

Role of brain renin–angiotensin system in the regulation of cerebral circulation and ischaemia

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Multiple lines of evidence support the existence and functional integration of a separate and distinct renin–angiotensin system (RAS) within the brain. All components of the angiotensin system, including angiotensin receptors, have been identified in the brain, where an intraneuronal location suggests a neurotransmitter or modulator role. In specific brain areas, the RAS appears to influence blood pressure regulation and cardiovascular homeostasis, as well as thirst and salt appetite. The contribution of an intrinsic brain RAS to cerebral function, cerebral blood flow autoregulation and ischaemia is receiving widespread attention. As a mediator of cellular growth, angiotensin-II may have unique function on carotid vascular structure and cerebral circulation. Furthermore, angiotensin-II has been demonstrated to play a potential role in the dysfunction of regulation of cerebral blood flow as well as ischaemic brain injury. Thus, elucidation of the precise mechanisms of cerebral ischaemia may lead to the development of novel therapeutic strategies for ischaemic brain injury and improvement in our understanding of the homeostasis of cerebral circulation.

THE renin–angiotensin system (RAS) is a complex, mixed enzymatic-hormonal system controlling electrolyte balance, blood volume and arterial blood pressure. The two enzymes renin and angiotensin converting enzyme (ACE) act in series to liberate the active octapeptide angiotensin-II. Angiotensin-II is well known to induce a positive inotropic effect in cardiac muscle and may be an important hormonal mediator of cardiac hypertrophy^{1,2} (Figure 1). The indirect effects of angiotensin-II include central nervous system (CNS) actions such as stimulation of thirst and sympathetic outflow, stimulation of aldosterone synthesis and release, decreased renal excretion of sodium, and maintenance of vascular tone³. In its classic definition, the RAS maintains blood pressure through angiotensin-II generated in the circulation. Several lines of evidence, however, suggest that a portion of angiotensin is not generated within the circulation but in peripheral tissues. An increasing number of studies suggested the existence of local RAS in several organs, such as the kidney, adrenal gland, brain, heart and blood

vessels⁴. In this context, a concept of paracrine-autocrine functions of the RAS in the regulation of bodily function has been developed, and it is also speculated that locally produced angiotensin-II influences local tissue function and structure⁵ (Figure 2). Differently regulated gene expression within several tissue RAS has been demonstrated in a variety of animal models, which provide further insight into the regulation of the RAS on a tissue level physiological functions⁶. The clinical relevance of the intracardiac RAS is indicated by the beneficial effects of ACE inhibitors, which block the production of angiotensin-II in several pathological conditions such as congestive heart failure, myocardial ischaemia, acute myocardial infarction, reperfusion arrhythmias and left ventricular hypertrophy, as well as vascular hypertrophy^{7,8}.

Recently, two types of angiotensin-II receptors have been distinguished using non-peptide antagonists^{9,10}. AT₁ receptors are specifically inhibited by Losartan, which are found in the adrenal cortex, vasculature, kidney and liver, and are responsible for all known actions of angiotensin-II. Conversely, AT₂ receptors are selectively inhibited by PD 123319 and have yet unknown functions. Most of the responses of the angiotensin-II appear to be dependent upon the calcium release within the cells. This calcium-signalling process is initiated by the binding of angiotensin-II at its membrane receptor site, which is functionally linked to a G-protein⁷. This G-protein stimulates an enzyme, phospholipase C, which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP₂). This hydrolysis of PIP₂ results in the formation of two second messengers, inositol 1,4,5-triphosphate (IP₃) and diacylglycerol (DAG). The IP₃ in turn results in the release of calcium from intracellular stores. The other second messenger, the DAG, activates protein kinase C which acts upon the terminal phosphate of adenosine triphosphate, resulting in the phosphorylation of many different proteins including those concerned with cellular growth (Figure 3). It has been known for some years that RAS may play a role in the cerebral blood flow autoregulation and ischaemia. This review summarizes emerging evidence for a separate brain RAS and also focuses upon the role of angiotensin-II in the cerebral

