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AT_1-receptors in the central nervous system

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Introduction

Angiotensin II (Ang II) acts at several different sites in the central nervous system (CNS) to exert physiological effects on cardiovascular, neuroendocrine and behavioural systems. These effects may be exerted either by systemic Ang II, acting on neurons that are located in regions lacking the blood-brain barrier, or by synaptically-released Ang II subsequent to its generation in the brain.

Angiotensinogen and processing enzymes

The existence of an endogenous source of brain Ang II is a long-established concept.[1-5] Ang II-like immunoreactivity occurs in a discrete pattern throughout the nervous system[6,7] having a predominant association with regions involved in fluid and electrolyte homeostasis, cardiovascular control and neuroendocrine regulation. There is a very high correlation between the distribution of Ang II-like immunoreactive nerve terminals and Ang II (AT_1- and AT_2-) receptors, suggesting that Ang II may act via direct release across synapses.[7-9] However, there has also been a suggestion that Ang II may act by volume transmission through the extracellular space and this is substantiated by the very high concentrations of angiotensinogen in the cerebrospinal fluid.[10]

Angiotensin receptors

Ang II elicits its biological actions by binding to specific membrane-bound receptors on target cells to activate multiple intracellular transduction pathways. Using selective receptor ligands, two major Ang II receptor subtypes (AT_1 and AT_2) were identified.[11] These were subsequently cloned and their intracellular signalling cascades identified.[12-15] Physiological and pharmacological studies with the receptor subtype-selective antagonists have revealed that the known biological actions of Ang II are mediated by AT_1-receptors.[11] By contrast, although AT_2-receptors have been reported to show biological activities in cultured cell lines *in vitro* including cellular antiproliferation and apoptosis,[16,17] their physiological role *in vivo* is still being elucidated.[18]

In addition to AT_1- and AT_2-receptors, other receptors for Ang peptides have been proposed but none have yet been cloned or definitively identified. These include receptors for Ang III, Ang [1-7] and Ang [3-8].[19]

The distribution of angiotensin AT_1- and AT_2-receptors in the brain

The distribution of AT_1- and AT_2-receptors in the CNS has been mapped in detail using *in vitro* autoradiography,[20-23] *in situ* hybridisation histochemistry[9,24-27] and immunohistochemistry.[27] These studies have been performed in a number of species including the human.[28-30] Detailed maps of the distributions of these receptors are included in several recent comprehensive reviews.[9,31,32]

Most circumventricular organs, including the subfornical organ, vascular organ of the lamina terminalis (OVLT), median eminence, anterior pituitary and the area postrema of the hindbrain, contain high densities of AT_1-receptors.[9,23] These regions are exposed to blood-borne Ang II and are the sites where systemic Ang II may act to alter drinking and salt appetite, blood pressure (BP), and pituitary hormone release. In the forebrain, AT_1-receptors also occur at many regions within the blood-brain barrier, such as the median preoptic nucleus, hypothalamic paraventricular nucleus, anteroventral preoptic, suprachiasmatic and periventricular nuclei, and discrete regions of the lateral and dorsomedial hypothalamus.[9,23]

In the hindbrain, a striking distribution of AT_1-receptors is observed in regions involved in regulation of autonomic activity and cardiovascular reflexes, for example, the lateral parabrachial nucleus, nucleus of the solitary tract, dorsal motor nucleus of the vagus, intermediate reticular nucleus and rostral and caudal ventrolateral medulla.[9,23] In the sympathetic preganglionic neurons of the spinal cord, a high density of AT_1-receptors is also found. Thus AT_1-receptors occur in the brainstem nuclei involved in the regulation of heart rate and sympathetic vasomotor activity, and thus BP.[31]

Overall, we can say that the distribution of the AT_1-receptor is highly conserved across all species studied and is associated with regions of the brain known to be involved in fluid and electrolyte balance, control of neuroendocrine function and central regulation of autonomic activity.[31] In contrast, AT_2-receptor distribution is very variable between species and the only constant site of expression in the adult brain is in the molecular layer of the cerebellar cortex.[32] Whilst having a wide distribution in the rat,[23,26] the AT_2-receptor only occurs in a very limited number of sites in the adult brain in other species.[28,29] Little is known about the function of the AT_2-receptor in the brain, although the AT_2-receptor knockout mouse has some behavioural deficits indicative of altered brain function.[33,34]

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Actions of systemic angiotensin on the brain

Blood-borne Ang II exerts a number of actions on the brain, despite its lack of passage across the blood-brain barrier. Included in the centrally-mediated responses that are stimulated by circulating Ang II, are water drinking and salt hunger, vasopressin (AVP) and adrenocorticotropic hormone (ACTH) secretion, and a centrally-mediated increase in arterial pressure.

Pressor responses

The proposal that the pressor response to systemic Ang II, which primarily involves constriction of vascular smooth muscle, also involves an action on the brain came from the work of Bickerton and Buckley.[35] Initially these observations were dismissed, owing to the supraphysiological doses of Ang employed. However, it was later shown that much lower doses were required when infused into the circulation supplying the brain.[36-38] The central pressor response to systemic Ang II involves direct sympatho-excitation, AVP release and inhibition of baroreceptor activity.[37,39-45]

Recent experiments, using specific AT_1-receptor antagonists (ARB) or angiotensin-converting enzyme inhibitors (ACE-I), have shown that, under many physiological and pathological conditions, systemic Ang II supports BP by activation of sympathetic efferent pathways and inhibition of baroreceptor reflex gain.[46-50] Systemic Ang II can affect either sympathetic vasomotor nerve activity or baroreceptor reflex gain through several sites, including the subfornical organ and area postrema centrally, and at the sympathetic ganglia and sympathetic nerve terminals peripherally.[51-55] The relative importance of these sites has not been determined.

