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Angiotensin receptor subtype mediated physiologies and behaviors: New discoveries and clinical targets

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Abstract

The renin–angiotensin system (RAS) mediates several classic physiologies including body water and electrolyte homeostasis, blood pressure, cyclicity of reproductive hormones and sexual behaviors, and the regulation of pituitary gland hormones. These functions appear to be mediated by the angiotensin II (AngII)/AT_1 receptor subtype system. More recently, the angiotensin IV (AngIV)/AT_4 receptor subtype system has been implicated in cognitive processing, cerebroprotection, local blood flow, stress, anxiety and depression. There is accumulating evidence to suggest an inhibitory influence by AngII acting at the AT_1 subtype, and a facilitory role by AngIV acting at the AT_4 subtype, on neuronal firing rate, long-term potentiation, associative and spatial learning, and memory. This review initially describes the biochemical pathways that permit synthesis and degradation of active angiotensin peptides and three receptor subtypes (AT_1, AT_2 and AT_4) thus far characterized. There is vigorous debate concerning the identity of the most recently discovered receptor subtype, AT_4. Descriptions of classic and novel physiologies and behaviors controlled by the RAS are presented. This review concludes with a consideration of the emerging therapeutic applications suggested by these newly discovered functions of the RAS.

Keywords: Renin–angiotensin system; Angiotensin receptor subtypes; Angiotensin II; Angiotensin III; Angiotensin IV; Angiotensin(1–7); Cardiovascular control; Thirst; Sodium appetite; Long-term potentiation; Learning and memory; Cerebroprotection; Seizure; Stress; Depression

Abbreviations: ACD, acyl-coenzyme A dehydrogenase; ACE, angiotensin converting enzyme; ACE_2, human angiotensin converting enzyme homologue; Ach, acetylcholine; ACTH, adrenocorticotrophin releasing hormone; Ang, angiotensin; Ang(1-9), angiotensin I(1-9); Ang(1–7), angiotensin II(1–7); Ang(2–7), angiotensin II(2–7); Ang(3–7), angiotensin II(3–7); AngI, angiotensin I; AngII, angiotensin II; AngIII, angiotensin III; AngIV, angiotensin IV; AP, area postrema; AP-A, aminopeptidase A; AP-N, aminopeptidase N; Arg, arginine; Asp, aspartate; AT, angiotensin receptor subtype; CA, Ammon's horn; Carb-P, carboxypeptidase P; CRH, cortiocotrophin-releasing hormone; CVOs, circumventricular organs; DA, dopamine; EC27, 2-amino-pentane-1,5-dithiol; EC33, 3-amino-4-mercapto-butyl-sultonic acid; ERK, extracellular signal-regulated kinase; GLUT, glucose transporter molecules; GST, glutathione-S-transferase; GTPγS, guanosine triphosphate γ sulfate; HEK, human embryonic kidney; HGF, hepatocyte growth factor; His, histidine; icv, intracerebroventricular; Ile, isoleucine; IRAP, insulin-regulated aminopeptidase; Leu, leucine; L-NAME, nomega-nitro-1-arginine methylester; LTD, long-term depression; LTP, long-term potentiation; LVV-H7, leucine-valine-valine-hemorphin-7; Nle, norleucine; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NTS, nucleus of the solitary tract; OVLT, organum vasculosum of the lamina terminalis; PAI-1, plasminogen activator inhibitor-1; PC18, 2-amino-4-methylsulfonyl butane thiol; Phe, phenylalanine; PL, phospholipase; PO, propyl oligopeptidase; Pro, proline; PVN, paraventricular nucleus; RAS, renin–angiotensin system; Sar, sarcosine; Sar^1,Ala^8-AngII, saralasin; Sar^1,Ile^8-AngII, sarile; SFO, subfornical organ; SH, sulfhyrdryl; SHRs, spontaneously hypertensive rats; SON, supraoptic nucleus; Tyr, tyrosine; Val, valine; VDCCs, voltage dependent calcium channels; VMN, ventral medial nucleus; VTA, ventral tegmental area.

