The Renin Angiotensin System and the Therapeutic Implications for PTSD

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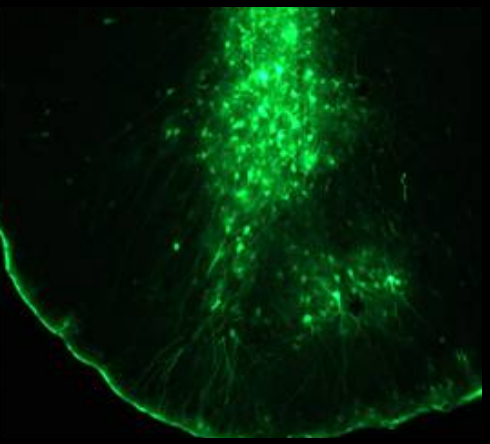
Assistant Professor
Department of Pharmacology & Physiology
George Washington University



GWU Psychiatry Grand Rounds
October 15, 2015

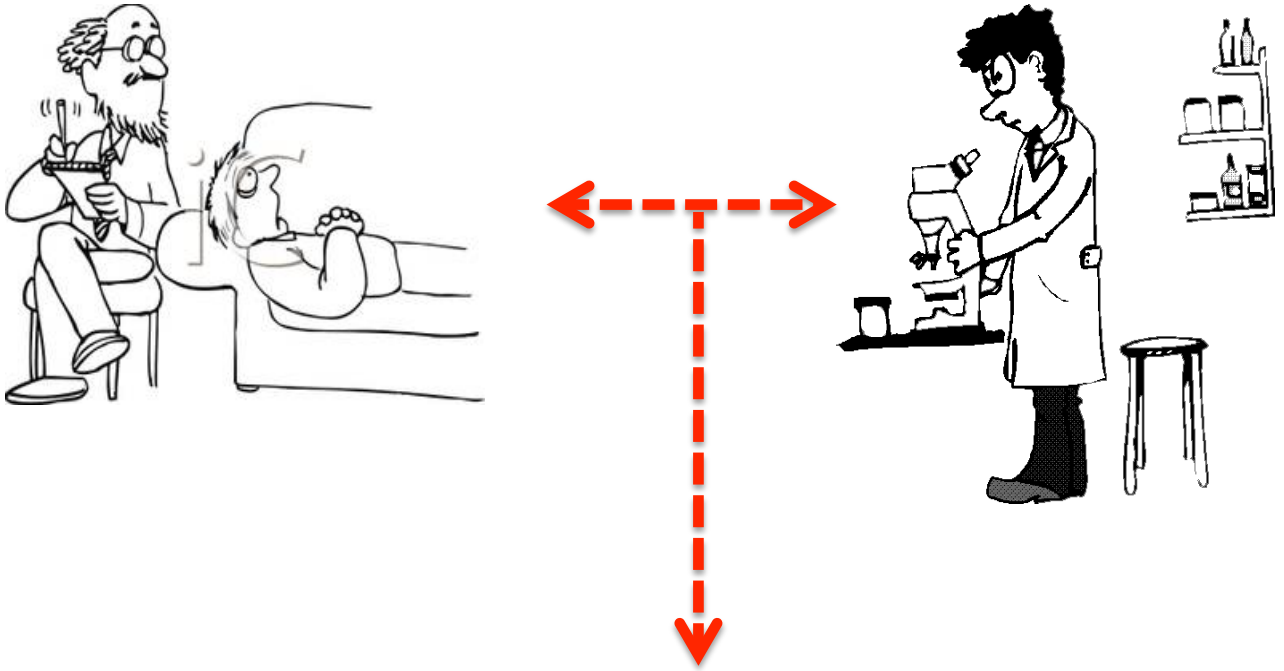
Overview of Presentation

- 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.

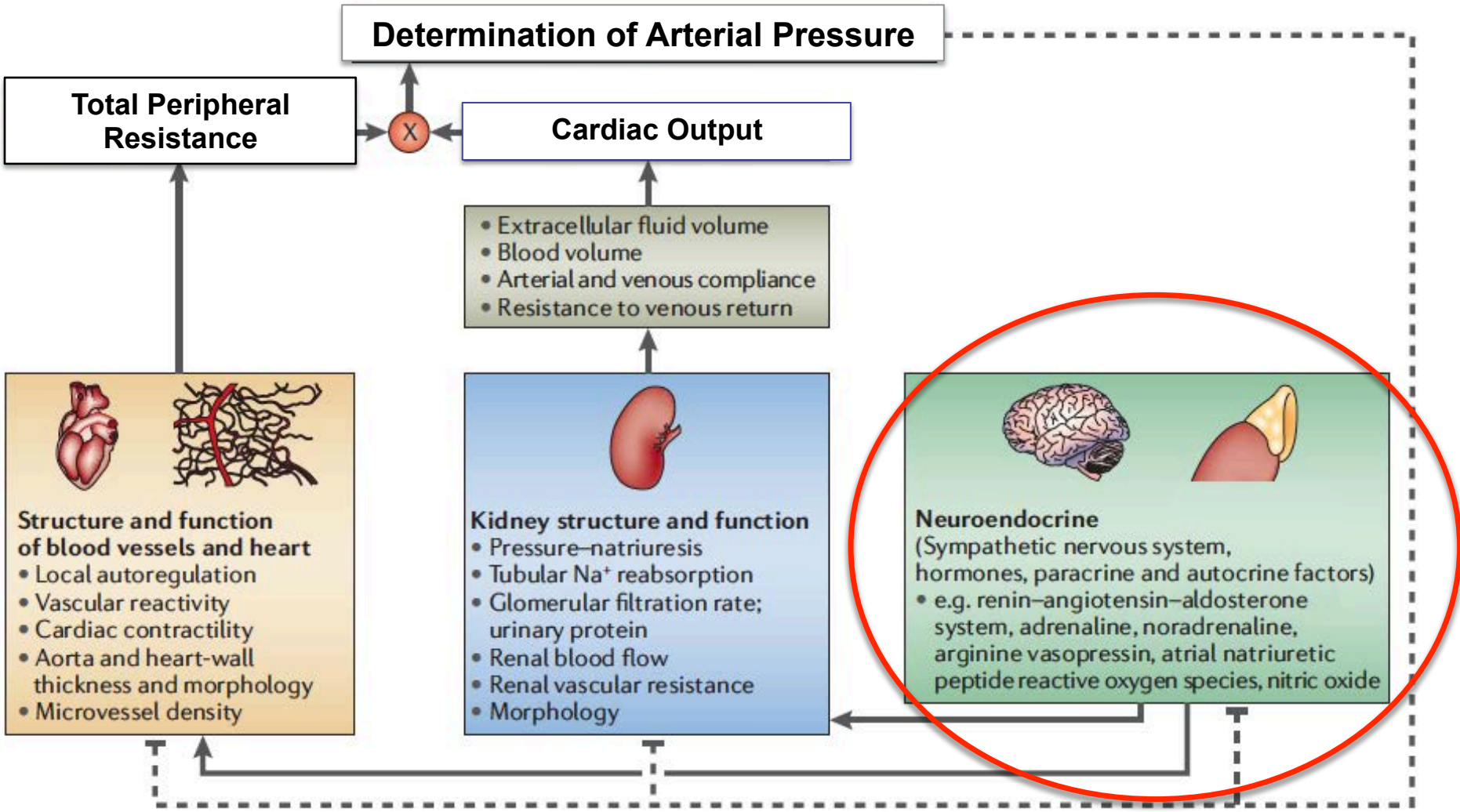
- Provide evidence for discussion regarding use of pharmacotherapies (ie; ARBs / ACE) for PTSD.

