Adrenergic facilitation by angiotensin: does it serve a physiological function?

B. G. ZIMMERMAN
Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota, U.S.A.

Introduction
A number of hormonal and pharmacological substances modulate adrenergic transmitter release by a presynaptic action (for reviews see Starke, 1977; Westfall, 1977). Prostaglandin E, acetylcholine, adenosine, dopamine and noradrenaline itself inhibit, whereas angiotensin II (ANG II), prostaglandin F$_{2\alpha}$ and isoproterenol enhance noradrenaline release. Thus stimulation of specific receptors by these substances can, through alteration in transmitter release, result in depression or augmentation, respectively, of adrenergic responses. Modulation is not limited to the adrenergic nerve terminal since with some of these agents an action on the postsynaptic site is also manifested (Malik, 1978; Verhaeghe, Lorenz, McGrath, Shepherd & Vanhoutte, 1978; Zimmerman, 1978). The purpose of this editorial review is to consider both peripheral and central adrenergic-modulating effects of angiotensin with respect to both the mechanism and the possible physiological importance. I shall not include discussion of adrenal medullary or ganglionic actions of ANG II.

Early investigations demonstrated both central and peripheral adrenergic interactions of ANG II. When administered via the dog's carotid or vertebral arterial blood supply, ANG II elicited a pressor response which was found to be mediated over the sympathetic nerves (Bickerton & Buckley, 1961; Dickinson, 1965; Ferrario, Dickinson & McCubbin, 1970). It is not certain whether the pressor response is due to direct stimulation of vasomotor neurons or to facilitation of tonic excitatory activity. The influence of ANG II on peripheral adrenergic nerves is one of facilitation of evoked nerve activity and is not caused by a direct release of catecholamines (tyramine-like effect) (Zimmerman, 1962; Benelli, Della Bella & Gandini, 1964; Starke, 1977). Since the original studies describing central and peripheral adrenergic interactions of ANG II, there have been advances in our understanding of these interactions and their mechanisms. For the sake of brevity, I shall refer to all central effects of angiotensin as central adrenergic facilitation and peripheral neurogenic effects as peripheral adrenergic facilitation. Although this is an oversimplification, and central and peripheral adrenergic facilitation may not be related to each other or to a common mechanism of action, it will assist my discussion to consider them together. Table 1 will serve as a reference for what I have defined as central adrenergic and peripheral adrenergic facilitation.

Mechanism of central adrenergic facilitation and peripheral adrenergic facilitation
Molecular mechanisms responsible for these phenomena are not known, but some information in this regard is available. Various types of experiments suggest that angiotensin, as well as...
other peptides, can affect the neuronal membrane, possibly resulting in a change of calcium flux. This may be responsible for the fact that direct application of ANG II to nerve cells (in area postrema, supraoptic nucleus and subfornical organ) increases the discharge rate of the cells (Barker, 1977). Facilitation of excitatory post-junctional potentials is brought about by repetitive adrenergic stimulation in guinea-pig vas deferens. ANG II caused an augmentation of this facilitatory activity (Bell, 1972). This phenomenon may help to explain the augmentation of adrenergic transmitter release for a given number of nerve impulses, which typifies peripheral adrenergic facilitation (Starke, 1977). Accompanying increased transmitter release in rabbit heart is an increase in dopamine β-hydroxylase (Ackerly, Blumberg & Peach, 1976). In the intact vascular bed and in isolated blood vessels peripheral adrenergic facilitation results in augmented noradrenaline release, but as yet evidence of increased release of dopamine β-hydroxylase is lacking.