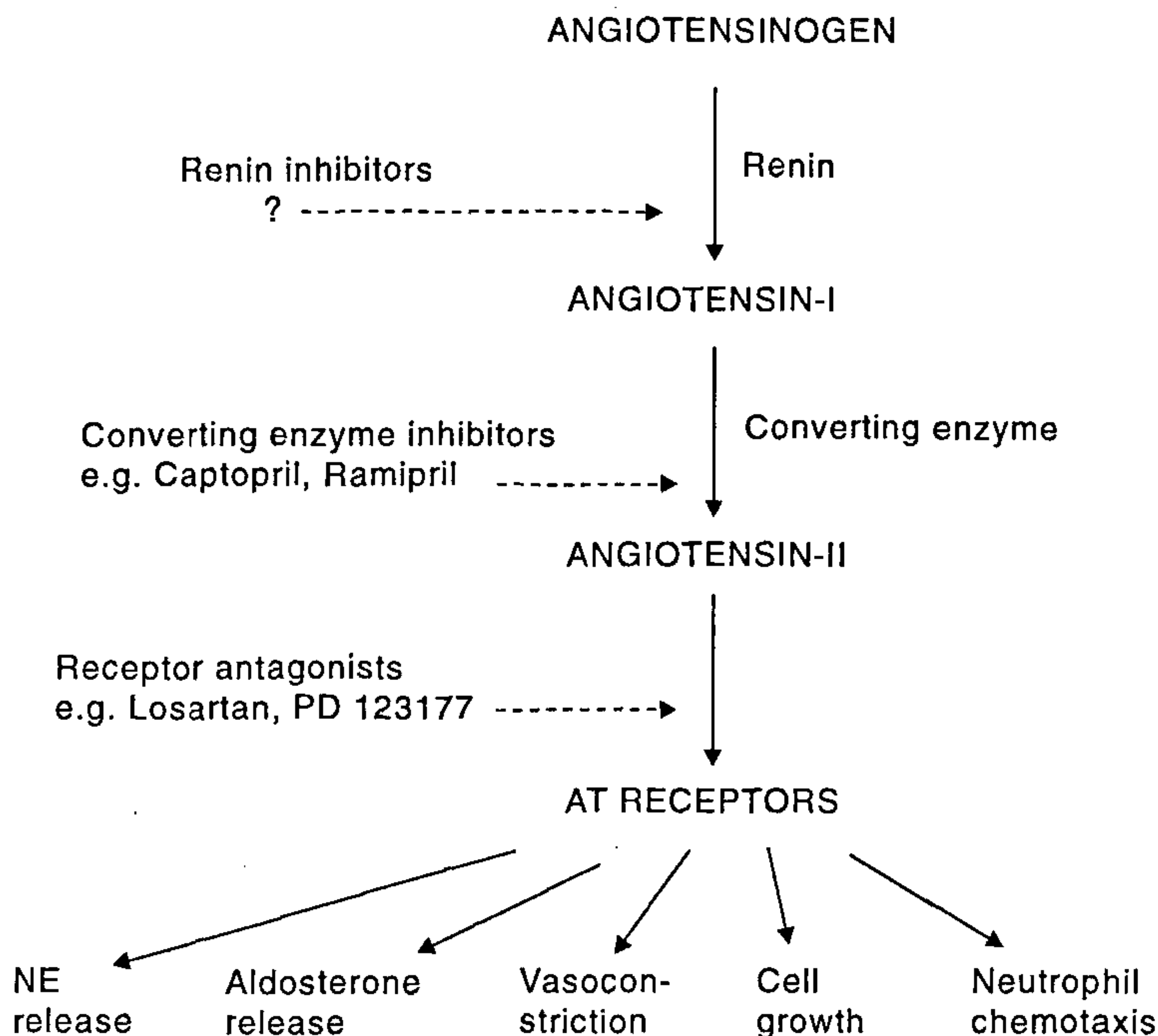


Figure 1. Pharmacological sites for inhibition of renin-angiotensin system.