Disclosures



Translating medical scienctific discoveries to improved clinical treatment strategies

Blood Pressure Homeostasis



Cowley et al *Nature Reviews Genetics* 7, 829–840 (November 2006)

nature REVIEWS GENETICS

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

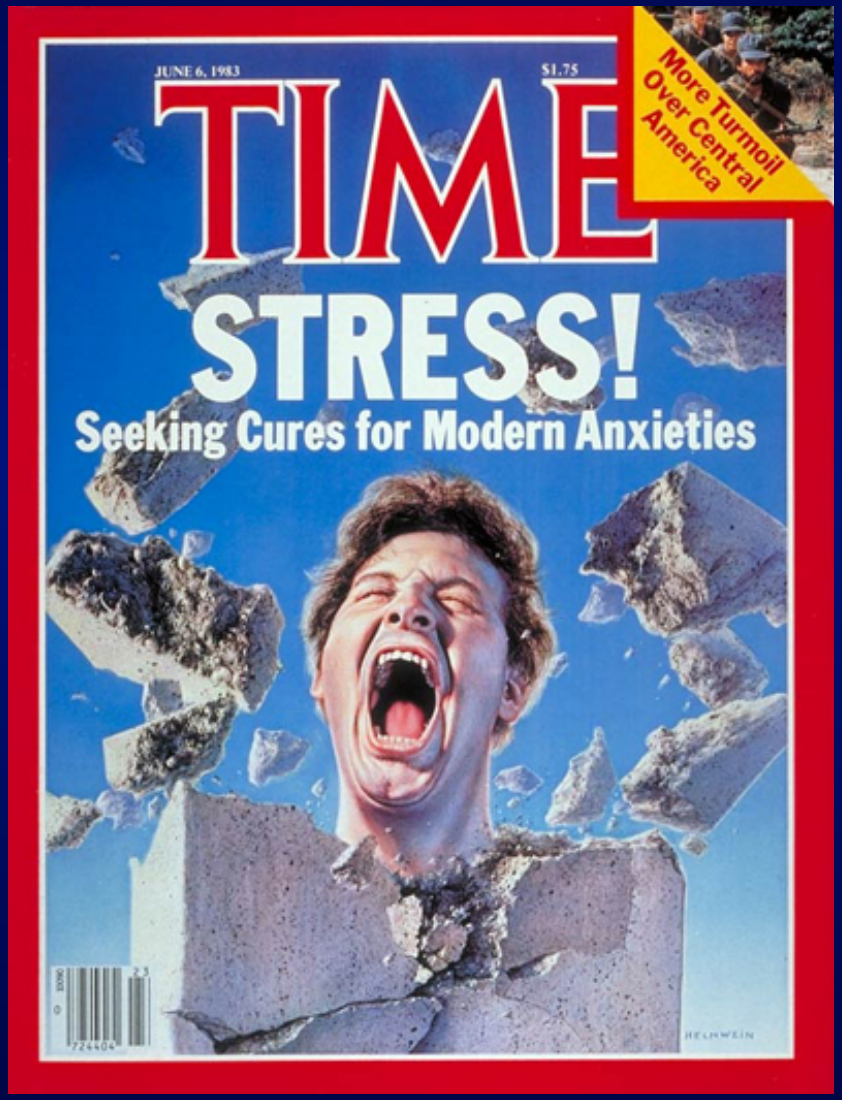
Kearney, P.M., et al. 2005. *Lancet.* 365:217–223)

http://www.americanheart.org/presenter.jhtml?identifier=2129

Contributing Factors to hypertension

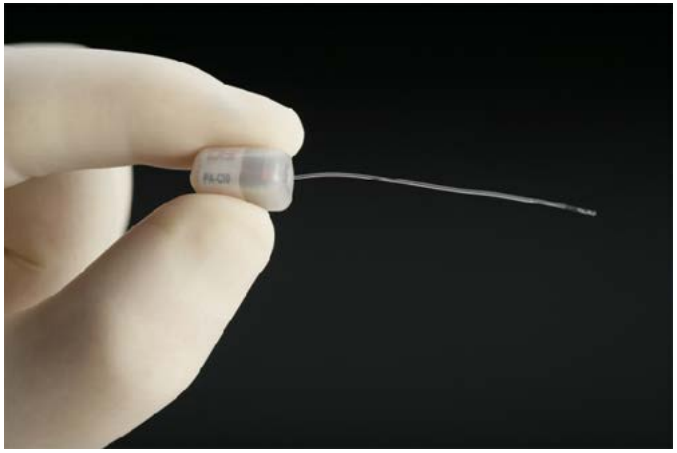
- ✧ Genetics
- ✧Race
- ✧ Age
- ✧ High sodium diet
- ✧ Lack of physical activity
- ✧ Obesity
- ✧ Stress (anxiety related disorders)
- ✧ Low-grade systemic Inflammation
- ✧ Renin Angiotensin System
- ✧Autonomic Dysfunction