Thirst

Following the early demonstrations by Fitzsimons and colleagues that water drinking was a response to stimulation of the renin-angiotensin-aldosterone system[56] or to systematically-administered Ang II,[57] the question arose as to its site of action in the brain. How could a circulating peptide like Ang II, which is unable to cross the blood-brain barrier, induce water drinking? Subsequent studies showed that two circumventricular organs, the subfornical organ and OVLT were involved in Ang II-induced drinking.[58,59] Neurons in both of these regions are rich in AT_1-receptors[23] and are activated (as shown by *c-fos* expression) by intravenous Ang II.[60] Although the down-stream neural pathways subserving Ang-induced thirst are not well understood, a pathway via the median preoptic nucleus is probably involved.[61]

Demonstration of a central dipsogenic action of Ang II in humans is lacking at present. Intravenously-infused Ang II at doses producing moderate physiological blood levels, did not significantly increase thirst scores in human volunteers.[62] However, the concomitant increase in arterial pressure that occurs with systemic infusion of Ang II may activate baroreceptors, providing a strong inhibitory influence on water drinking. Such an inhibitory effect has been demonstrated in rats,[63] but would not be expected to result from increased endogenously-generated Ang II which occurs under physiological conditions of hypovolaemia or sodium depletion, where BP does not rise. Evidence that is suggestive of a central dipsogenic effect of circulating Ang II in humans is the intense thirst observed in patients with chronic renal failure undergoing intermittent renal haemodialysis.[64,65] These patients have elevated plasma levels of renin and Ang II and their intense thirst is extinguished by treatment with ACE-I.[65]

Vasopressin secretion

Systemic infusion of Ang II can also result in AVP secretion if the concomitant pressor response to the infused Ang II is counteracted.[66] The site(s) of action of blood-borne Ang II which results in AVP secretion appear to be the subfornical organ, although the OVLT may also play a role. There are direct projections from the subfornical organ to the sites of the AVP-secreting neurons in the supraoptic and paraventricular nuclei,[67,68] and ablation of the subfornical organ prevents AVP secretion in response to systemically-administered Ang II.[69] In addition, a role for the OVLT in Ang II-mediated vasopressin secretion is possible, because ablation of this site blocks vasopressin secretion in response to intravenous infusion of Ang II in the dog.[59]

Adrenocorticotropic hormone (ACTH) secretion

Increased circulating levels of ACTH and corticosteroids may be stimulated by systemic infusion of Ang II in dogs and rats.[66,70,71] This increased steroid secretion is more pronounced if the infusion is made directly into the carotid artery.[66] As secretion of corticotropin-releasing hormone in the pituitary portal blood is observed, an action of Ang II on the brain is likely to be responsible. The circumventricular organs have been suggested as the sites at which Ang II exerts this response,[71] but which of the circumventricular organs mediates this response is still unresolved. The median eminence seems a likely site of action in view of the high levels of AT_1-receptors there, and evidence that the subfornical organ is not the site of action of Ang II for this response.[71]

Sodium intake

Circulating Ang II acting on circumventricular organs plays a significant role in the initiation of sodium appetite by salt-deficient animals. In rats, systemic infusion of Ang II increases sodium intake[72] and high doses of ACE-I block salt appetite during sodium depletion.[73-75]

Actions of centrally generated angiotensin

In addition to the actions of blood-borne Ang II on circumventricular organs, there is now considerable evidence that Ang generated within the brain may influence central neural pathways regulating a number of functions.

Pressor responses
Depending on the cerebral site stimulated, the pressor response to Ang II in the brain involves changes in autonomic efferent activity, inhibition of baroreceptor reflex function and stimulation of vasopressin release.

Sympathetic nerve activity
Intracerebroventricular (ICV) administration of Ang II results in increases in BP due to a combination of increased vasopressin release and sympathetic nerve activity.[76,77] However, direct recordings in the rat suggest that the changes in sympathetic nerve activity are not the primary cause of increased BP in response to ICV Ang II.[78] In addition, renal sympathetic nerve activity appears to be inhibited by central Ang II, independent of changes in BP and baroreceptor reflex alterations.[79]

Microinjections of Ang II into distinct brain nuclei induce sympathetically-mediated increases in BP. Ang II excites neurons in the hypothalamic paraventricular nucleus with identified projections to the spinal cord.[80] Activation of these neurons may explain the increase in BP produced by direct microinjection of Ang II into the paraventricular nucleus.[81] Microinjection of Ang II into the nucleus of the solitary tract produces depressor (low-dose) and pressor responses.[82,83] The pressor response involves activation of sympathetic efferent pathways. The rostral ventrolateral medulla contains a population of sympathetic premotor neurons whose tonic activity is essential for the maintenance of sympathetic vasomotor tone and normal resting BP.[84] Microinjection of Ang II into the rostral ventrolateral medulla causes a sympathetically-mediated pressor response.[85-87] Similarly, intrathecal injections of Ang II induce a sympathetically-mediated increase in BP, presumably by activation of sympathetic preganglionic neurons in the intermediolateral cell column.[88]

The precise site in the brain at which ICV-administered Ang II inhibits renal sympathetic nerve activity is not known, although stimulation of the hypothalamic paraventricular nucleus (PVN) can produce an inhibition of the renal nerve activity.[89] Microinjections of Ang II into the caudal ventrolateral medulla inhibit sympathetic vasomotor activity and produce a decrease in BP.[90] The physiological role of Ang II at this site is not clear.