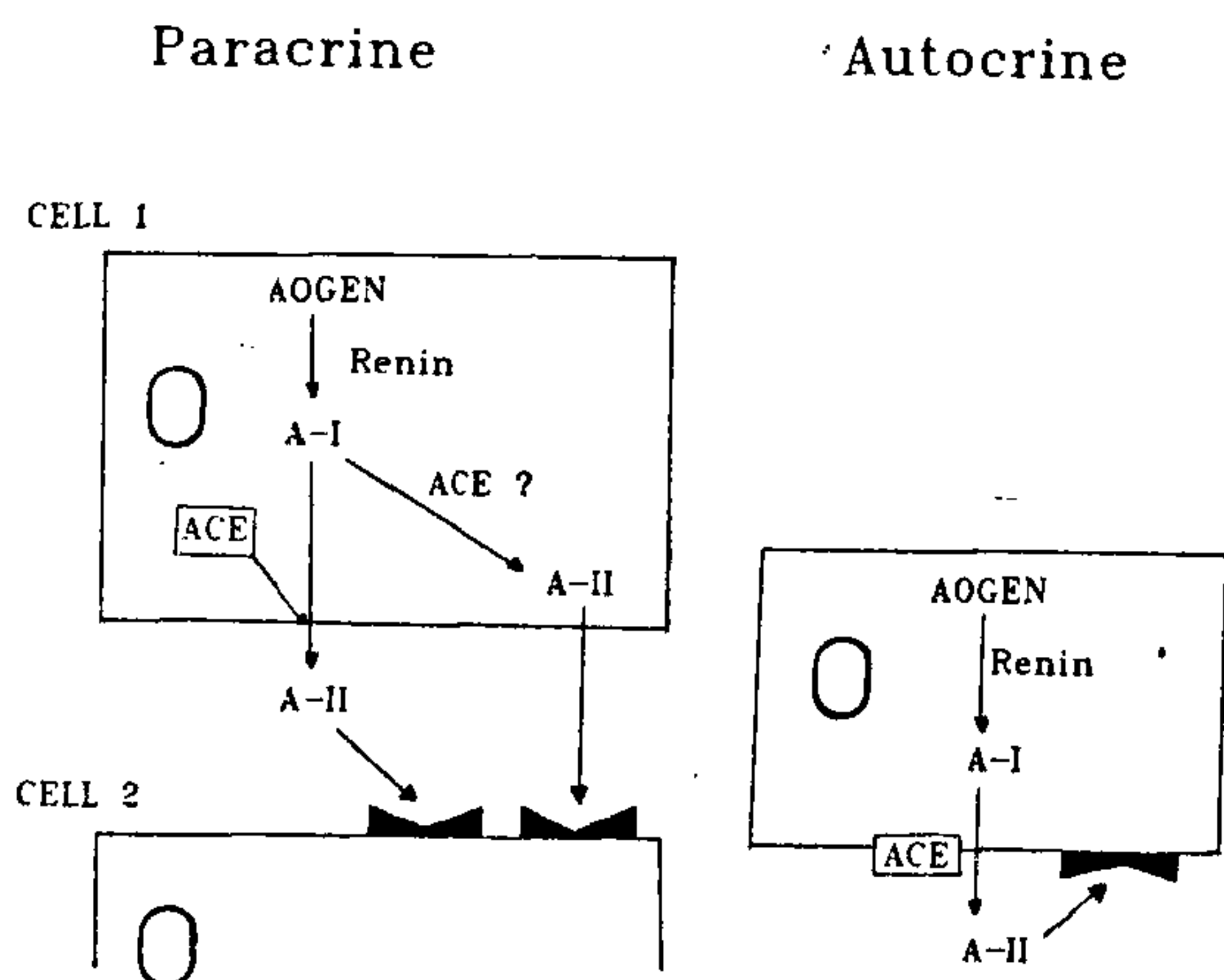


Figure 2. Schematic representation of cellular actions of local renin-angiotensin systems. In paracrine actions, intracellular formation of angiotensin (A-I) from angiotensinogen (Aogen) by the synthesizing cell leads to release of angiotensin-II, which acts on specific AT receptors at the surface of neighbouring cells, whereas in autocrine actions, angiotensin-II is synthesized cellularly and acts on receptor on the cell of its synthesis. Moreover, the presence of all components of the renin-angiotensin system in the cell may not be necessary, because it is also possible that angiotensin-I may be secreted and then activated extracellularly by ACE on the cell membrane, and so on.