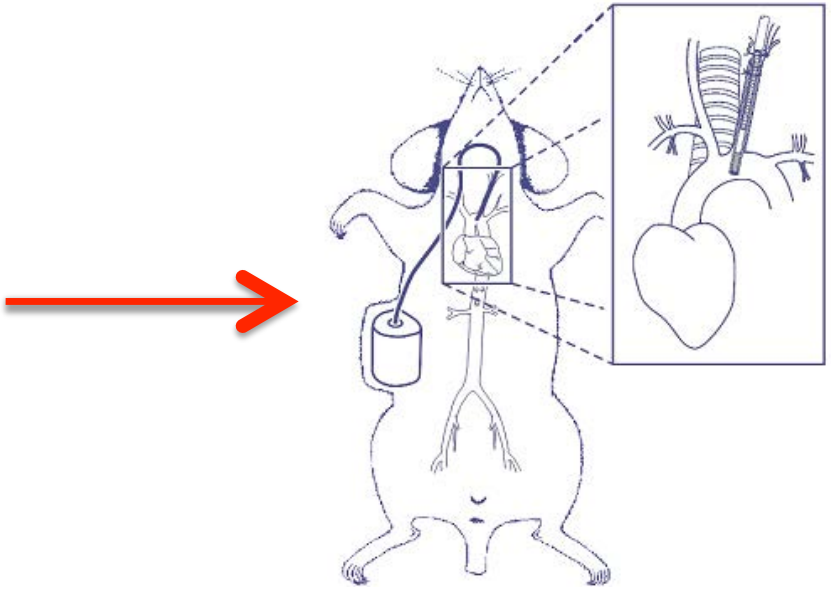
Psychological Stress

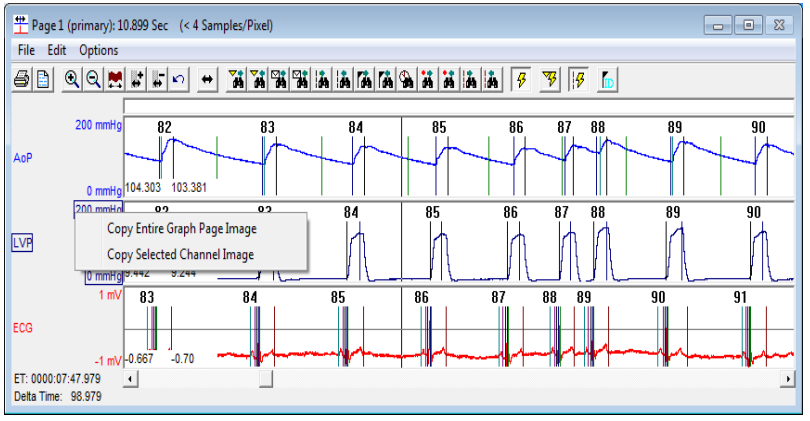


Cardiovascular Disease

Method of Blood Pressure Analysis: Radio Telemetry implantable probes in mice



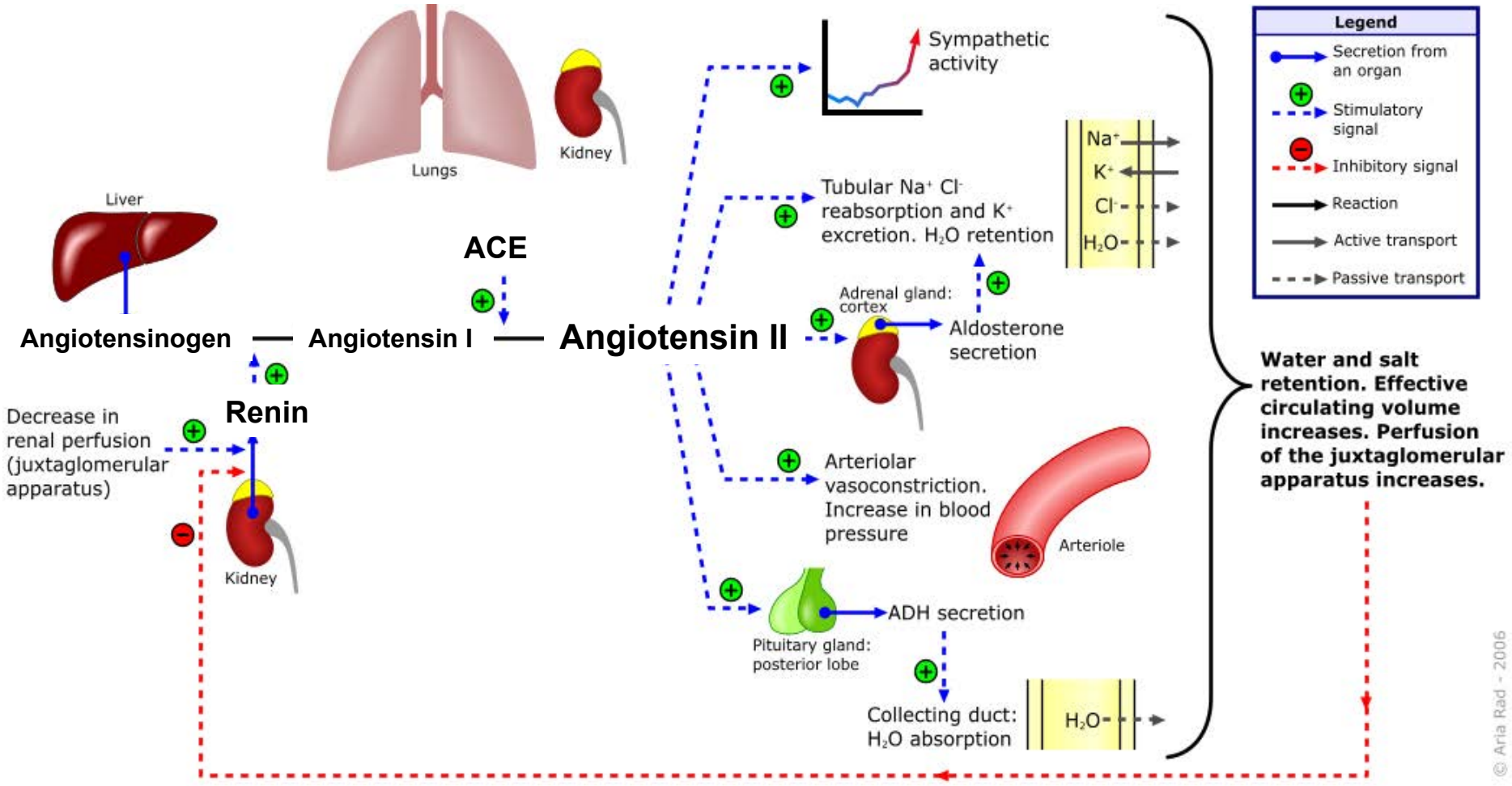




Experimental Animal Models

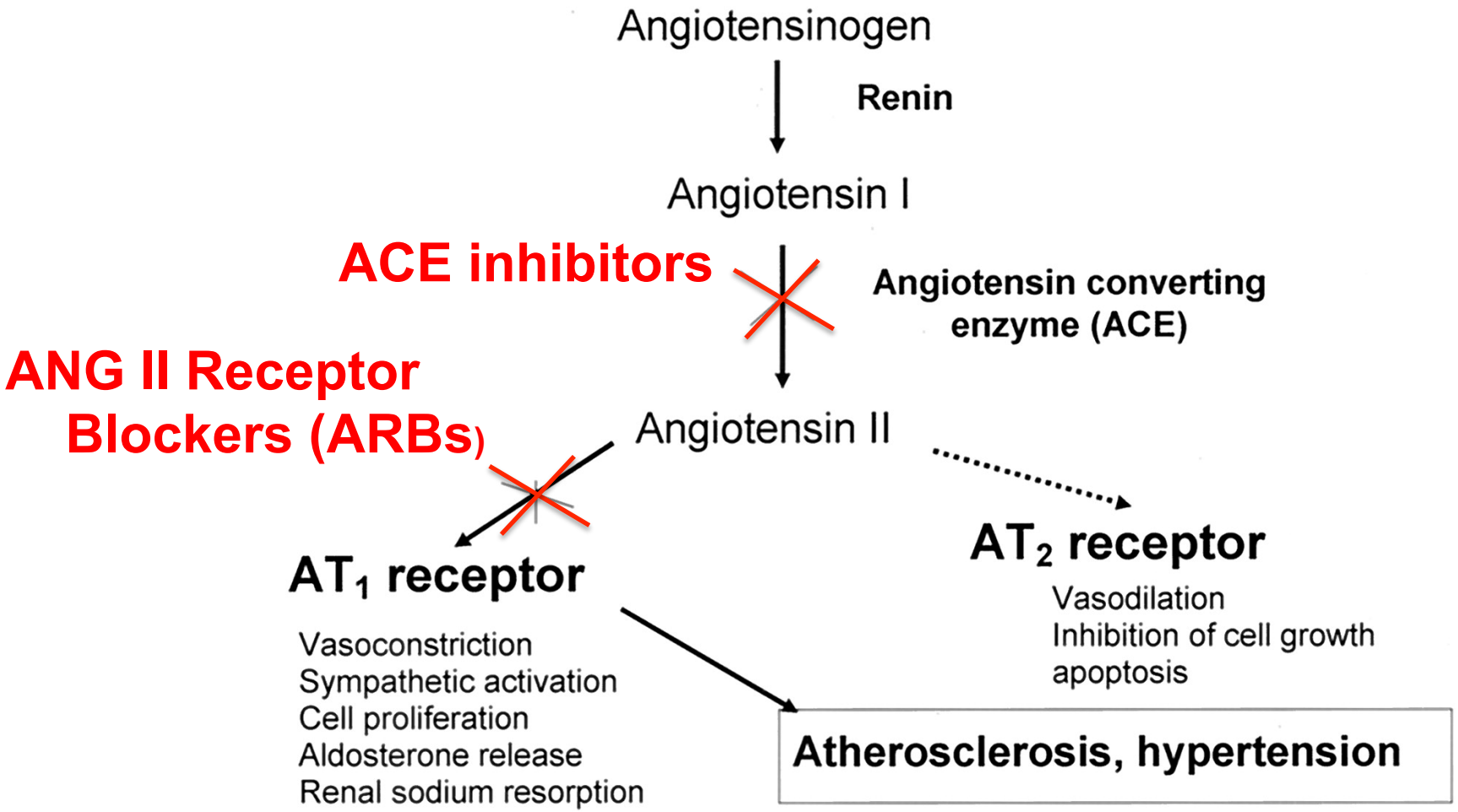
Experimental Hypertension (Pharmacological subcutaneous infusions)

