Role of angiotensin II in regulating long term levels of sympathetic activity

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Angiotensin II is recognised to play a critical role in the regulation of arterial pressure. In addition to its direct vasoconstrictive actions there is strong evidence to indicate that angiotensin II maintains arterial pressure through an excitatory action on the sympathetic nervous system. This action may be via a direct action on central nervous system pathways involved in generating and regulating sympathetic nerve activity (SNA) or via an action on a pathway such as the arterial baroreflex, that plays an important role in regulating short term SNA. One concern is that the data used to base such hypotheses are generally taken from short-term recordings of SNA (generally less than 3 hours). Thus the mechanisms that regulate SNA under such conditions may not necessarily reflect those seen under more chronic conditions and thus be reflective of the human condition.

To address the question of how angiotensin II regulates SNA chronically we developed technology which enables us to record SNA for up to 50 days via telemetry in rabbits. We made continuous recordings of renal SNA before, during and after one week of angiotensin II based hypertension in rabbits living in their home cages. Angiotensin II infusion (50 $ng.kg^{-1}.min^{-1}$) caused a sustained increase in arterial pressure (18 ± 3 mmHg). There was a sustained decrease in SNA, from 18 ± 2 normalised units (n.u.) before angiotensin II to 8 ± 2 n.u. on day 2 and 9 ± 2 n.u. on day 7 of the angiotensin II infusion ($P < 0.01$) before recovering to 17 ± 2 n.u. after ceasing angiotensin II. Analysis of the baroreflex response showed that while angiotensin II induced hypertension led to resetting of the MAP-HR relationship, there was no evidence of resetting of the MAP-SNA relationship. We propose that the lack of resetting of the MAP-SNA curve, with the resting point lying near the lower plateau suggests the sustained decrease in SNA during angiotensin II is baroreflex mediated.

Subsequently, to address whether the action of angiotensin II was solely via a sustained non-resetting of arterial baroreflexes or via a central action, we followed the same protocol as above but in sino-aortically denervated animals. Under these conditions the increase in arterial pressure was the same as previously observed in intact animals however there was no evidence of a reduction in SNA. Indeed mean SNA was unchanged after 7 days for angiotensin II infusion. These results suggest that the action of peripheral angiotensin II on SNA appear to be determined primarily via an arterial pressure dependent action through non-resetting of arterial baroreflexes. While a central action of angiotensin II on SNA may exist, we suggest that the lack of alteration in SNA levels in baroreceptor denervated animals indicates that this effect may be relatively minor.

Overall these results suggest two surprising findings; firstly that angiotensin II is sympathoinhibitory and not sympathoexcitatory as previously indicated, and that baroreflex control of renal SNA and thus renal function is likely to play a significant role in the control of arterial pressure in the long-term (Barrett *et al.*, 2003; Lohmeier, 2003).

Barrett C.J, Ramchandra R., Guild S.J., Lala A., Budgett D.M. & Malpas S.C. (2003). *Circulation Research,* 92, 1330-1336.

Lohmeier, T.E. (2003). *Circulation Research,* 92, 1282-1284.