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Contents

1. Introduction . . . 158
2. Biochemistry of the renin–angiotensin system . . . 159
   2.1. Formation of angiotensin ligands . . . 159
   2.2. Angiotensin receptor subtypes . . . 160
      2.2.1. AT_1 and AT_2 receptor subtypes . . . 160
      2.2.2. AT_4 receptor subtype . . . 161
      2.2.3. Is the AT4 receptor c-Met or insulin-regulated aminopeptidase (IRAP)? . . . 161
      2.2.4. Angiotensin(1–7) . . . 162
   2.3. Cerebral distributions of angiotensin receptor subtypes . . . 163
3. Classic angiotensin-mediated physiologies and behaviors . . . 164
   3.1. Cardiovascular control . . . 164
   3.2. Angiotensin II . . . 164
   3.3. Angiotensin III and shorter fragments . . . 165
      3.3.1. Thirst . . . 166
   3.4. Angiotensin II . . . 166
   3.5. Angiotensin III and shorter fragments . . . 166
      3.5.1. Sodium appetite . . . 166
4. Novel angiotensin-mediated physiologies and behaviors . . . 167
   4.1. Long-term potentiation . . . 167
   4.2. Learning, memory and cognition . . . 167
      4.2.1. Angiotensin converting enzyme (ACE) inhibitors and cognition . . . 168
      4.2.2. Angiotensin II . . . 168
      4.2.3. Angiotensin IV . . . 169
   4.3. Cerebroprotection . . . 170
      4.3.1. Ischemia-induced damage . . . 170
      4.3.2. Seizure . . . 171
   4.4. Renal blood flow and natriuresis . . . 171
   4.5. Stress . . . 172
   4.6. Depression . . . 172
5. Potential therapeutic applications . . . 173
   5.1. The angiotensin II/AT_1 receptor subtype system . . . 173
   5.2. The angiotensin IV/AT_4 receptor subtype system . . . 173
6. Conclusion . . . 173
   Acknowledgements . . . 174
   References . . . 174

1. Introduction

Well over 100 years ago Tiegerstedt and Bergman (1898) discovered a pressor agent extracted from the kidney that they called ''renin''. Some 40 years later this finding led to the isolation of a vasoconstrictor agent from the ischemic kidneys of Goldblatt hypertensive dogs (Braun-Menendez et al., 1940). Page and Helmer (1940) independently isolated the same agent after injecting renin into intact animals and they also identified a ''renin activator'', later determined to be angiotensinogen (de Gasparo et al., 2000). The vasoconstrictor agent was determined to be an octapeptide and was variously called ''renin substrate'', ''angiotonin'', and ''hypertensin'' but was later termed angiotensin II (AngII; Bumpus et al., 1957, 1958; Elliott and Peart, 1956; Skeggs et al., 1957). From this beginning many additional findings have been made including the observation that intracerebroventricular (icv) AngII produced brain-mediated pressor (Bickerton and Buckley, 1961) and drinking responses (Epstein et al., 1970). Ganten et al. (1971a,b) isolated renin in the dog brain; while Fisher-Ferraro et al. (1971) identified both renin and AngII in the dog brain. Sirrett et al. (1977) developed a radio-receptor binding assay permitting the identification and localization of angiotensin receptors in the brain and throughout the body. Taken together these findings suggested the presence of an independent brain renin–angiotensin system (RAS). Confirmation of this hypothesis required several additional years of laboratory work utilizing a variety of techniques including radioimmunoassay, immunohistochemistry, radio-receptor binding assays, and Northern blots of renin and angiotensinogen mRNAs (Dzau et al., 1986; Ganten et al., 1983; Harding et al., 1981; Hermann et al., 1984; Lynch et al., 1986; Phillips et al., 1979).

Two recent discoveries have further extended our understanding of the RAS: (1) the angiotensin receptor proteins AT_1 and AT_2 were cloned and sequenced (Chiu et al., 1989; Whitebread et al., 1989; Iwai et al., 1991; Murphy et al., 1991; Kambayashi et al., 1993; Mukoyama et al., 1993). (2) A third angiotensin receptor subtype, AT_4, was discovered (Harding et al., 1992) that appears to mediate a number of novel functions