Renin-Angiotensin-Aldosterone System



http://en.wikipedia.org/wiki/File:Renin-angiotensin-aldosterone_system.png

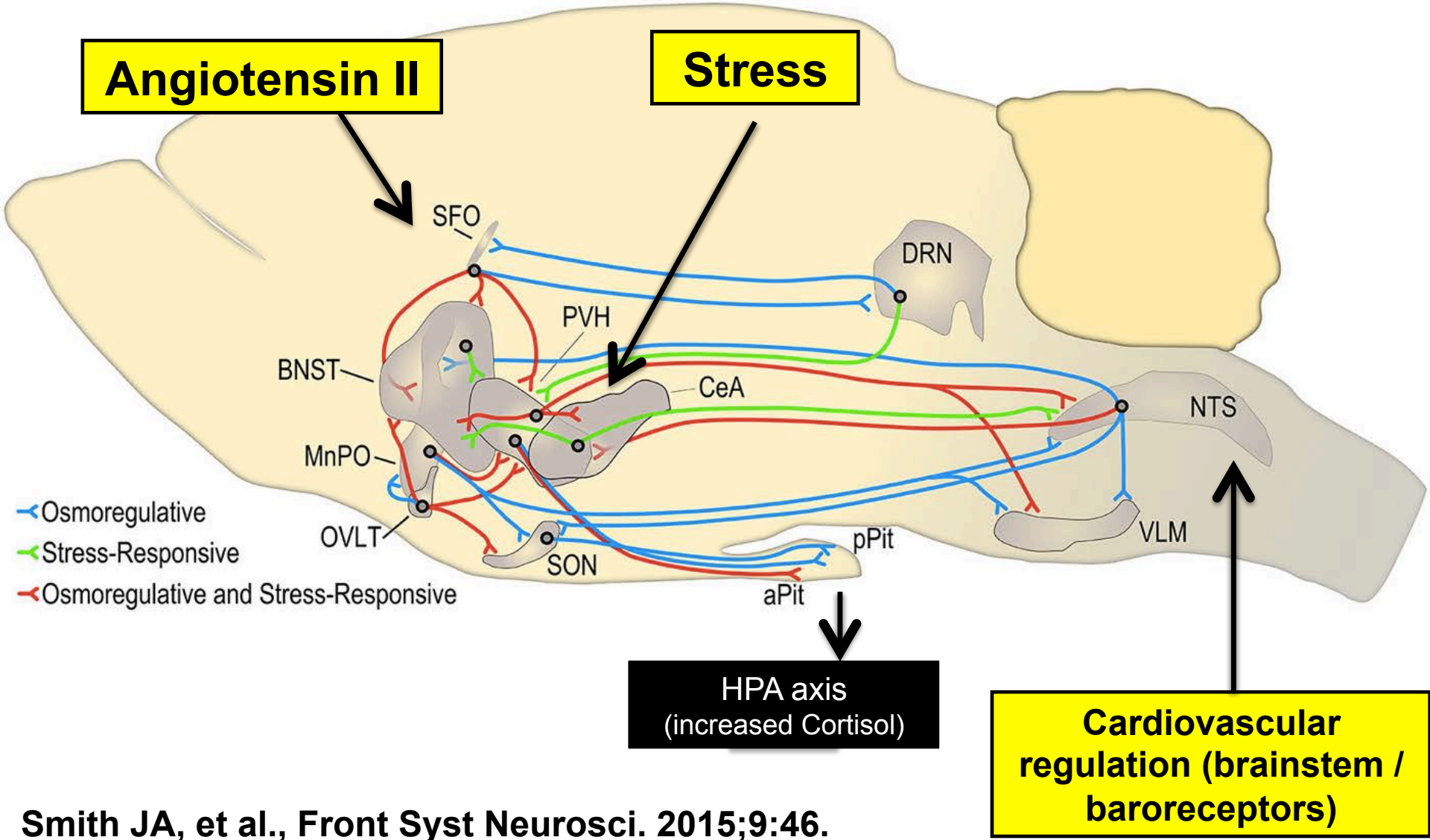
Therapeutic Targets of Angiotensin (Ang II)



Angiotensin II Exacerbates the Blood Pressure Response to acute and chronic Stress

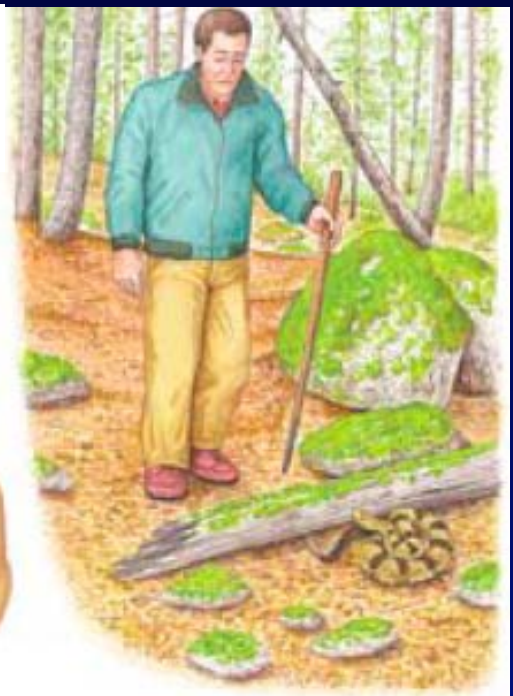
Acute and Chronic Stress

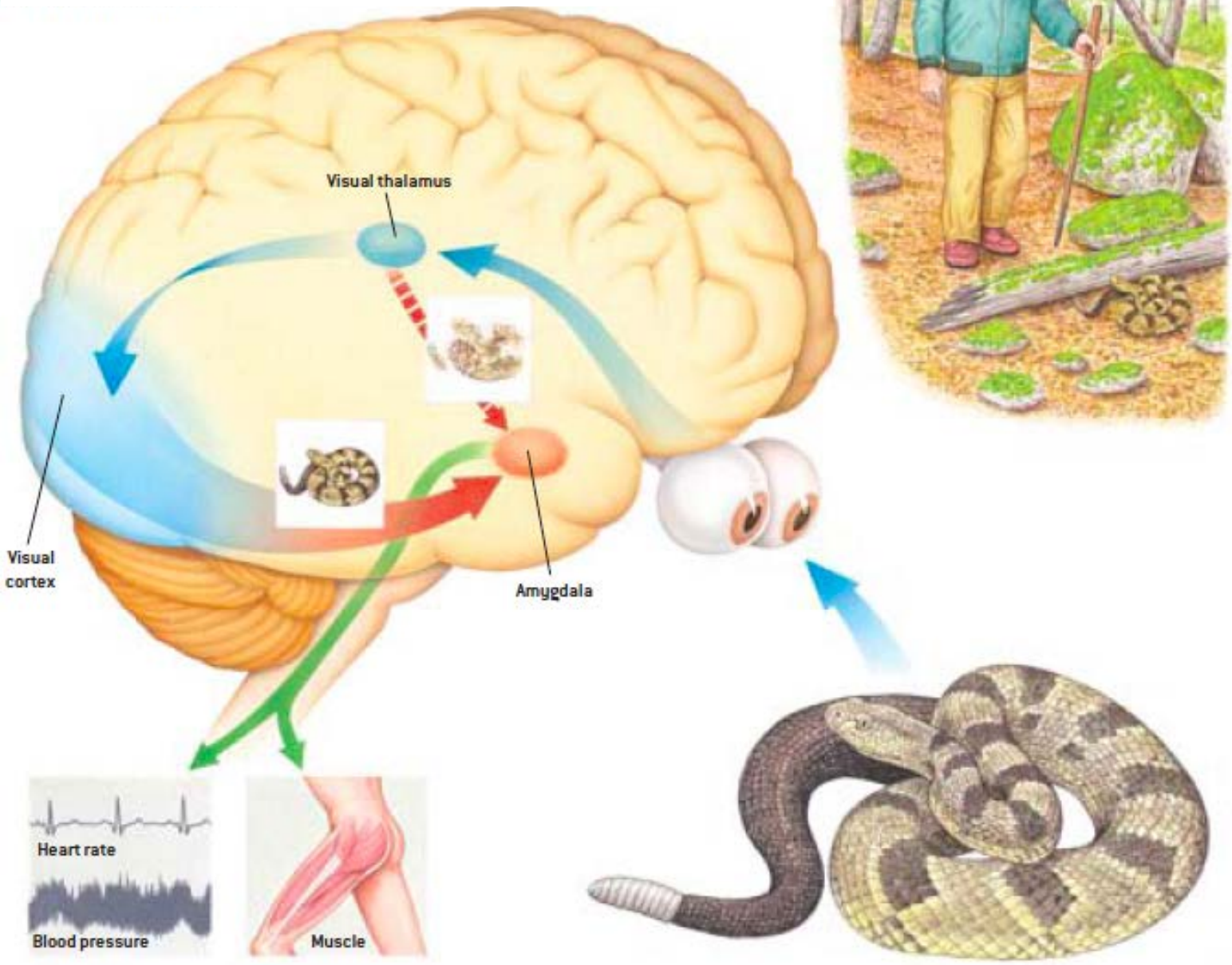
Key hypothalamic circuits that mediate the behavioral, endocrine, and autonomic stress-response



