peptides involved, in symbiotic effects influencing blood pressure control and the regulation of water and electrolyte homeostasis.

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CROSSWORD 2

CLAUSES ACROSS:
1. Corrupts with debt epidemic (10)
6. Boast about returned clothes (4)
10. Cougher or coffer? (5)
11. Knock back below Australia (4, 5)
12. Escort around Cape Horn (8)
13. See 9 Down.
15. Incisive art study (7)
17. Supports the rejects (7)
19. Seek any confused Americans? (7)
21. Back hit song — “Fever” (7)
22. Overindulge in Cheddar (5)
24. Worn out when wet (8)
27. Given in ward ten — matter varied! (9)
28. Celestial ford (5)
29. Window in Oxford’s Ashmoleum Museum (4)
30. Fill in missing tooth (4, 3, 3)

CLAUSES DOWN:
1. Long for dermatologist (4)
2. New French bread causes more suffering (5, 4)
3. Cross and lacerated (3, 2)
4. I try Sid out — isn’t clean (2, 5)
5. Lets out; calms down (7)
6. Mixed aid or maybe linked with therapy (5)
7. Great stand upset? No, sit on it! (6, 4)
9. AND 13 Put on to 3 (8, 5)
14. Sounds like a horse illness (10)
16. Puts on weight as votes are recast (8)
18. Retailing but not selling (9)
20. Present different symbol of healing (7)
21. Grass up below sea — on the mast (7)
23. Winds up and staggers (5)
25. Clerical material (5)
26. Break up utensils (4)

See page 64 for Crossword solutions.