The Renin Angiotensin System and the Therapeutic Implications for PTSD

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Overview of Presentation

- Brief overview of the neurophysiology and cardiovascular roles of the renin angiotensin system.

- Review current pre-clinical (animal) and clinical data for the angiotensin system in stress disorders.

- Provide evidence for discussion regarding use of pharmacotherapies (ie; ARBs / ACE) for PTSD.
Disclosures

Translating medical scientific discoveries to improved clinical treatment strategies
Blood Pressure Homeostasis

Determination of Arterial Pressure

Total Peripheral Resistance → Cardiac Output

- Extracellular fluid volume
- Blood volume
- Arterial and venous compliance
- Resistance to venous return

Kidney structure and function
- Pressure–natriuresis
- Tubular Na+ reabsorption
- Glomerular filtration rate; urinary protein
- Renal blood flow
- Renal vascular resistance
- Morphology

Neuroendocrine
(Sympathetic nervous system, hormones, paracrine and autocrine factors)
- e.g. renin–angiotensin–aldosterone system, adrenaline, noradrenaline, arginine vasopressin, atrial natriuretic peptide reactive oxygen species, nitric oxide

Structure and function of blood vessels and heart
- Local autoregulation
- Vascular reactivity
- Cardiac contractility
- Aorta and heart-wall thickness and morphology
- Microvessel density

Hypertension and its cardiovascular consequences contribute to the leading causes of morbidity and mortality worldwide.

77% of Americans treated for a first stroke have blood pressure over 140/90.

69% of Americans who have a first heart attack have blood pressure over 140/90.

74% of Americans with congestive heart failure have blood pressure over 140/90.


http://www.americanheart.org/presenter.jhtml?identifier=2129
Contributing Factors to Hypertension

- Genetics
- Race
- Age
- High sodium diet
- Lack of physical activity
- Obesity
- Stress (anxiety related disorders)
- Low-grade systemic inflammation
- Renin Angiotensin System
- Autonomic Dysfunction
Psychological Stress  <->  Cardiovascular Disease
Method of Blood Pressure Analysis: Radio Telemetry implantable probes in mice
Experimental Animal Models

Experimental Hypertension (Pharmacological subcutaneous infusions)

ALZET Pump model 2002
0.5 μL/hr/2 wks
Renin-Angiotensin-Aldosterone System

Angiotensinogen → Angiotensin I → Angiotensin II

- Renin
- ACE
- Lungs
- Kidney
- Liver
- Arteriole
- Pituitary gland: posterior lobe
- Adrenal gland: cortex
- Collecting duct: H₂O absorption

Decrease in renal perfusion (juxtaglomerular apparatus)

Sympathetic activity

Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion. H₂O retention

Aldosterone secretion

Arteriolar vasoconstriction. Increase in blood pressure

ADH secretion

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.

Legend:
- Blue: Secretion from an organ
- Blue dashed: Stimulatory signal
- Red: Inhibitory signal
- Black: Reaction
- Gray: Active transport
- Gray dashed: Passive transport

Therapeutic Targets of Angiotensin (Ang II)

Angiotensinogen → Renin → Angiotensin I → Angiotensin converting enzyme (ACE) → Angiotensin II

ACE inhibitors

ANG II Receptor Blockers (ARBs)

AT₁ receptor
- Vasoconstriction
- Sympathetic activation
- Cell proliferation
- Aldosterone release
- Renal sodium resorption

AT₂ receptor
- Vasodilation
- Inhibition of cell growth
- Apoptosis

Atherosclerosis, hypertension
Angiotensin II Exacerbates the Blood Pressure Response to acute and chronic Stress
Key hypothalamic circuits that mediate the behavioral, endocrine, and autonomic stress-response

Angiotensin II

Stress

Cardiovascular regulation (brainstem / baroreceptors)

HPA axis (increased Cortisol)

The Fear Response
The Fear Response is a Hardwired Process involving the Amygdala

**Fear / Panic Symptoms:**

- Heart rate, blood pressure
- Bradycardia, ulcers
- Panting, respiratory distress
- Arousal, vigilance, attention
- Increased startle response
- Freezing, social interaction
- Corticosterone release

**Fear Learning**

**Expression of Fear**

- Lateral hypothalamus
- Dorsal vagal N.
- Parabrachial N.
- Basal forebrain
- Retic. Pontis Caudalis
- Central Gray Area
- Paraventricular N.

*Modified from Davis (1992) Ann Rev Neurosci 15: 353-*
PANIC ATTACK:
"All of a sudden I felt dizzy, my legs gave out on me, and I couldn't catch a breath. It felt like someone was choking me. I could feel my heart was beating too fast and I was terrified I was dying. I knew I had to get away before I lost it."