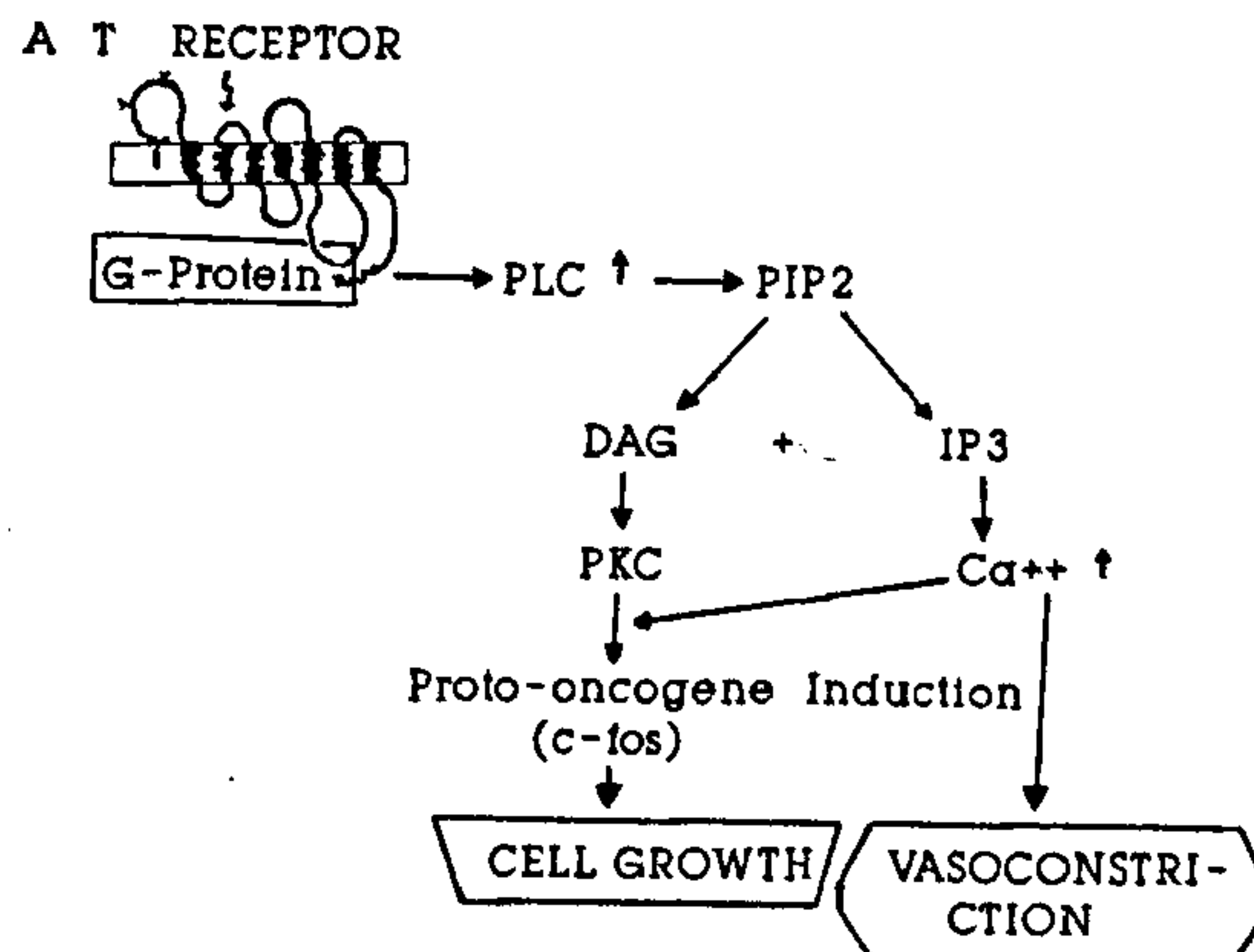


Figure 3. Signalling mechanism of angiotensin-II induced vasoconstriction and cell growth.

circulation and dysfunctions of regulation of blood flow as well as ischaemic brain injury.

Brain renin-angiotensin system

Multiple lines of evidence support the existence and functional integration of a separate and distinct RAS within the CNS¹¹⁻¹⁵. The precursors and enzymes for the formation and metabolism of active forms of an-

giotensin have been identified in brain and several subtypes of binding sites for angiotensin-II have also been localized. It appears that brain RAS can function independent of circulating RAS, but mutual interactions exist in controlling various physiological functions. Moreover, brain RAS is a target for several neuro-modulator and neurotransmitter systems¹⁶. Angiotensin receptors have been identified in circumventricular organ, anterior pituitary, median eminence, subfornical organ, area postrema, and organum vasculosum of lateral terminalis¹⁷⁻²⁰. Several nuclei of hypothalamus such as paraventricular, supraoptic, ventromedial, suprachiasmatic, median eminence and preoptic regions have large number of binding sites for angiotensin-II²¹. Angiotensin-II binding to cerebral AT₁ receptors can be blocked by Losartan, and AT₂ receptors by PD123177 (Figure 4) or CGP42112A. AT₁ receptors are present in paraventricular nuclei²²⁻²⁴, area postrema²³, nucleus tractus solitarius²⁵, organum vasculosum of the lateral ter-

