Unique structure and function of lamprey angiotensin II suggest a separate path of renin-angiotensin system evolution

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We have cloned and characterized a native angiotensinogen gene from lamprey, which gives rise to a unique angiotensin II (LpAng II; EEDYDERPYMQPF) of which the three-dimensional structure is different from those of other vertebrates. Phylogenetic analyses indicated that the lamprey angiotensinogen is an evolutionary link between serine-protease inhibitors and other angiotensinogens. We have developed a specific radioimmunoassay to measure LpAng II and the plasma concentrations are comparable to those of other vertebrates (157.4 ± 35.2 fmol/mL, n=6). In conscious, cannulated lamprey, a bolus injection of LpAng II at 100 pmol/kg elicited a transient vasodepressor effect instead of a vasopressor effect observed in other vertebrates. A biphasic response, with an initial vasodepressor effect followed by a transient rebound vasopressor effect, was observed in a dose-dependent manner at doses higher than 300 pmol/kg. In eel, LpAng II injection up to 3 nmol/kg did not affect any cardiovascular parameters, indicating that a separate evolutionary path has been taken by LpAng II and its receptors and thus led to such functional dissimilarity. Our results suggest that the renin-angiotensin system appeared before cyclostomes evolved and LpAng II could be important for cardiovascular regulation because of its potent and acute effect.