Increased heart rate
Chills, hotflushes
Nausea / abdominal distress
Shortness of breath
Expressions of fear

Chest discomfort
Sweating
Lightheadedness / faint
Choking sensation
Fear of dying / losing control

PANIC ATTACK = ‘Fear Attack’ in Fear-related Disorders

PANIC ATTACK
- Panic Disorder
- Simple Phobia
- Social Phobia (Agoraphobia)
- Posttraumatic Stress Disorder
- Acute Stress Disorder
2009-2011

Stress Disorders (PTSD) ↔ Cardiovascular Disease (hypertension)

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Mclean Hospital
Harvard Medical School

David G. Harrison, MD
Clinical Pharmacology
Vanderbilt University
Brain renin angiotensin system

Sympathetic Nervous System

Renin

Stress

PTSD

anxiety

trauma

hypervigilance

flashbacks

traumatic

thinking

irritable

symptoms

trauma

flashbacks

PTSD
Chronic Stress Increases Activity of the Central and Peripheral Renin Angiotensin System

Repeated restraint stress increases Ang II receptor expression in the Paraventricular Nucleus (PVN)

Reduced blood pressure response in AT1-/- mice to acute stressors (cage-switch stress)


The potential of DuP753, an angiotensin II receptor antagonist, to inhibit the suppressed behaviour of mice in a light/dark aversion test was investigated. The aversive response to the light compartment of the apparatus was reduced (increase in latency to move from the light to the dark compartment and decreases in rears, line crossings and percentage of time spent in the dark compartment) following treatment with DuP753 (0.1–1000 μg kg⁻¹ p.o., 45 min before the test). These results further implicate the modulation of mental function by angiotensin II.

Key words: Anxiolytic-like action, Angiotensin II receptor antagonist, DuP753

Anxiolytic-like action of DuP753, a non-peptide angiotensin II receptor antagonist

Nicholas M BarnesCA, Brenda Costall, M Elizabeth Kelly, Deborah A Murphy and Robert J Naylor

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Angiotensin II Receptor Blockade Improves Stress Related Pathology

**A**
- **Decrease central sympathetic activation**
- Tyrosine hydroxylase in Locus Coeruleus

**B**
- Prevent a somatic stress disorder: Gastric ulcers
- Cold-restrain stress Gastric mucosa

**C**
- **Decrease anxiety**

Expert Opinion

Angiotensin as a target for the treatment of Alzheimer's disease, anxiety and depression

Paul R Gard
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The brain renin-angiotensin system (RAS), which is comprised of a variety of peptides including angiotensin II, angiotensin III and angiotensin IV acting on AT$_1$, AT$_2$ and AT$_4$ receptors, is important in cognition and anxiety. Perturbation of the RAS improves basal cognition and reverses age-, scopolamine-, ethanol- and diabetes-induced deficits. In studies of dementias and Alzheimer's disease (AD), some studies have shown that antihypertensive drugs, including angiotensin-converting enzyme inhibitors, have some moderate effects on cognitive decline, but that the angiotensin receptor antagonist losartan has a significantly beneficial effect. These findings suggest that angiotensin receptor ligands may have potential in the prevention or even reversal of vascular dementias and AD. With respect to depression and anxiety, there is similar experimental evidence from animal models that drugs acting on the RAS may be antidepressant or anxiolytic, but insufficient clinical data exist. Such effects, if proven, could promote the use of such agents in the treatment of hypertension coexisting with depression or anxiety.
Post Traumatic Stress Disorder (PTSD)

✧ A debilitating anxiety disorder thought to manifest after exposure to a traumatic event.

✧ Characterized by the re-experiencing of a trauma, hyperarousal, and avoidance.
Post Traumatic Stress Disorder (PTSD)

- PTSD is a prevalent, disabling, and costly condition.
- The societal impact of PTSD is likely to increase in coming years, given high rates of PTSD in service members returning from the conflicts in Iraq and Afghanistan.
- Current pharmacological therapies - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) provide substantial benefit to only 30-40% of patients (Ravindran and Stein, 2009, 2010).
- The current need for effective PTSD treatments is great.
ACE-I / ARB medication is associated with decreased PTSD symptoms in a traumatized community sample