Vagal efferent nerve activity
Microinjections of Ang II into the dorsal motor nucleus of the vagus induce a decrease in BP and heart rate which is proposed to be due to inhibition of cardiac vagal motor neurons.[91]

Modulation of baroreceptor reflex function
Microinjections of Ang II into the nucleus of the solitary tract (NTS) inhibit baroreceptor reflex control of sympathetic nerve activity and heart rate.[92,93] The involvement of Ang II in modulation of visceral reflexes in the NTS has recently been comprehensively reviewed.[94] Inhibition of baroreceptor reflex function is proposed to occur via potentiation of inhibitory interneuron activity within the NTS possibly involving nitric oxide production. In addition, Ang II potentiates chemoreflex function possibly via presynaptic facilitation of substance P release from primary afferents.[94-97]

Thirst mechanisms
Probably the most spectacular demonstration that Ang II acts within the brain as a neurotransmitter is the rapid and copious water drinking that occurs within seconds of its injection into the hypothalamic/preoptic region of the brain or the cerebral ventricles.[98]

A likely site at which Ang II exerts this effect is the median preoptic nucleus in the anterior wall of the third ventricle. This nucleus is rich in both AT_1-receptors and Ang II-containing nerve terminals.[7,23] Direct injection of Ang II into the median preoptic nucleus rapidly stimulates water drinking.[99] Ablation of the median preoptic nucleus,[61] but not subfornical organ,[100] abolishes drinking induced by centrally-injected Ang II. The administration of AT_1-receptor antagonists (ARBs), such as losartan, directly into the brain, have been shown to effectively block some physiological drinking responses.[101-104]

Vasopressin secretion
ICV injection of Ang II stimulates vasopressin secretion.[105] It is unlikely that this is a direct action via AT_1-receptors on the AVP-containing neurons of the supraoptic and paraventricular nuclei of the hypothalamus.[9,23] Neuronal inputs to the supraoptic and paraventricular nuclei come from several regions rich in Ang II receptors and Ang II-containing terminals, including the caudal ventrolateral medulla, NTS and the lamina terminalis.[106] Thus, these may be sites at which Ang II acts as a neurotransmitter to influence vasopressin release.[107]

ACTH secretion
In addition to Ang II from the circulation stimulating the hypothalamo-pituitary-adrenal (HPA) axis, there is also evidence of a central angiotensinergic influence on corticotropin-releasing hormone and ACTH secretion. Infusions of Ang II into the lateral or third cerebral ventricle increases plasma concentrations of corticosteroids or ACTH in a number of species.[71,108,109] A possible site of action of Ang II to influence the HPA axis is the corticotropin-releasing hormone-containing parvocellular neurons of the PVN. These neurons are rich in AT_1-receptors.[110,111]

Sodium appetite
Centrally-administered renin or Ang II can cause a long-lasting stimulation of salt appetite in species as diverse as rats, pigeons, sheep and pigs,[112] suggesting that angiotensinergic mechanisms within the brain participate in regulating sodium appetite. In contrast to the water drinking that is quickly initiated following central injection of Ang II, the increased sodium intake may occur only after several hours and may persist for days. Interpretation of this Ang II-induced sodium hunger is difficult because of its long latency and long-lasting effect and the fact that part of it (but not all) may be secondary to sodium depletion,

resulting from a natriuretic response that also occurs in response to centrally-administered Ang II.[113] Central administration of AT_2-, as well as AT_1-antagonists has been shown to reduce sodium intake in response to ICV Ang II.[102] Regions of the brain that have been implicated in central Ang II-induced sodium appetite include the ventral lamina terminalis and the amygdala.[114]

Natriuresis

Contrasting with the sodium-retention and increased aldosterone secretion that result from circulating Ang II, is the natriuretic effect that occurs in response to ICV administration of Ang II in a number of species.[113,115] The rapid natriuresis following ICV injection of Ang II may come about because BP increases (causing a pressure natriuresis), renal sympathetic nerve activity is suppressed,[79] plasma levels of renin fall,[116] vasopressin secretion increases,[105,117] or a natriuretic agent is released into the circulation. One of these factors, alone or in combination with one or more of the others, may be the link between brain and kidney mediating this response. Ablation of the Ang II receptor-rich region of the AV3V region of the brain abolishes the natriuretic response to ICV Ang II in sheep (Pennington and McKinley, unpublished observations), suggesting that the median preoptic nucleus and/or OVLT are sites of such central Ang action.

Renin secretion

Circulating Ang II exerts a powerful inhibitory influence on renin secretion by the kidney. There is also evidence that a central angiotensinergic influence may inhibit renal renin secretion. In several species, ICV infusion of Ang II reduces renin secretion by the kidney.[116,118-120] ICV Ang II reduces plasma renin levels in sodium-depleted sheep without inducing a pressor response, indicating that the inhibition of renin secretion is not secondary to baroreceptor activation.[118] Prior ICV treatment with losartan blocks this response and, in fact, central losartan treatment further increases plasma renin levels in sodium-depleted sheep,[118] indicating AT_1-receptor involvement. Central administration of Ang II to the lateral ventricle also causes a reduction in renal sympathetic nerve activity,[81] which may be a factor contributing to the reduction in plasma renin levels with this treatment.

Thermoregulation

Indications that central angiotensinergic mechanisms participate in thermoregulation came initially from observations that centrally-administered Ang II produced a reduction in body temperature in monkeys and rabbits.[121,122] This effect is due to increased heat radiation from the skin and decreased metabolic heat production.[122,123] The effects of ICV Ang II on thermoregulation in the rat can be blocked by losartan,[124] indicating an AT_1-receptor mediated response.