minalis²⁶, septum amygdala, anterior pituitary and nucleus of the lateral olfactory tract²³, whereas AT₂ receptors predominate in thalamus, septum, basal ganglia, amygdala, locus coeruleus, ventral tegmental area, and hypoglossal nucleus^{23,27,28}. The AT₁ site appears to mediate the classic angiotensin responses concerned with body water balance, maintenance of blood pressure, and perhaps reproductive hormones and sexual behaviour. Less is known about the AT₂ site which may play a role in cell growth in cardiovascular and other systems. Recently, an AT₃ site was discovered in cultured neuroblastoma cells²⁹⁻³¹, and an AT₄ site which preferentially binds a 3-8 amino acid chain of angiotensin-II, a fragment of angiotensin-II now referred to as angiotensin-IV. The AT₄ site has been implicated in memory acquisition and retrieval, and the regulation of blood flow³²⁻³⁵. The brain RAS has been implicated in a myriad of pathophysiological conditions such as modulation of sensory system especially olfaction, audition, and sensation of pain and temperature, modulation of motor systems, memory and cognition, depression, Alzheimer's disease, long-term potentiation, cerebral blood flow and ischaemia, physiological stress and regulation of alcohol consumption¹⁶ (Figure 5). However, the functions of each of the receptor subtype in different physiopathological conditions are not yet clear. Because of the diverse nature of the brain RAS, a number of potential dysfunctions are possible. Of related importance is the role of angiotensins in blood flow and the possibility that dysfunctional autoregulation may contribute to sensory cell death. However, the precise role and anatomical locations have yet to be delineated. It is hoped that, in view of the emerging importance of brain RAS in the ongoing regulation of physiological