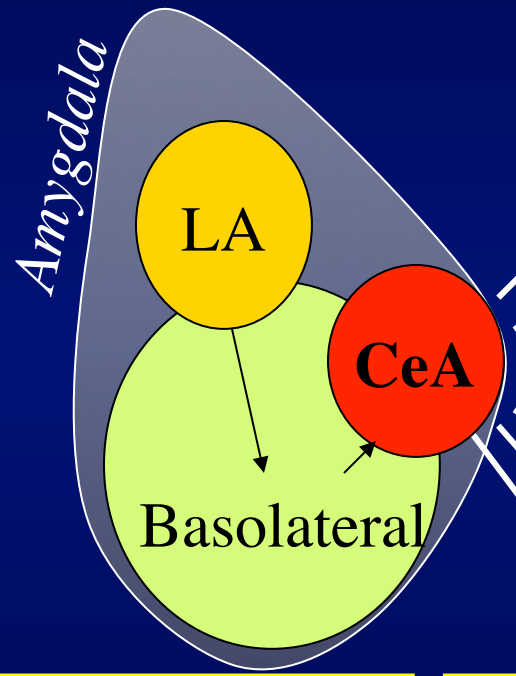
Smith JA, et al., Front Syst Neurosci. 2015;9:46.

The Fear Response





The Fear Response is a Hardwired Process involving the Amygdala



Fear / Panic Symptoms:

Lateral hypothalamus	→	**heart rate, blood pressure**
Dorsal vagal N.	→	**bradycardia, ulcers**
Parabrachial N.	→	**panting, respiratory distress**
Basal forebrain	→	**arousal, vigilance, attention**
Retic. Pontis Caudalis	→	**increased *startle response***
Central Gray Area	→	***freezing*, social interaction**
Paraventricular N.	→	**corticosteroid release**

Fear Learning

Expression of Fear

Modified from Davis (1992) Ann Rev Neurosci 15: 353-

PANIC ATTACK:

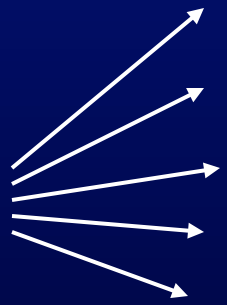
"All of a sudden I felt dizzy, my legs gave out on me, and I couldn't catch a breath. It felt like someone was choking me. I could feel my heart was beating too fast and I was terrified I was dying. I knew I had to get away before I lost it."

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

EMORY UNIVERSITY | Scholars Program in Interdisciplinary Neuroscience Research

2009-2011

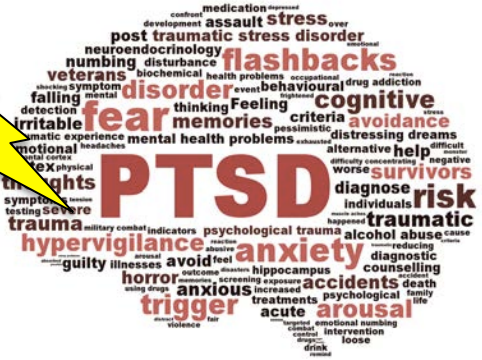
Stress Disorders (PTSD)

Kerry J. Ressler, MD/Phd
Mclean Hospital
Harvard Medical School

Cardiovascular Disease (hypertension)

David G. Harrison, MD
Clinical Pharmacology
Vanderbilt University

Stress

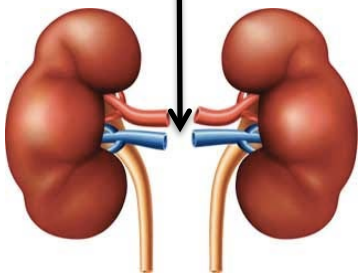


↑ Brain renin angiotensin system

↓

↑ Sympathetic Nervous System

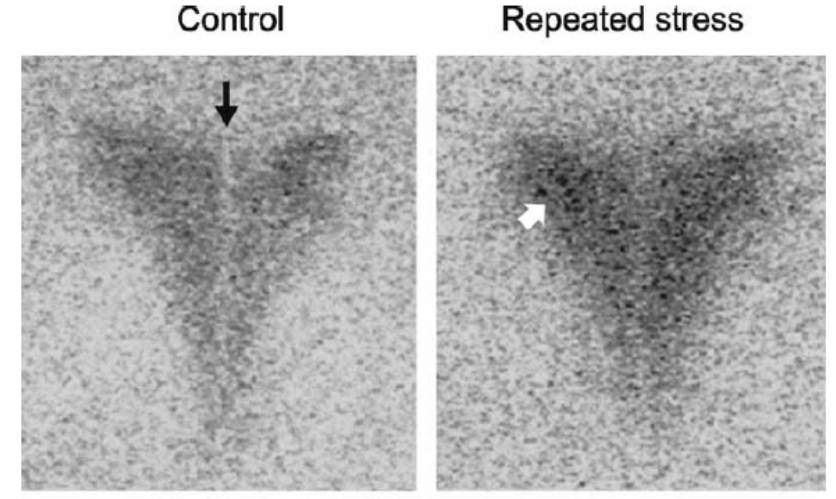
↓



← ↑ Renin

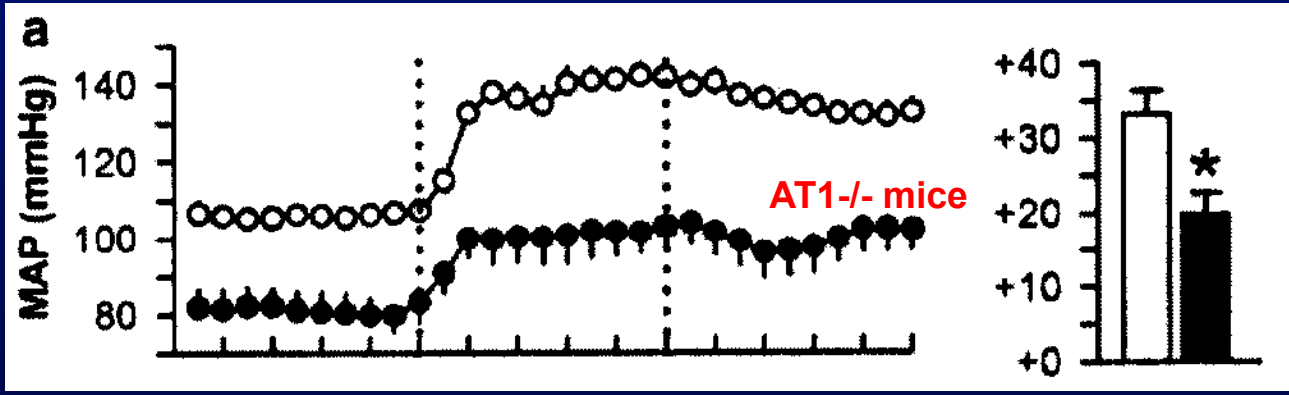
Chronic Stress Increases Activity of the Central and Peripheral Renin Angiotensin System

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



Castre´n E, Saavedra JM. Endocrinology 1988 122:370–372.