Memory

There is considerable evidence linking brain Ang II with a role in cognition. Behavioural studies have reported that exogenous administration of renin or Ang II, acting through AT_1-receptors, disrupts learning and memory in passive avoidance, operant and retention behaviour paradigms.[125-128] In line with this behavioural observation, Ang II inhibits depolarisation-induced release of acetylcholine from rat entorhinal and human temporal cortex.[129,130] Thus, Ang II might inhibit cognitive performance by inhibiting cholinergic function. Interestingly, ACE-I improve the cognitive performance of mice or rats.[131]

Conclusion

Angiotensin exerts a wide range of actions in the brain, following either delivery from the circulation to reach AT_1-receptors in the circumventricular organs, or following generation within the brain to access AT_1-receptors at sites within the blood-brain-barrier. Many of these actions concern central pressor, autonomic and renal effects which, in concert with neuroendocrine and behavioural actions, help to maintain BP and body fluid and electrolyte homeostasis. In addition, Ang II has actions in other areas including thermoregulation, modulation of catecholaminergic and cholinergic neurotransmission and effects on cognition. By contrast to these AT_1-receptor-mediated effects, the role of Ang II acting at brain AT_2-receptors is yet to be determined. Much remains to be learned about the role of Ang II in the brain. For example, our understanding of the details of the biochemical and cellular pathways of the formation of brain Ang II remains unclear. The action of Ang II at the majority of CNS sites containing AT_1-receptors is not known. Thus, we have only just begun to explore the central roles of this important physiological regulator.

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References

1. Phillips MI. Functions of angiotensin in the central nervous system. *Ann Rev Physiol* 1987;**49**:413-35.
2. Fischer-Ferraro C, Nahmod VE, Goldstein DJ, Finkielman S. Angiotensin and renin in rat and dog brain. *J Exp Med* 1971; **133**:353-61.
3. Ganten D, Minnich JL, Granger P *et al.* Angiotensin-forming enzyme in the brain tissue. *Science* 1971;**173**:64-5.
4. Hirose S, Yokosawa H, Inagami T. Immunochemical identification of renin in rat brain and distinction from acid proteases. *Nature* 1978;**274**:392-3.
5. Campbell DJ. Angiotensin peptides in the brain. *Adv Exp Med Biol* 1995;**377**:349-55.
6. Fuxe K, Ganten D, Hokfelt T, Bolme P. Immunohistochemical evidence for the existence of angiotensin II-containing nerve terminals in the brain and spinal cord of the rat. *Neurosci Lett* 1976;**2**:229-34.
7. Lind RW, Swanson LW, Ganten D. Organization of angiotensin II immunoreactive cells and fibres in the rat central nervous system. *Neuroendocrinology* 1985;**40**:2-24.
8. Allen AM, Paxinos G, Song KF, Mendelsohn FAO. Localization of angiotensin receptor binding sites in the rat brain. In: Bjorkland A, Hokfelt T, Kuhar MJ (eds). *Handbook of Chemical Neuroanatomy: Neuropeptide receptors in the CNS.* Amsterdam: Elsevier, 1992;**11**:1-35.
9. Lenkei Z, Palkovits M, Corvol P, Llorens-Cortes C. Expression of angiotensin type-1 (AT_1) and type-2 (AT_2) receptor mRNAs in the adult rat brain: a functional anatomical review. *Front Neuroendocrinol* 1997;**18**:383-439.

