Brain angiotensin and body fluid homeostasis

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The angiotensin AT1 receptor is expressed in many regions of the mammalian brain. High concentrations of AT1 receptors are found in the subfornical organ, organum vasculosum of the lamina terminalis (OVLT) and area postrema, regions of the brain that lack a blood-brain barrier. The endogenous ligand for these AT1 receptors is angiotensin II derived from the blood. Circulating angiotensin II is prevented from having access to the AT1 receptors in other of the brain regions such as the hypothalamic paraventricular nucleus, median preoptic nucleus, lateral parabrachial nucleus, nucleus of the solitary tract or ventrolateral medulla by the blood-brain barrier. It seems likely that the endogenous ligand for these AT1 receptors may be angiotensin synthesised within the brain. We have utilised pharmacological agents to investigate possible roles of brain angiotensin in body fluid homeostasis and cardiovascular control in sheep. Intracerebroventricular (ICV) administration of the AT1 receptor antagonist losartan in conscious sheep has been shown to block water drinking, vasopressin secretion, reduced renin secretion, reduced renal sympathetic nerve activity, and the pressor response to centrally administered hypertonic saline as well as to ICV angiotensin II, suggesting that an angiotensinergic pathway within the brain may have a role in osmoregulation. However, when we tested the effect of the same dose of ICV losartan on the water drinking response to systemic infusion of hypertonic saline which gradually increased plasma osmolality over 30 min, there was no inhibition of the water drinking response, which challenges the idea that a central angiotensinergic pathway mediates physiological osmoregulatory drinking. Moreover, we have recently observed in mice (Agt-/- mice) in which the angiotensinogen gene had been deleted by gene targetting techniques, that they are able to respond to osmotic challenges (water deprivation for 24 hours or intraperitoneal injection of hypertonic saline) with appropriate increases in water intake. In rats, we observed that ICV administration of an 18-mer antisense oligonucleotide directed against part of the angiotensinogen gene in order to reduce angiotensinogen synthesis in the brain caused a large reduction in the water drinking response to ICV renin (administered 24 h later), suggesting that brain angiotensinogen levels had fallen. However, such antisense treatment did not reduce water drinking in response to systemically administered hypertonic saline or to water deprivation, also suggesting that brain angiotensinergic mechanisms are not mediating osmoregulatory thirst. Thus, our data in several species does not favour a major role for brain angiotensinergic mechanisms in osmoregulation.