**Table 4. Multi-Variable Linear Regression of PSS and CAPS Score**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ACE Inhibitor or ARB $\beta$ Estimate</th>
<th>SE</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSS total score (n = 467)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted effect</td>
<td>-3.51</td>
<td>1.4</td>
<td>-2.47</td>
<td>.014</td>
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<tr>
<td>Adjusted$^a$ effect</td>
<td>-2.83</td>
<td>1.4</td>
<td>-2.02</td>
<td>.044</td>
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<td><strong>PSS hyperarousal score (n = 467)</strong></td>
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<td></td>
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<tr>
<td>Unadjusted effect</td>
<td>-1.30</td>
<td>0.5</td>
<td>-2.59</td>
<td>.010</td>
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<tr>
<td>Adjusted$^b$ effect</td>
<td>-1.22</td>
<td>0.6</td>
<td>-2.20</td>
<td>.028</td>
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<tr>
<td><strong>PSS avoidance numb score (n = 459)</strong></td>
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<td></td>
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<tr>
<td>Unadjusted effect</td>
<td>-0.94</td>
<td>0.6</td>
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<td>.138</td>
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<td>Adjusted$^c$ effect</td>
<td>-0.92</td>
<td>1.1</td>
<td>-1.12</td>
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<td><strong>PSS intrusive score (n = 467)</strong></td>
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<tr>
<td>Unadjusted effect</td>
<td>-1.27</td>
<td>0.4</td>
<td>-2.86</td>
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<tr>
<td>Adjusted$^d$ effect</td>
<td>-1.01</td>
<td>0.5</td>
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<td><strong>Lifetime CAPS score (n = 467)</strong></td>
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<tr>
<td>Unadjusted effect$^e$</td>
<td>-4.90</td>
<td>3.95</td>
<td>-1.24</td>
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<tr>
<td>Adjusted$^f$ effect$^e$</td>
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<td>0.56</td>
<td>-2.20</td>
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<td><strong>Current CAPS score (n = 417)</strong></td>
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<tr>
<td>Unadjusted effect$^e$</td>
<td>-5.05</td>
<td>2.91</td>
<td>-1.74</td>
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<td>Adjusted$^g$ effect$^e$</td>
<td>-7.16</td>
<td>2.78</td>
<td>-2.57</td>
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</tbody>
</table>

*Taking ACE-I or ARB Medication*

Khoury, Marvar et al., *Journal of Clinical Psychiatry* 2012
First clinical study to show that ACE-inhibitors and ARB medications may have protective effects against PTSD symptoms among individuals exposed to trauma (Khoury et al., 2012).

Genetic Polymorphisms in Angiotensin-Converting Enzyme associated with PTSD symptom severity (Nylocks et al., 2015)

Neuorobiological mechanism(s) unclear??
Modeling Fear Disorders

Pavlovian Fear Conditioning = animal model of PTSD

Transgenic mouse models

Joseph LeDoux, PhD – Pioneer in the understanding of Fear Memory
http://www.cns.nyu.edu/labs/ledouxlab/overview.htm
Neutral conditioned stimulus (CS)—light or tone—is paired with aversive unconditioned stimulus (US)—foot shock.

After a number of pairings, subject forms an association between the CS and US.

Elicits a fear response when presented with the innocuous CS, even in the absence of the US.
How we measure fear in animals?
Fear-Potentiated Startle & Freezing

Fear Conditioning

[Graph showing the percentage of freezing to tones from Tone 1 to Tone 6]
Freezing Response During Extinction Training to Conditioned Cue (Tone)

Video Courtesy of Brian G. Dias, PhD – Emory University Dept. of Psychiatry
Extinction of Fear Memory

- Exposure therapy is modeled in the lab via an extinction learning paradigm, once an animal has been fear conditioned.

- Increased understanding of the mechanisms underlying deficits in extinction learning will aid in the development of new therapies to treat anxiety and fear-related disorders, such as PTSD.
Angiotensin type 1 receptor inhibition enhances the extinction of learned fear

Chronic inhibition of angiotensin type 1 receptor enhances extinction of learned fear

Amygdala and Fear

- Required for both the acquisition of classically-conditioned fear, and the extinction of conditioned fear

- Lesions in the BLA in animal models lead to an inability to extinguish conditioned fear responses
Chronic inhibition of angiotensin type 1 receptor enhances extinction of learned fear

Systemic administration of ARBs does not address whether ARBs are acting centrally and which cell types they are acting on?

Determine whether AT1aR deletion from a genetically defined neural population—(corticotropin-releasing factor (CRF)-expressing cells)—affects the expression of conditioned fear.
AT1 receptor and CRF co-localize in subsets of PVN and Amygdala neurons

Hurt RC, Marvar et al., Genes Brain Behav. August 2015.
Decreased AT1R expression in the PVNs of CRF-AT1aR(-/-) mice compared to controls.
AT1R knockout from CRFergic cells decreases fear expression and enhances extinction retention.
Fear Circuits and the Renin Angiotensin System as a Therapeutic Target?

Pre-existing Sensitivity (gene + environment)

Learning of Fear (Traumatic event)

Consolidation of Fear
Hours – days following event (Genes of consolidation i.e BDNF)

Expression of Fear
Memories, Nightmares, Flashbacks
Avoidance, Sympathetic Response, Startle

ACE polymorphism (Nylocks et al., 2015)

Angiotensin II

ARBs

Genes - BDNF, PACAP, FKB5, Nk3
PTSD and Cardiovascular Disease

* PTSD (veteran and non-veteran populations) is associated with major forms of cardiovascular disease.  

* More likely to have hypertension, hyperlipidemia, obesity, and cardiovascular disease.  
Targeting the angiotensin system could provide an additional avenue for *treating co-morbid PTSD and cardiovascular disease?*
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"It's just something I do every day at 5:00 to get rid of stress before I go home."