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



Davern et al., Hypertension. 2009 Dec;54(6):1262-8.

neuroReport Neuropharmacology and Neurotoxicology

NeuroReport 1, 20–21 (1990)

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

Nicholas M Barnes[CA], Brenda Costall, M Elizabeth Kelly, Deborah A Murphy and Robert J Naylor

Postgraduate Studies in Pharmacology, The School of Pharmacy, University of Bradford, Bradford, West Yorkshire, BD7 1DP, UK

[CA]Corresponding Author

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 $\mu g\ kg^{-1}$ p.o., 45 min before the test). These results further implicate the modulation of mental function by angiotensin II.

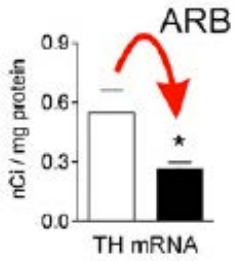
Key words: Anxiolytic-like action, Angiotensin II receptor antagonist, DuP753

Barnes NM, et al., NeuroReport 1, 20-21 November 1990:1–2.

Angiotensin II Receptor Blockade Improves Stress Related Pathology

A

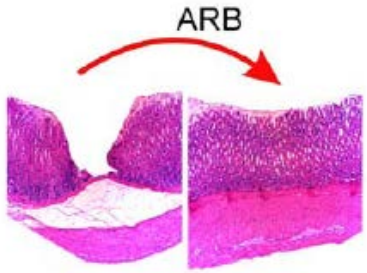
Decrease central Sympathetic activation



Tyrosine hydroxylase in Locus Coeruleus

B

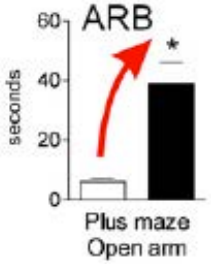
Prevent a somatic stress disorder: Gastric ulcers



Cold-restrain stress Gastric mucosa

C

Decrease anxiety



Time spent on the open arm Plus maze

Saavedra et al., Psychoneuroendocrinology. 2011 Jan;36(1):1-1

Expert Opinion

Central & Peripheral Nervous Systems

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

Paul R Gard
School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton BN2 4GJ, UK

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.

Gard PR.. Expert Opin Ther Targets. 2004;8(1):7–14.

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.

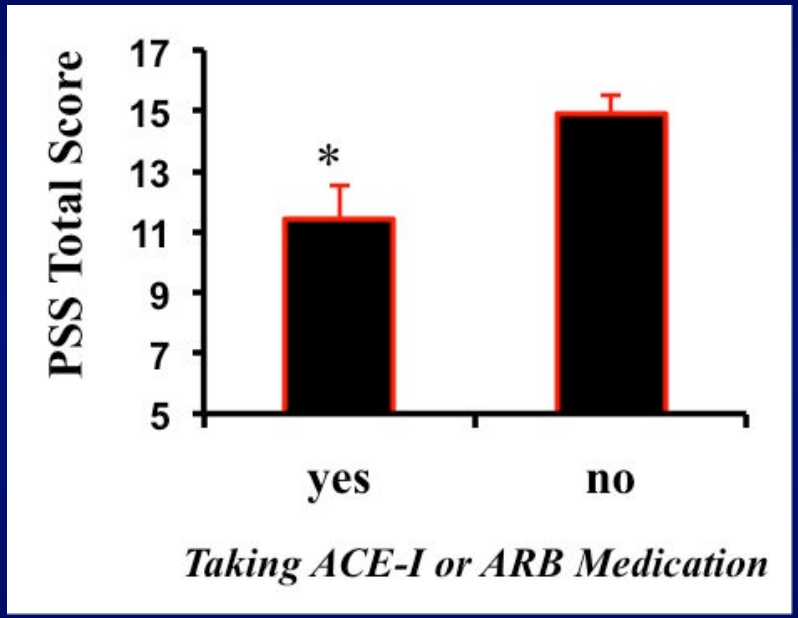
Post Traumatic Stress Disorder (PTSD)

- 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

Outcome	ACE Inhibitor or ARB β Estimate	SE	*t*	*P*
PSS total score (n = 467)				
Unadjusted effect	−3.51	1.4	−2.47	.014
Adjusted[a] effect	−2.83	1.4	−2.02	.044
PSS hyperarousal score (n = 467)				
Unadjusted effect	−1.30	0.5	−2.59	.010
Adjusted[b] effect	−1.22	0.6	−2.20	.028
PSS avoidance numb score (n = 459)				
Unadjusted effect	−0.94	0.6	−1.49	.138
Adjusted[c] effect	−0.92	1.1	−1.12	.161
PSS intrusive score (n = 467)				
Unadjusted effect	−1.27	0.4	−2.86	.005
Adjusted[d] effect	−1.01	0.5	−2.20	.029
Lifetime CAPS score (n = 467)				
Unadjusted effect[e]	−4.90	3.95	−1.24	.216
Adjusted[f] effect[e]	−1.22	0.56	−2.20	.028
Current CAPS score (n = 417)				
Unadjusted effect[e]	−5.05	2.91	−1.74	.083
Adjusted[g] effect[e]	−7.16	2.78	−2.57	.010



Khoury, Marvar et al., Journal of Clinical Psychiatry 2012

Summary

- 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

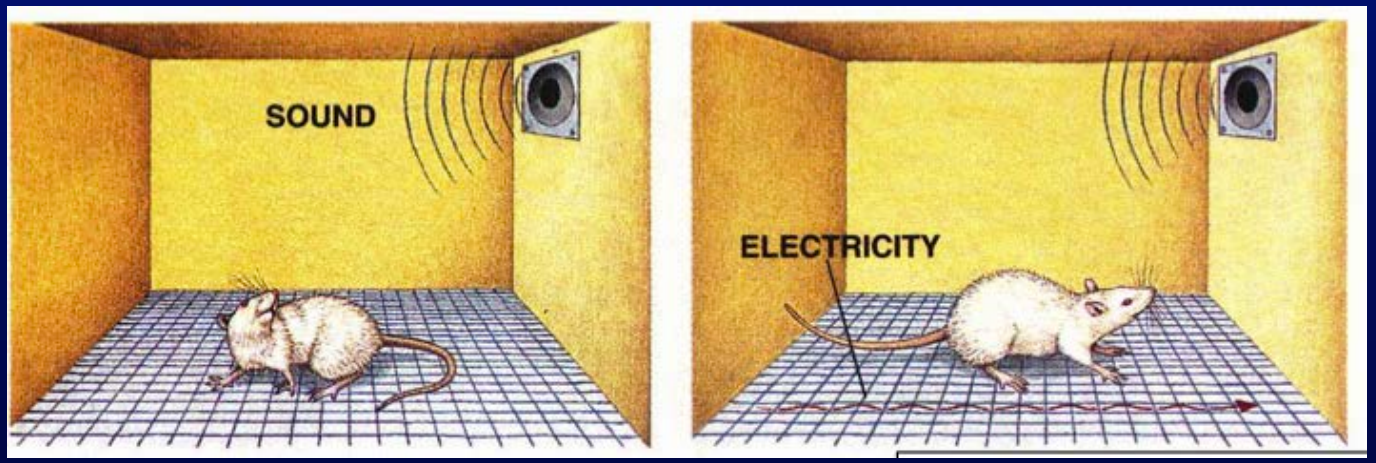
Joseph LeDoux, PhD – Pioneer in the understanding of Fear Memory
http://www.cns.nyu.edu/labs/ledouxlab/overview.htm