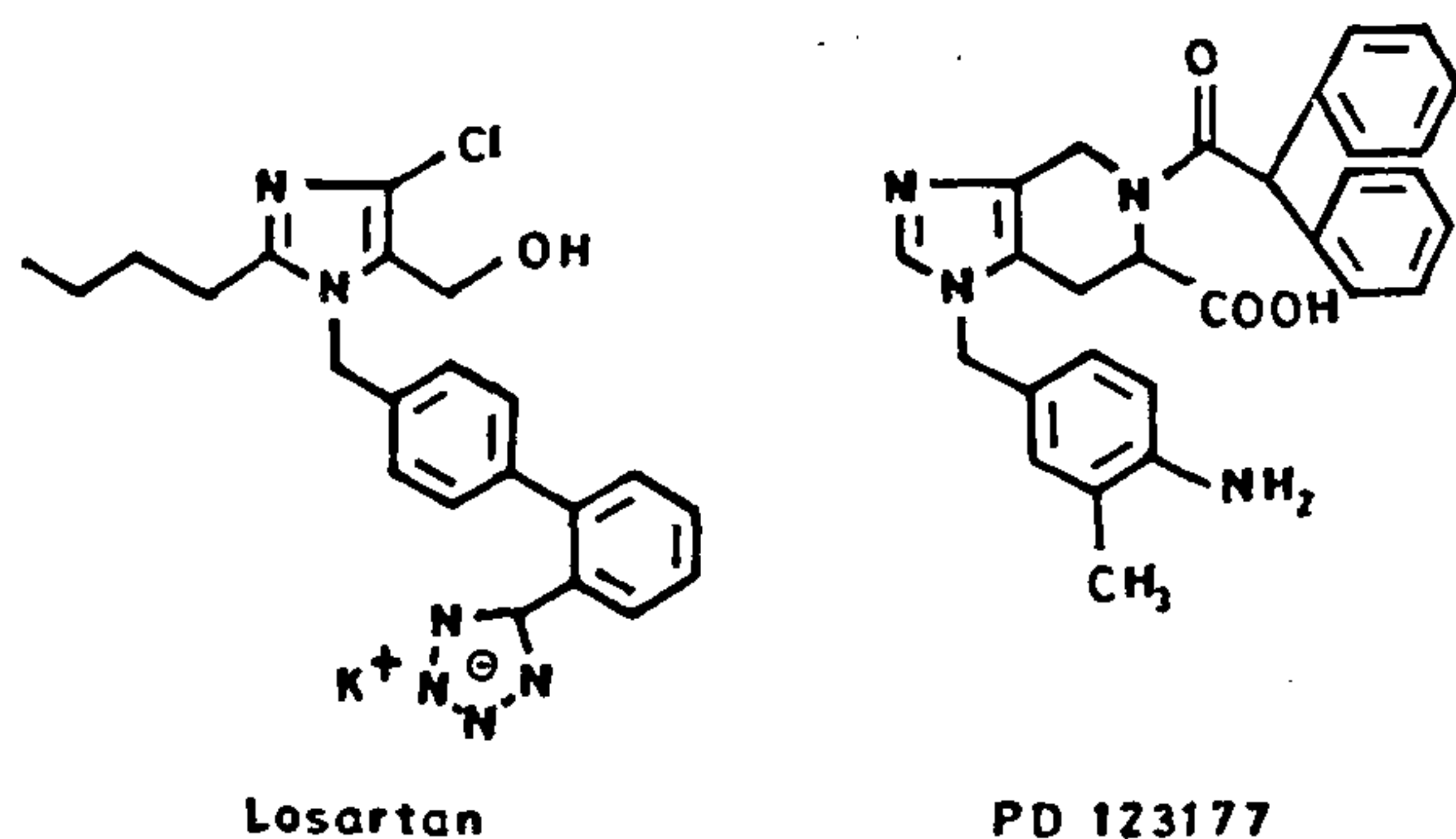


Figure 4. Chemical structures of AT receptor antagonists Losartan and PD 123177.

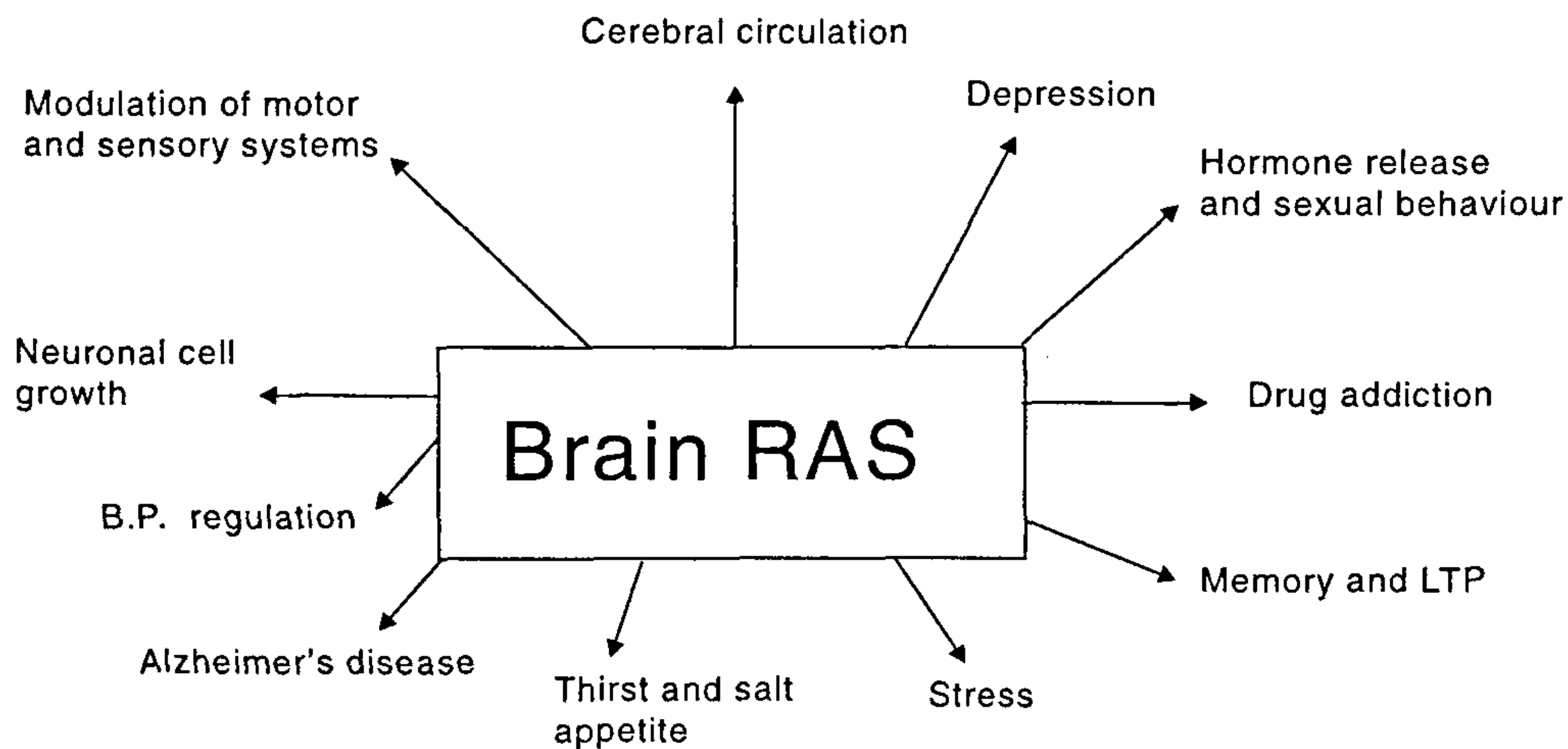


Figure 5. Postulated brain renin-angiotensin system-mediated neuropathophysiological actions.

and behavioural functions and its complex interactions with other neurotransmitters, further unfolding of brain RAS by molecular biological and discrete cellular techniques may increase our understanding of neurobiology of brain RAS.