Angiotensin antagonists interfere with peripheral adrenergic facilitation and thus it would appear that angiotensin receptors mediate peripheral adrenergic facilitation (Westfall, 1977). According to one study on rabbit heart the susceptibility to blockade of presynaptic angiotensin receptors was much less than that of the postsynaptic receptors (Blumberg, Ackerly & Peach, 1975). The antagonist/agonist ratio was 500:1 for almost complete blockade of the presynaptic effect. There may be a difference in susceptibility of presynaptic angiotensin receptors in heart and blood vessels, since a much lower antagonist/agonist ratio (4:1) was needed for almost complete blockade of peripheral adrenergic facilitation in the intact vascular bed (Zimmerman, 1973). More recent work indicated that β-adrenoceptor antagonists also antagonize peripheral adrenergic facilitation in rat mesenteric artery (Jackson & Campbell, 1980). The fact that D-propranolol, which lacks specific β-adrenoceptor antagonist properties, as well as L- and DL-propranolol, shared this effect makes it unlikely that β-adrenoceptors are acted on by angiotensin to cause peripheral adrenergic facilitation. Other work as well has led to the conclusion that presynaptic α or β-adrenoceptors are not involved in peripheral adrenergic facilitation by angiotensin (Starke, 1977).

Mechanisms of central adrenergic facilitation are even less well defined than those of peripheral adrenergic facilitation. As mentioned above, it is uncertain whether angiotensin modulates adrenergic transmission in the brain. Suggestions along this line have been made. Angiotensin facilitates noradrenaline release by high potassium and transmural stimulation in rabbit hypothalamic slices (Garcia-Sevilla, Dubocovich & Langer, 1979), but others were unsuccessful in detecting augmented release from brain (Taube, Starke & Borowski, 1977). Central catecholamines have also been associated with the drinking and pressor response to angiotensin, since lateral ventricular injections of 6-hydroxydopamine which depleted central catecholamines attenuated these responses (Gordon, Brody, Fink, Buggy & Johnson, 1979). It has also been reported that ANG II can, in high dosage, block catecholamine uptake in brain tissue (Palaic & Khairallah, 1967). Conceivably such an action of angiotensin could be tied in with central adrenergic facilitation.

Pathophysiological involvement

Up to this point I have described pharmacological aspects of central adrenergic facilitation and peripheral adrenergic facilitation. It is most difficult to decide whether these effects of angiotensin tell us anything about how endogenous angiotensin affects physiological processes. The remainder of this review will deal with potential roles for and suggestions of involvement of central adrenergic facilitation and peripheral adrenergic facilitation in certain pathophysiological conditions.

Basic components of the renin–angiotensin system are present at the sites where central adrenergic facilitation and peripheral adrenergic facilitation are manifested. In the brain both enzymes, renin and angiotensin-converting enzyme, appear to comprise a central isorenin–angiotensin system (Fischer-Ferraro, Nahmod, Goldstein & Finkielman, 1971; Ganten, Minnich, Granger, Hayduk, Brecht, Barbeau, Boucher & Genest, 1971) and this central system is believed to be physiologically active. There has been controversy about whether brain renin is a specific enzyme; however, I will not deal with this. The vascular wall has long been known to contain renin which it seems can affect vascular tone (Swales, 1979). Endogenous angiotensin I formed from tetradecapeptide substrate was found capable of inducing peripheral adrenergic facilitation in rat mesenteric artery in which the adrenergic innervation was transmurally stimulated (Malik & Nasjletti, 1976). Thus angiotensin produced locally in the vasculature could conceivably induce peripheral adrenergic facilitation in pathophysiological states. There are
several conditions in which participation of central adrenergic facilitation or peripheral facilitation has been proposed: hypertension, hypovolaemia and low-salt states.

Hypertension

The interesting postulate was made soon after discovery of peripheral adrenergic facilitation that this action of angiotensin might play a role in the chronic phase of renovascular hypertension (McCubbin & Page, 1963). It appeared that peripheral adrenergic facilitation might explain: (1) the persistence of the renal hypertensive condition despite waning of the elevated renin level in the acute phase and (2) the known participation of the sympathetic nervous system in the chronic phase. There have been suggestions as to central adrenergic facilitation and peripheral adrenergic facilitation involvement in renovascular hypertension and spontaneous hypertension in the rat, as well as in other conditions characterized by elevated renin levels. Such involvement, however, has been difficult to prove conclusively because of the potent direct vasoconstrictor action of angiotensin which may act with peripheral adrenergic facilitation.