Pavlovian Fear Conditioning

- 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

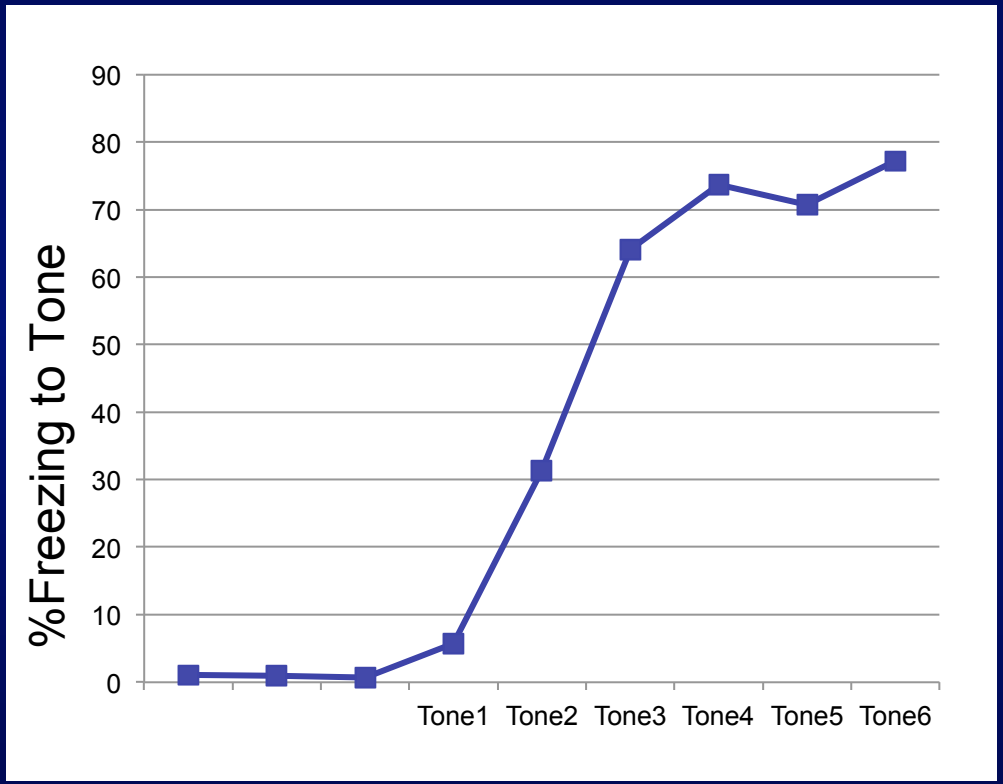
- Elicits a fear response when presented with the innocuous CS, even in the absence of the US.



Tone & Foot shock pairing **24 hours later (Tone Alone)**

How we measure fear in animals?
Fear-Potentiated Startle & Freezing

Fear Conditioning



Freezing Response During Extinction Training to Conditioned Cue (Tone)

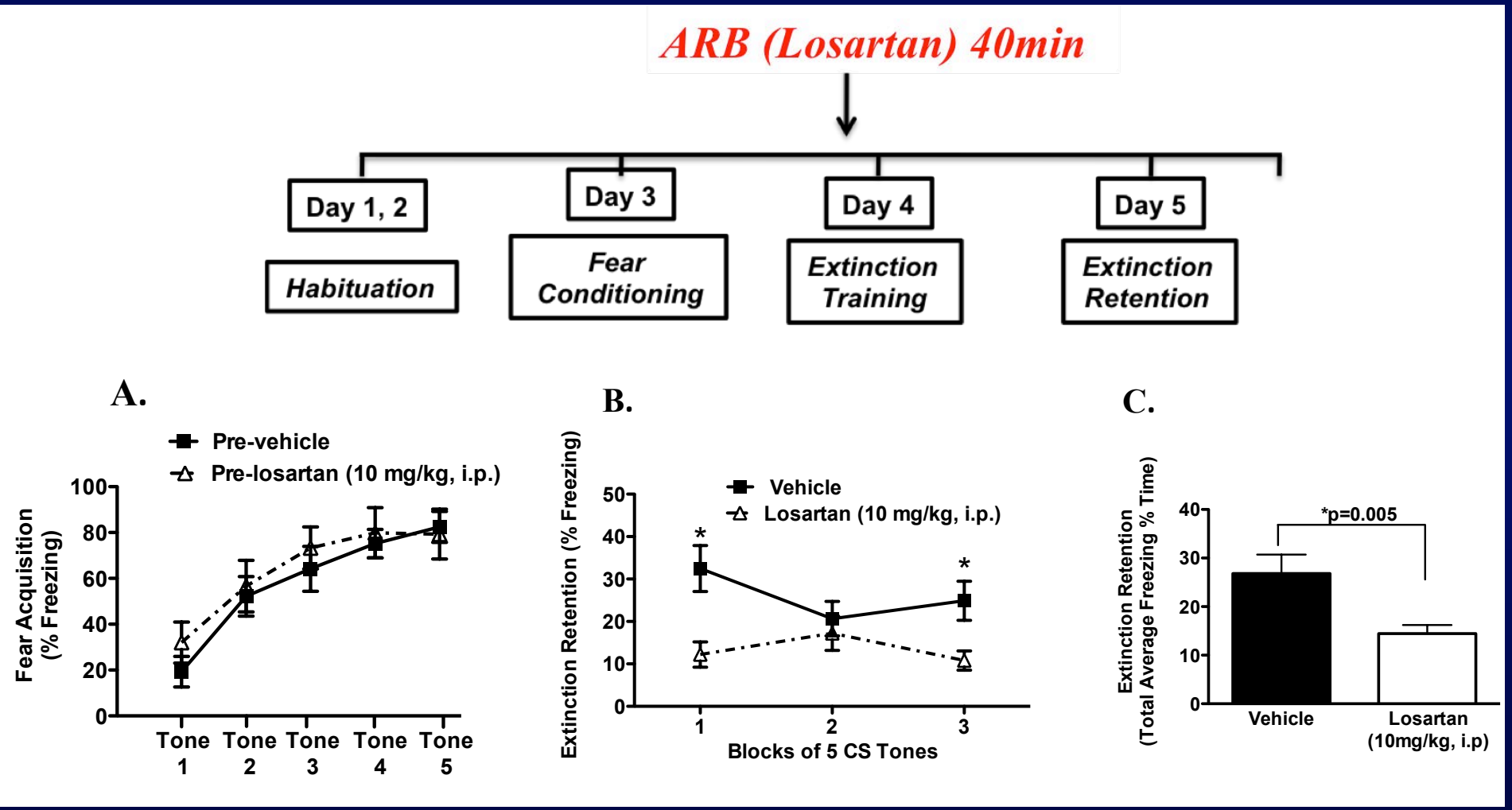
Video Courtesy of Brian G. Dias, PhD – Emory University Dept. of Psychiatry