10. Hilgenfeld U. Angiotensinogen in rat cerebrospinal fluid. *Clin Exper Hypertens* 1984;**6**:1815-24.
11. Timmermans PBMW, Wong PC, Chiu AT *et al*. Angiotensin II receptors and angiotensin II receptor antagonists. *Pharmacol Rev* 1993;**45**:205-51.
12. Murphy TJ, Alexander RW, Griendling KK, Runge MS, Bernstein KE. Isolation of a cDNA encoding the vascular type-1 angiotensin II receptor. *Nature* 1991;**351**:233-6.
13. Sasaki K, Yamano Y, Bardhan S *et al*. Cloning and expression of a complementary DNA encoding a bovine adrenal angiotensin II type-1 receptor. *Nature* 1991;**351**:230-3.
14. Kambayashi Y, Bardhan S, Takahashi K *et al.* Molecular cloning of a novel angiotensin II receptor isoform involved in phosphotyrosine phosphatase inhibition. *J Biol Chem* 1993;**268**:24543-6.
15. Mukoyama M, Nakajima M, Horiuchi M, Sasamura H, Pratt RE, Dzau VJ. Expression cloning of type 2 angiotensin II receptor reveals a unique class of seven-transmembrane receptors. *J Biol Chem* 1993;**268**:24539-42.
16. Stoll M, Steckelings UM, Paul M, Bottari SP, Metzger R, Unger T. The angiotensin AT_2-receptor mediates inhibition of cell proliferation in coronary endothelial cells. *J Clin Invest* 1995; **95**:651-7.
17. Yamada T, Horiuchi M, Dzau VJ. Angiotensin II type 2 receptor mediates programmed cell death. *Proc Natl Acad Sci USA* 1996; **93**:156-60.
18. Horiuchi M, Akishita M, Dzau VJ. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. *Hypertension* 1999; **33**:613-21.
19. Moeller IM, Allen AM, Chai SY, Zhuo J, Mendelsohn FAO. Bioactive angiotensin peptides. *J Hum Hypertens* 1998;**12**: 289-93.
20. Rowe BP, Grove KL, Saylor DL, Speth RC. Angiotensin II receptor subtypes in the rat brain. *Eur J Pharmacol* 1990;**186**:339-42.
21. Wamsley JK, Herblin WF, Hunt M. Evidence for the presence of angiotensin II type receptors in brain. *Brain Res Bull* 1990;**25**:397-400.
22. Song K, Allen AM, Paxinos G, Mendelsohn FAO. Angiotensin II receptor subtypes in rat brain. *Clin Exper Pharmacol Physiol* 1991;**18**:93-6.
23. Song K, Allen AM, Paxinos G, Mendelsohn FAO. Mapping of angiotensin II receptor subtype heterogeneity in rat brain. *J Comp Neurol* 1992;**316**:467-84.
24. Bunnemann B, Iwai N, Metzger R, Fuxe K, Inagami T, Ganten D. The distribution of angiotensin II AT1 receptor subtype mRNA in the rat brain. *Neurosci Lett* 1992;**142**:155-8.
25. Lenkei Z, Corvol P, Llorens-Cortes C. The angiotensin receptor subtype AT1A predominates in rat forebrain areas involved in blood pressure, body fluid homeostasis and neuroendocrine control. *Mol Brain Res* 1995;**30**:53-60.
26. Lenkei Z, Palkovits M, Corvol P, Llorens-Cortes C. Distribution of angiotensin II type-2 receptor (AT2) mRNA expression in the adult rat brain. *J Comp Neurol* 1996;**373**:322-39.
27. Giles ME, Fernley RT, Nakamura Y *et al.* Characterization of a specific antibody to the rat AT1 receptor. *J Histochem Cytochem* 1999;**47**:507-15.
28. Aldred GP, Chai SY, Song K, Zhuo J, MacGregor DP, Mendelsohn FAO. Distribution of angiotensin II receptor subtypes in the rabbit brain. *Regul Pept* 1993;**44**:119-30.
29. MacGregor DP, Murone C, Song K, Allen AM, Paxinos G, Mendelsohn FAO. Angiotensin II receptor subtypes in the human central nervous system. *Brain Res* 1995;**675**:231-40.
30. Barnes JM, Steward U, Barber PC, Barnes NM. Identification and characterization of angiotensin II receptor subtypes in human brain. *Eur J Pharmacol* 1993;**231**:251-8.
31. Allen AM, Oldfield BJ, Giles ME, Paxinos G, McKinley MJ, Mendelsohn FAO. Localization of angiotensin receptors in the nervous system. In: Quirion R, Bjorklund A, Hokfelt T (eds). *Handbook of Chemical Neuroanatomy*. Amsterdam: Elsevier, 2000;79-124.
32. Allen AM, MacGregor DP, McKinley MJ, Mendelsohn FAO. Angiotensin II receptors in the human brain. *Reg Pept* 1999;**79**:1-7.
33. Hein L, Barch GS, Pratt RE, Dzau VJ, Kobilka BK. Behavioural and cardiovascular effects of disrupting the angiotensin II type-2 receptor gene in mice. *Nature* 1995;**377**:744-7.
34. Ichiki T, Labosky PA, Shiota C *et al.* Effects on blood pressure and exploratory behaviour of mice lacking angiotensin II type-2 receptor. *Nature* 1995;**377**:748-50.
35. Bickerton RK, Buckley JP. Evidence of a central mechanism in angiotensin-induced hypertension. *Proc Soc Exper Biol Med* 1961;**106**:834-6.
36. Dickinson CJ, Lawrence JR. A slowly developing pressor response to small concentrations of angiotensin: its bearing on the pathogenesis of chronic renal hypertension. *Lancet* 1963;**1**:1354-6.
37. Scroop GC, Lowe RD. Efferent pathways of the cardiovascular response to vertebral artery infusions of angiotensin in the dog. *Clin Sci* 1969;**37**:605-19.
38. Ferrario CM, Dickinson CJ, McCubbin JW. Central vasomotor stimulation by angiotensin. *Clin Sci* 1970;**39**:239-43.
39. Ferrario CM, Gildenberg PL, McCubbin JW. Cardiovascular effects of angiotensin mediated by the central nervous system. *Circ Res* 1972;**30**(3):257-62.
40. Fukiyama K. Central action of angiotensin and hypertension increased vasomotor outflow by angiotensin. *Jpn Circ J* 1972; **36**:599-603.
41. Bonjour JP, Malvin RL. Stimulation of ADH release by the renin-angiotensin system. *Am J Physiol* 1970;**218**:1555-9.
42. Lumbers ER, McClosky DI, Potter EK. Inhibition by angiotensin II of baroreceptor-evoked activity in cardiac vagal efferent nerves in the dog. *J Physiol* 1979;**294**:69-80.
43. Guo GB, Abboud FM. Angiotensin II attenuates baroreflex control of heart rate and sympathetic activity. *Am J Physiol* 1984;**246**:H80-H89.
44. Stein RD, Stephenson RB, Weaver LC. Central actions of angiotensin II oppose baroreceptor-induced sympathoinhibition. *Am J Physiol* 1984;**246**:R13-R19.
45. Keil LC, Summy-Long J, Severs WB. Release of vasopressin by angiotensin II. *Endocrinology* 1975;**96**:1063-8.
46. Brooks VL. Interactions between angiotensin II and the sympathetic nervous system in the long-term control of arterial pressure. *Clin Exper Pharmacol Physiol* 1997;**24**:83-90.
47. DiBona GF, Jones SY, Brooks VL. Ang II receptor blockade and arterial baroreflex regulation of renal nerve activity in cardiac failure. *Am J Physiol* 1995;**269**:R1189-R1196.
48. Dibner-Dunlap ME, Smith ML, Kinugawa T, Thames MD. Enalaprilat augments arterial and cardiopulmonary baroreflex control of sympathetic nerve activity in patients with heart failure. *Am Coll Cardiol* 1996;**27**:358-64.
49. Xu L, Brooks VL. Ang II chronically supports renal and lumbar sympathetic activity in sodium-deprived, conscious rats. *Am J Physiol* 1996;**271**:H2951-H2958.
50. Heesch CM, Crandall ME, Turbek JA. Converting enzyme inhibitors cause pressure–independent resetting of baroreflex control of sympathetic outflow. *Am J Physiol* 1996;**270**:R728-R737.
51. Mangiapane ML, Simpson JB. Subfornical organ lesions reduce the pressor effects of systemic angiotensin. *Neuroendocrinology* 1980;**31**:380-84.
52. Gildenberg PL, Ferrario CM, McCubbin JW. Two sites of cardiovascular actions of angiotensin II in the brain of the dog. *Clin Sci* 1973;**44**:417-22.
53. Lewis GP, Reit E. The action of angiotensin and bradykinin on the superior cervical ganglion of the cat. *J Physiol* 1965;**179**:538-53.
54. Zimmerman BG. Effect of acute sympathectomy on responses to angiotensin and norepinephrine. *Circ Res* 1962; **11**:780-87.
55. Hughes J, Roth RH. Evidence that angiotensin enhances transmitter release during sympathetic nerve stimulation. *Br J Pharmacol* 1971; **41**:239-55.
56. Fitzsimons JT. The role of a renal thirst factor in drinking induced by extracellular stimuli. *J Physiol* (London) 1969; **201**:349-68.
57. Fitzsimons JT, Simons B. The effect on drinking in the rat of intravenous infusion of angiotensin, given alone or in combination with other stimuli of thirst. *J Physiol* 1969;**203**:45-57.
58. Simpson JB, Epstein AN, Cammardo JS. Localization of receptors for the dipsogenic action of angiotensin II in the subfornical organ of rat. *J Comp Physiol Psychol* 1978; **92**:581-608.
59. Thrasher TN. Circumventricular organs, thirst, and vasopressin secretion. In: Schrier RW (ed). *Vasopressin*. New York: Raven Press, 1985.
60. McKinley MJ, Badoer E, Oldfield BJ. Intravenous angiotensin II induces Fos-immunoreactivity in circumventricular organs of the lamina terminalis. *Brain Res* 1992;**294**:295-300.
61. Cunningham JT, Beltz TG, Johnson RF, Johnson AK. The effects of ibotenate lesions of the median preoptic nucleus on experimentally induced and circadian drinking behaviours in rats. *Brain Res* 1992;**580**:325-30.
62. Phillips PA, Rolls BJ, Ledingham JG. Angiotensin II-induced thirst and vasopressin release in man. *Clin Sci* 1995;**68**:669-74.
63. Robinson MM, Evered MD. Pressor action of intravenous angiotensin II reduces drinking in rats. *Am J Physiol* 1987;**252**:R754-R759.