Cerebral circulation and ischaemia

The cerebral blood flow is controlled by the process of autoregulation, whereby cerebral blood flow is kept within defined limits despite wide variations in systemic perfusion pressure. The main control is exerted at the level of small resistance vessels, which dilate in response to a fall in perfusion pressure and constrict in response to a rise in perfusion pressure³⁶. The vessels constrict as the perfusion pressure rises until the upper limit of cerebral autoregulation, and above this forceful dilation of the vessels occurs and blood flow increases. The blood-brain barrier may then be disrupted, and areas of oedema result. When perfusion pressure falls, the vessels dilate until the lower limit of autoregulation, below which cerebral blood flow falls and results in ischaemia. A myriad of factors affect the cerebral blood flow autoregulation, especially arterial oxygen, carbon dioxide tension and sympathetic nervous system activity³⁷. Sympathetic nervous system activity augments the cerebral autoregulation and participates in the homeostasis. The lower limit of autoregulation is in the mean arterial pressure (MAP) range of 50–70 mmHg, and the upper limit is 25–35 mmHg above the resting pressure³⁸.

Severe hypertension accompanied by sympathetic activation shifts the upper limit of autoregulation to the right. Cerebral blood flow in hypertensive humans is the same as in normotensive individuals. The resistance vessels of the brain show ultrastructural changes, including medial smooth muscle hypertrophy and hyperplasia because of higher mean arterial pressure³⁹. The vessel wall thickening and luminal narrowing of this vascular remodelling limit the ability of the resistance vessels to dilate. Such changes are thought to protect the brain against high perfusion pressure but at the same time impair dilation of vessels at low pressure, shifting both the lower and upper limits of cerebral blood flow autoregulation to the right. In hypertensive patients, the lower limit has been estimated to lie in the MAP range 85–150 mmHg compared with 50–70 mmHg in normotensives. There is also a shift in the lowest tolerable blood pressure from 35 mmHg in normotensives to 85 mmHg in hypertensive subjects⁴⁰. The rightwards shift in the lower limit appears to be proportional to the severity of the hypertension. With increasing age these vascular changes become irreversible and reduced baroreflex sensitivity becomes manifest. Antihypertensive therapy may fail to normalize cerebral blood flow

autoregulation. The upwards shift in the lower limit of cerebral flow autoregulation leaves the brain more susceptible to an acute reduction in blood pressure and reports indicate lowering of blood pressure to normal has resulted in cerebral damage⁴¹. These effects may be precipitated by age, the increasing stiffness of vessels, making them less able to adjust to acute falls in blood pressure.

Blood flow to the brain is often reduced in diseases such as congestive heart failure despite the normal maintenance of autoregulation^{42,43}. Activation of sympathetic nervous system occurs⁴⁴, with a shift of the autoregulation curve to the right, reduced large arterial compliance⁴⁵, and impaired carotid baroreceptor function⁴⁶, resulting in further sympathetic activation. Autoregulation is impaired in ischaemic brain tissue after stroke. Many stroke patients have a history of chronic hypertension, again predisposing to a shift of autoregulation curve. Reduction of blood pressure and subsequently of cerebral blood flow might reduce flow to that area of the brain in the area of the infarct which, although viable, but ischaemic resulting in increased infarct size. Alternatively, failure to reduce an abnormally high blood pressure might increase cerebral oedema and causes increased infarct size. Therefore, the loss of autoregulatory function in the ischaemic brain might complicate the issue of blood pressure management in these diseases⁴⁷.

Role of angiotensin-II

The role of the renin-angiotensin system in cerebrovascular disease has been discovered in recent years. Angiotensin-II has been proposed to exacerbate the vasoconstriction associated with acute stroke⁴⁸, and it might play a protective role in the cerebral circulation by maintaining blood pressure during relative or absolute hypotension and by dilating smaller cerebral vessels via release of vasodilator prostaglandins⁴⁹. Several changes occur in the control of cerebral blood flow in pathological conditions such as congestive heart failure and hypertension. There is mounting evidence that ACE inhibitors influence cerebral blood flow differently from other antihypertensive and vasodilator agents. Available studies suggest that ACE inhibitors have modulatory role on cerebral blood flow after stroke, focal ischaemia and in the prevention of primary and secondary stroke. In animals ACE inhibitors shift the lower and upper limits of cerebral autoregulation to the left. Both in normotensive and in SHR rats given captopril this leftwards shift of the curve is associated with shortening of the autoregulatory plateau⁵⁰. Recently, the effects of ACE inhibition on the autoregulatory curve have been demonstrated with captopril, which proportionately reduced the upper limit⁵⁰, or with perindopril in the