Page, Kaneko & McCubbin (1966) provided some indirect support of a neurogenic influence of angiotensin, possibly peripheral adrenergic facilitation, in renovascular hypertension. In the acute phase of one-kidney, one-clip Goldblatt hypertension, in which plasma renin activity was presumed to be high, there was accentuation of various agonist-induced pressor responses, particularly that to tyramine. Since tyramine acts through the release of endogenous noradrenaline, augmentation of the tyramine response was thought to represent peripheral adrenergic facilitation. During the chronic phase of perinephritic hypertension there was, however, a heightened response only to tyramine and not the other agonists. These investigators concluded that a neural component, probably mediated by angiotensin, contributed to the chronic, but not acute, phase of renal hypertension. Evidence for altered adrenergic transmitter release in the cutaneous (paw) vascular bed of two-kidney Goldblatt hypertensive dogs was obtained 8–34 days after clamping one or both renal arteries (Zimmerman, Rolewicz, Dunham & Gisslen, 1969). There was no clear-cut difference between results obtained in the earlier or later intervals of the hypertension in this study. Altered transmitter release was characterized by a greater peak concentration of catecholamine in the venous outflow of the paw at the time correspon-
tions of endogenously generated angiotensin (Zimmerman, 1978).

Saralasin was used to ascertain whether endogenously generated angiotensin may produce peripheral adrenergic facilitation during suprarenal aortic constriction in the anaesthetized dog (Zimmerman & Kraft, 1979). Saralasin was infused intra-arterially to the pump-perfused dog paw in these experiments and was found to suppress the vasoconstrictor response to adrenergic nerve stimulation during constriction above both renal arteries. The degree of peripheral adrenergic facilitation evoked in these experiments depended on the magnitude of the increase in the plasma renin level, since the effect was significant only when a very high increase in renin (approx. 27 ng of ANG I h⁻¹ ml⁻¹) was obtained during constriction above both renal arteries. It is possible that a more moderate increase in plasma renin present over very long periods of time may bring about peripheral adrenergic facilitation, which is a situation more comparable with what exists in acute or even chronic renovascular hypertension. This question is certainly important to answer before accepting the idea that moderately elevated levels of renin achieve endogenous concentrations of angiotensin which are capable of evoking peripheral adrenergic facilitation.

Involvement of central adrenergic facilitation in experimental hypertension has also been studied. Intraventricular administration of saralasin has been shown by several groups of investigators to lower blood pressure in the spontaneously hypertensive rat (Brody, Haywood & Touw, 1980). An angiotensin antagonist and converting enzyme inhibitor given intraventricularly decreased blood pressure also in the renal hypertensive rat (Sweet, Columbo & Gaul, 1976). More recently an apparent role of central adrenergic facilitation in the spontaneously hypertensive rat was verified by intraventricular administration of captopril, another angiotensin-converting enzyme inhibitor. The implication inherent in these studies is that angiotensin most probably produced locally in the brain exerts a stimulatory action on centres governing the control of blood pressure. Blockade of these central angiotensin receptors, as well as inhibition of ANG II formation locally in the brain, is believed to counteract this angiotensin-mediated facilitatory effect. An important, yet unproven, facet of the central antihypertensive action of blockers of the renin–angiotensin system would be to demonstrate that these agents are acting simply to decrease central sympathetic outflow. To my knowledge this has not been shown. It is conceivable that central administration of these agents, often in doses which produce very high local concentrations, could elicit other actions, e.g. the release of a depressor substance from the brain which might produce a hypotensive response.