64. Rogers PW, Kurzman NA. Renal failure, uncontrollable thirst and hyper-reninaemia. Cessation of thirst with bilateral nephtrectomy. *JAMA* 1973;**225**:1236-8.
65. Yamamoto T, Shimuzu M, Morioka M. Role of angiotensin II in the pathogenesis of hyperdipsia in chronic renal failure. *JAMA* 1986;**25**:604-8.
66. Reid IA. Actions of angiotensin II on the brain: mechanisms and physiologic role. *Am J Physiol* 1984;**246**:F533-F543.
67. Miselis RR. The efferent projections of the subfornical organ of the rat: A circumventricular organ with a neural network subserving water balance. *Brain Res* 1981;**230**:1-23.
68. Lind RW, van Hoesen GW, Johnson AK. An HRP study of the connections of the subfornical organ of the rat. *J Comp Neurol* 1982;**210**:265-77.
69. Mangiapane ML, Thrasher TN, Keil LC, Simpson JG, Ganong WF. Role for the subfornical organ in vasopressin release. *Brain Res Bull* 1984;**13**:43-7.
70. Reid IA, Brooks VL, Rudolph CD, Keil LC. Analysis of the action of angiotensin on the central nervous system of conscious dogs. *Am J Physiol* 1982;**243**:R82-R91.
71. Ganong WF, Murakami K. The role of angiotensin II in the regulation of ACTH release. *Ann NY Acad Sci* 1987;**512**:176-86.
72. Findlay ALR, Epstein AN. Increased sodium intake is somehow induced in rats by intravenous angiotensin II. *Horm Behav* 1980; **14**(1):86-92.
73. Moe KE, Weiss ML, Epstein AN. Sodium appetite during captopril blockade of endogenous angiotensin II formation. *Am J Physiol* 1984;**247**:R356-R365.
74. Weisinger RS, Denton DA, Di Nicolantonio R, McKinley MJ. The effect of captopril or enalaprilic on the Na appetite of Na-deplete rats. *Clin Exp Pharmacol Physiol* 1988;**15**:55-65.
75. Thunhorst RL, Fitts DA. Peripheral angiotensin causes salt appetite in rats. *Am J Physiol* 1994;**2267**:R171-R177.
76. Falcon JE, Phillips MI, Hoffman WE, Brody MJ. Effects of intraventricular angiotensin II mediated by the sympathetic nervous system. *Am J Physiol* 1978;**235**:H392-H397.
77. Severs WB, Daniels-Severs A. Effects of angiotensin on the central nervous system. *Pharmacol Rev* 1973;**25**:415-63.
78. Unger T, Becker H, Petty M *et al.* Differential effects of central angiotensin II and substance P on sympathetic nerve activity in conscious rats. *Circ Res* 1985;**56**:563-75.
79. May CN, McAllen RM. Baroreceptor-independent renal nerve inhibition by ICV angiotensin II in conscious sheep. *Am J Physiol* 1997;**273**:R560-R567.
80. Bains JS, Ferguson AV. Paraventricular nucleus neurons projecting to the spinal cord receive excitatory input from the subfornical organ. *Am J Physiol* 1995;**268**:R625-R633.
81. Bains JS, Potyok A, Ferguson AV. Angiotensin II actions in paraventricular nucleus: functional evidence for a neurotransmitter role in efferents originating in subfornical organ. *Brain Res* 1992;**599**:223-9.
82. Casto R, Philips MI. Cardiovascular actions of microinjections of angiotensin II on the brain stem of rats. *Am J Physiol* 1984; **246**:R811-R816.
83. Rettig R, Healy DP, Printz MP. Cardiovascular effects of microinjections of angiotensin II into the nucleus tractus solitarii. *Brain Res* 1986; **364**:233-40.
84. Dampney RAL. Functional organisation of central pathways regulating the cardiovascular system. *Physiol Rev* 1994;**74**:323-64.
85. Allen AM, Dampney RAL, Mendelsohn FAO. Angiotensin receptor binding and pressor effects in the cat subretrofacial nucleus. *Am J Physiol* 1988;**255**:H1011-H1017.
86. Andreatta SH, Averill DB, Santos RAS, Ferrario CM. The ventrolateral medulla: A new site of action of the renin-angiotensin system. *Hypertension* 1988;**11**[Suppl I]:I-163–I-166.
87. Sasaki S, Dampney RAL. Tonic cardiovascular effects of angiotensin II in the ventrolateral medulla. *Hypertension* 1990;**15**:274-83.
88. Lewis DI, Coote JH. Angiotensin II in the spinal cord of the rat and its sympatho-excitatory effects. *Brain Res* 1993;**614**:1-9.
89. Gardner J, Coote JH. Cluster analysis of the effects on renal and adrenal nerve activity of stimulation of the paraventricular nucleus in the rabbit. *J Physiol* 1996;**497**:17(Abstract).
90. Allen AM, Mendelsohn FAO, Gieroba ZJ, Blessing WW. Vasopressin release following microinjection of angiotensin II into the caudal ventrolateral medulla in the anaesthetized rabbit. *J Neuroendocrinol* 1990;**2**:867-74.
91. Diz DI, Barnes KL, Ferrario CM. Hypotensive actions of microinjections of angiotensin II into the dorsal motor nucleus of the vagus. *J Hypertens* 1984;**2**[Suppl 3]:53-6.
92. Casto R, Phillips MI. Angiotensin II attenuates baroreflexes at nucleus tractus solitarius of rats. *Am J Physiol* 1986;**250**:R193-R198.