lower limit⁵¹. Administration of captopril into the cerebral ventricles had no effect on autoregulation suggesting that captopril does not cross the blood-brain barrier⁵². Thus, the effect of captopril is mediated via dilation of the large arteries supplying the brain. However, studies of the effects of ACE inhibitors on cerebral blood flow and autoregulation in humans are limited and unclear. In hypertensive humans, the effects on the autoregulatory curve are similar to those seen in animals, although the shift to the left is more consistent in the lower limit of autoregulation⁵³. Similar effects on the autoregulatory curve have been observed with fosinopril⁵⁴ and ceranapril⁵⁵ in experimental models. ACE inhibition in hypertension has no effect on cerebral blood flow, despite a fall in MAP⁵⁶. Cerebral blood flow appears to be well maintained in congestive heart failure treated with ACE inhibitors, despite a fall in MAP⁴³. Although resting cerebral blood flow in these patients is often reduced compared with normal, ACE inhibition restores the cerebral blood flow towards normal levels.

Recently it has been demonstrated that cerebral blood flow increases by 20% after 4–15 days treatment with captopril⁴². Other studies have failed to show such a change⁴³. In one study lisinopril showed an increase in common carotid artery diameter, cerebral resistance index and cerebral vasodilatory reserve, but no effect on middle cerebral artery blood flow velocity⁵⁷. These data suggest that vasoconstriction of the small cerebral resistance vessels occurs as a result of direct compensatory dilation of the large arteries. Moreover, ACE inhibitors are found to be different from other antihypertensive agents and vasodilators with respect to their modulatory effects on cerebral circulation⁵⁸. Further, it is speculated that the major effect of ACE inhibitors is to dilate the large arteries supplying brain, and cerebral circulation is maintained by constriction of small resistance vessels^{59,60}.

In both hypertension and congestive heart failure, ACE inhibitors improve carotid artery compliance. This effect has been shown for captopril, enalapril, perindopril^{61,62} and ramipril⁶⁰, which is distinct to the effect of other agents^{62–66}. The normalization of blood pressure in hypertensive rats with lisinopril is also associated with inhibition of cerebrospinal fluid ACE^{67,68}. There is ample evidence that ACE inhibitors exert beneficial effects on the small resistance vessels of the brain, mainly by preventing angiotensin-II formation. Cilazapril is effective in reducing the diameter of pial arterioles in SHR⁶⁹, protects against focal cerebral ischaemia⁷⁰ and decreases mortality in genetically stroke-prone spontaneously hypertensive rats. It decreases medial thickness and increases external diameter of cerebral arterioles and inhibits the injury-induced proliferation of smooth muscle cells⁷¹. Perindopril reverses the medial hypertrophy seen in renovascular hypertensive rats^{68,72}. An interaction between the autonomic nervous system and

the brain renin-angiotensin system has been postulated⁷³, but remains controversial. However, it is interesting that the shift in the upper limit of autoregulation to the left elicited by captopril is attenuated by sympathetic activation⁷⁴.

Conclusions

For many years angiotensin-II was considered to be circulating hormone and the renin-angiotensin system to function largely by action on the kidney, adrenal cortex, heart and on arterial vascular structures and confines to the extracranial vasculature. But with the emerging evidence for a local RAS in brain, it is apparent that angiotensin-II may play an important role in the CNS (Figure 2). All components of the RAS, including angiotensin receptors, have been identified in the brain, where an intraneuronal location suggests a neurotransmitter or modulator role. In specific brain areas the RAS appears to influence blood pressure regulation and cardiovascular homeostasis, as well as thirst and salt appetite. The contribution of an intrinsic brain RAS to cerebral function and cerebral blood flow autoregulation and ischaemia is receiving widespread attention (Figure 5). Both in hypertension and in congestive heart failure, ACE inhibitors exert beneficial effects on the structure and function of small and large arteries of intra- and extracranial carotid circulation. Because ACE inhibitors do not cross the blood-brain barrier, it appears that such effects are mediated on the luminal side of carotid arterial wall, suggesting a role for angiotensin-II, either circulating or produced locally, in the maintenance of vascular tone. As angiotensin-II is an important growth factor⁸, it may have unique function on vascular structure and cerebral circulation.

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