Low-salt state

Low-salt states resulting from dietary restriction of sodium or intense diuretic therapy have a profound effect on plasma renin activity. As a consequence of these stimuli, a mechanism involving the macula densa of the distal renal tubule causes renin release from the juxtaglomerular cells (Davis & Freeman, 1976). The resulting increase in the concentration of circulating ANG II exerts an important vasoconstrictor influence on the kidney (Freeman, Davis, Vitale & Johnson, 1973) and increases resistance in other vascular regions as well (Coleman, Cowley & Guyton, 1975). Conceivably, endogenous angiotensin may evoke peripheral adrenergic facilitation and central adrenergic facilitation in these conditions and intensify sympathetic reflexes. However, the carotid occlusion baroreceptor reflex is less effective in regulating blood pressure in the sodium-depleted state. Rocchini, Cant & Barger (1977) found that dogs on a low-salt diet (10⁻⁶ mol of sodium/day) exhibited a smaller pressor response to carotid occlusion than those on normal (70⁻⁶ mol of sodium/day) or high (110⁻⁶ mol of sodium/day) salt diets. They postulated that the renin–angiotensin system plays a more dominant role than the sympathetic nervous system in blood pressure homeostasis in salt depletion. Carriere, Cardinal & LeGrimellec (1979) determined the effect of acute volume depletion by frusemide in anaesthetized normal and teprotide-treated dogs on blood pressure maintenance, carotid occlusion response and plasma catecholamines. They detected no influence of prior administration of teprotide on the blood pressure response to frusemide, carotid occlusion reflex or noradrenaline level and they concluded that ANG II exerted no direct or sympathetic effect on the blood pressure response to acute volume depletion. When the order of drug administration is reversed, i.e. when an angiotensin antagonist is administered 3 h after the administration of frusemide, hypotension and renal vasodilatation do occur in the conscious dog (Zimmerman et al., 1980). This we have ascribed to an angiotensin-mediated influence on the renal vasculature and blood pressure due to acute volume depletion. Absence of an anaesthetic or allowing time for the
immediate effect of frusemide to subside may be necessary to unmask this influence. It is clear that the interaction between sodium, angiotensin and the sympathetic nervous system is complex, and a change in one factor may counteract the influence of the other in blood pressure and vascular resistance control. An interesting concept has been put forth that regions in the brain sensitive to salt may be capable of affecting the brain isorenin system and central catecholaminergic neurons in a reciprocal fashion (Ferrario, Barnes, Brosnihan & McCubbin, 1980). Thus low-salt intake would inhibit the sympathetic activity. The opposite would occur with high-salt intake. Central interaction between these systems is also envisioned to occur. It will be of great interest to see how the functioning of these central systems correlates with the peripheral influences of the renin–angiotensin and adrenergic systems.

Lower-body suction elicits compensatory cardiovascular reflexes by unloading cardiopulmonary and to a minor extent carotid–aortic baroreceptors (Shepherd & Vanhoutte, 1979). Renin release is also evoked during lower-body suction as a result of increased sympathetic drive and possibly other factors (Shepherd & Vanhoutte, 1979). Adigun, Clough, Conway & Hatton (1980) reported that injection of the angiotensin-converting enzyme inhibitor teprotide caused a larger than normal fall in blood pressure during the elicitation of the reflex response to lower-body suction in the cat. The greater hypotensive effect was attributed to blockade of peripheral adrenergic facilitation. It is unlikely that the blocker acts in this case by preventing the direct vasoconstrictor action of an increased level of circulating renin, since the response preceded any elevation in the plasma renin activity.

Conclusions

Since their discovery in the early 1960s it was not certain whether the central and peripheral adrenergic facilitating effects of ANG II were pharmacological curiosities or whether these effects were involved in the pathophysiology of endogenously produced angiotensin. The introduction of angiotensin antagonists and converting enzyme inhibitors has enabled investigators to search for an answer to this question. Although it may be premature to offer a definite opinion on the evidence which has been gathered to date, it does appear, based on the findings presented in the present review, that peripheral adrenergic facilitation may contribute to induction of renovascular hypertension and central adrenergic facilitation is involved in spontaneous hypertension in the rat. The facilitating effect of angiotensin on reflex vasoconstriction due to the cardiopulmonary reflex appears also to be a potential mode of action of angiotensin which is normally present in the circulation or vascular wall.

References


B. G. Zimmermann