93. Campagnole-Santos MJ, Diz DI, Ferrario CM. Baroreceptor reflex modulation by angiotensin II at the nucleus tractus solitarii. *Hypertension* 1988; **11** [Suppl I]:I-167-I-171.
94. Paton JFR, Kasparov S. Sensory channel specific modulation in the nucleus of the solitary tract. *J Auton Nerv Syst* 2000; **80**:117-29.
95. Lewis SJ, Allen AM, Verberne AJM, Figdor R, Jarrott B, Mendelsohn FAO. Angiotensin II receptor binding in the rat nucleus tractus solitarii is reduced after unilateral nodose ganglionectomy or vagotomy. *Eur J Pharmacol* 1986;**125**:305-7.
96. Diz DI, Barnes KL, Ferrario CM. Contribution of the vagus nerve to angiotensin II binding sites in the canine medulla. *Brain Res Bull* 1986;**17**:497-506.
97. Qu L, McQueeney AJ, Barnes KL. Presynaptic or postsynaptic location of receptors for angiotensin II and substance P in the medial solitary tract nucleus. *J Neurophysiol* 1996;**75**:2220-8.
98. Fitzsimons JT. Angiotensin stimulation of the central nervous system. *Rev Physiol Biochem Pharmacol* 1980;**87**:117-67.
99. O'Neill TP, Brody MJ. Role for the median preoptic nucleus in centrally evoked pressor responses. *Am J Physiol* 1987;**252**:R1165-R1172.
100. Buggy J, Fisher AE. Anteroventral third ventricle site of action of angiotensin induced thirst. *Pharmacol Biochem Behav* 1976;**4**:651-60.
101. Fregly MJ, Rowland NE. Effect of DuP 753, a non-peptide angiotensin II receptor antagonist, on the drinking responses to acutely administered dipsogenic agents in rats. *Proc Soc Exp Biol Med* 1992;**199**:158-64.
102. Rowland NE, Rozelle A, Riley PJ, Fregly MJ. Effect of non-peptide angiotensin receptor antagonists on water and salt intake in rats. *Brain Res Bull* 1992;**29**:389-93.
103. Blair-West JR, Denton DA, McKinley MJ, Weisinger RS. Thirst and brain angiotensin in cattle. *Am J Physiol* 1992;**262**:R204-R210.
104. Mathai M, Evered MD, McKinley MJ. Intracerebroventricular losartan inhibits post-prandial drinking in sheep. *Am J Physiol* 1997;**272**:R1055-R1059.
105. Andersson B, Eriksson L, Fernandez O, Kolmodin C-G, Oltner R. Centrally mediated effects of sodium and angiotensin II on arterial pressure and fluid balance. *Acta Physiol Scand* 1972;**85**:398-407.
106. Wilkin LD, Mitchell LD, Ganten D, Johnson AK. The supraoptic nucleus: afferents from areas involved in control of body fluid homeostasis. *Neuroscience* 1989;**28**:573-83.
107. Bealer S, Phillips MI, Johnson AK, Schmid PG. Anteroventral third ventricle lesions reduce antiduiretic responses to angiotensin II. *Am J Physiol* 1979;**236**:E610-E615.
108. Scholkens BA, Jung W, Rasher W, Dietz R, Ganten D. Intracerebroventricular angiotensin II increases arterial blood pressure in Rhesus Monkeys by stimulation of pituitary hormones and the sympathetic nervous system. *Experientia* 1982;**38**:469-73.
109. Sumitomo T, Suda T, Nakano Y, Tozawa F, Yamada M, Demura H. Angiotensin II increases the corticotropin releasing factor messenger ribonucleic acid level in the rat hypothalamus. *Endocrinology* 1991;**128**:2248-52.
110. Aguilera G, Young WS, Kiss A, Bathia A. Direct regulation of hypothalmic corticotropin releasing hormone neurons by angiotensin II. *Neuroendocrinology* 1995;**61**:437-44.
111. Oldfield BJ, Davern PJ, Giles ME, Allen AM, Badoer E, McKinley MJ. Efferent neural projections of angiotensin receptor (AT_1) expressing neurons in the hypothalamic paraventricular nucleus. *J Neuroendocrinology* 2001;**13**:139-46.
112. Fitzsimons JT. Angiotensin, thirst and sodium appetite. *Physiol Rev* 1998;**78**:583-682.
113. Coghlan JP, Considine PJ, Denton DA *et al.* Sodium appetite in sheep induced by cerebral ventricular infusion of angiotensin: Comparison with sodium deficiency. *Science* 1981;**214**:195-7.
114. Galaverna O, Deluca LA, Schulkin J, Yao SZ, Epstein AN. Deficits in NaCl ingestion after damage to the central nucleus of the amygdala in the rat. *Brain Res Bull* 1992;**28**:89-98.
115. Unger T, Horst PJ, Bauer M, Demmert G, Rettig R. Natriuretic action of central angiotensin II in conscious rats. *Brain Res* 1999;**486**:33-8.
116. Eriksson L, Fyhrquist F. Plasma renin activity following central infusions of and altered CSF sodium concentration in the conscious goat. *Acta Physiol Scand* 1976;**48**:209-16.
117. Mathai ML, Evered MD, McKinley MJ. Central losartan blocks natriuretic, vasopressin and pressor responses to central hypertonic NaCl in sheep. *Am J Physiol* 1998;**275**:R548-R554.
118. McKinley MJ, Evered M, Mathai M, Coghlan JP. Effects of central losartan on plasma renin and centrally mediated natriuresis. *Kidney Int* 1994;**46**:1479-82.

119. Malayan SA, Keil LC, Ramsay DJ, Reid IA. Mechanism of suppression of plasma renin activity by centrally administred angiotensin II. *Endocrinology* 1979;**104**:672-5.
120. Weekly LB. Renal renin secretion and norepinephrine secretion rate in response to centrally administered angiotensin II: Role of medial basal forebrain. *Clin Exp Hypertension* 1992;**14**:923-45.
121. Sharpe LG, Swanson LW. Drinking induced by injections of angiotensin into forebrain and midbrain sites of the monkey. *J Physiol* (Lond.) 1974;**239**:595-622.
122. Lin MT. Effects of angiotensin II on metabolic, respiratory and vasomotor activities as well as body temperature in the rabbit. *J Neural Transmission*1980;**49**:197-204.
123. Shido O, Nagasaka T. Effects of intraventricular angiotensin II on heat balance at various ambient termperatures in rats. *Jap J Physiol* 1985;**35**:163-7.
124. Fregly MJ, Rowland NE. Effect of losartan potassium and deoxycorticosterone acetate on tail skin temperature response to acute amdinistration of angiotensin II. *Pharmacol Biochem Behav* 1992;**43**:229-33.
125. Melo JC, Graeff FG. Effect of intracerebroventricular bradykinia and related peptides on rabbit operant behaviour. *J Pharmacol Exper Ther* 1975;**193**:1-10.
126. Morgan TM, Routtenberg A. Angiotensin injected into the neostriatum after learning disrupts retention performance. *Science* 1977;**196**:87-9.
127. Koller M, Krause HP, Hoffmeister F, Ganten D. Endogenous brain angiotensin II disrupts passive avoidance behaviour in rats. *Neurosci Lett* 1979;**14**:71-5.
128. DeNoble VJ, DeNoble KF, Spencer KR, Chiu AT, Wong PC, Timmermans BM. Non-peptide angiotensin II receptor antagonist and angiotensin-converting enzyme inhibitor: Effect on a renin-induced deficit of a passive avoidance response in rats. *Brain Res* 1991;**561**:230-5.
129. Barnes JM, Barnes NM, Costall B *et al*. Angiotensin II inhibits cortical cholinergic function: Implications for cognition. *J Cardiovasc Pharmacol* 1990;**16**:234-8.
130. Barnes JM, Barnes NM, Costall B *et al.* Angiotensin II inhibits acetylcholine release from human temporal cortex: Implications for cognition. *Brain Res* 1990;**507**:341-3.
131. Costall B, Coughlan J, Horovitz ZP, Kelly ME, Naylor RJ, Tomkins DM. The effects of ACE inhibitors captopril and SQ29852 in rodent tests of cognition. *Pharmacol Biochem Behav* 1989;**33**:573-80.