Extinction of Fear Memory

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

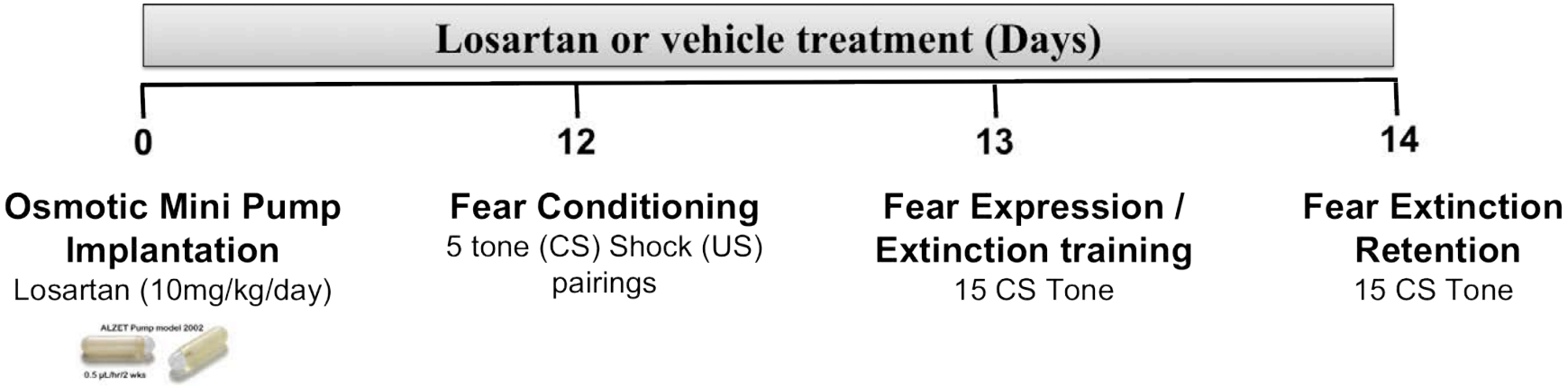
- *Increased understanding of the mechanisms underlying deficits in extinction learning will aid in the development of new therapies to treat anxiety and fear-related disorders, such as PTSD.*

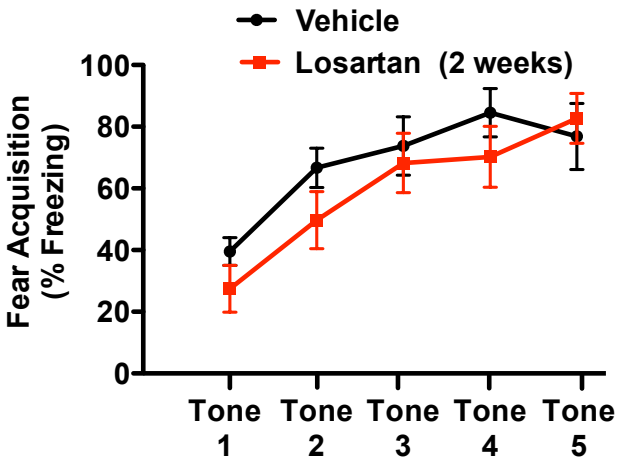
Angiotensin type 1 receptor inhibition enhances the extinction of learned fear

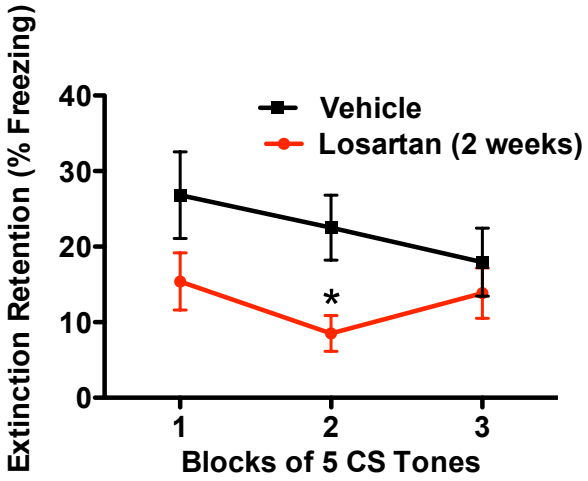


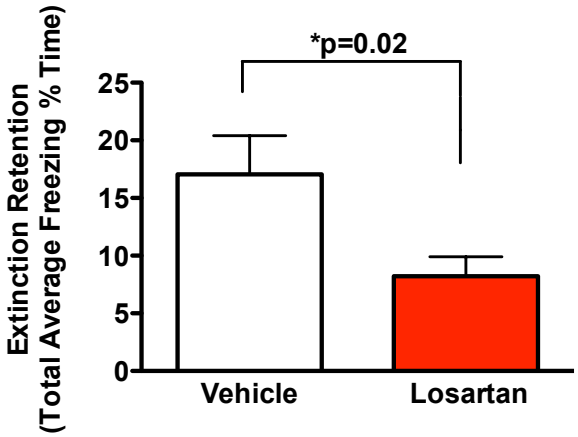
Marvar PJ, et al., Biol Psychiatry. 2014;75(11):864–872.

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





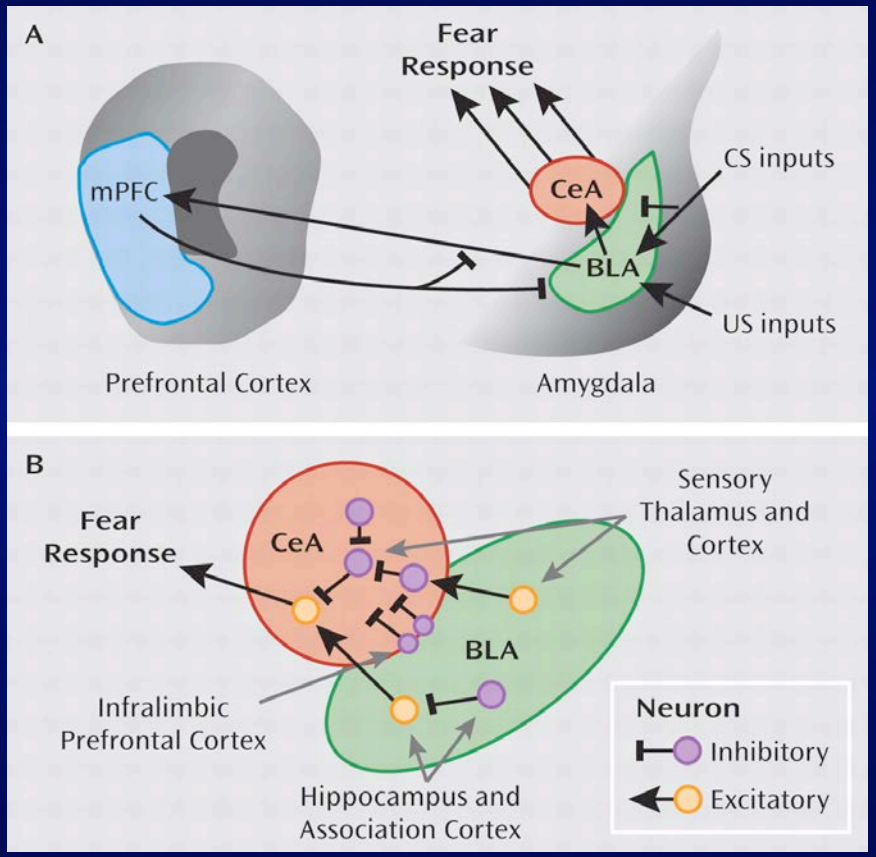




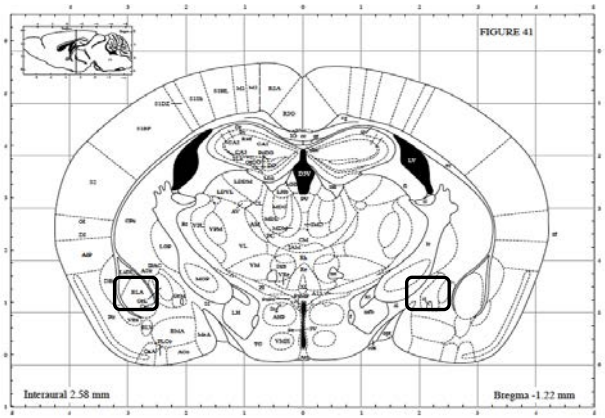
Marvar PJ, et al., Biol Psychiatry. 2014;75(11):864–872.

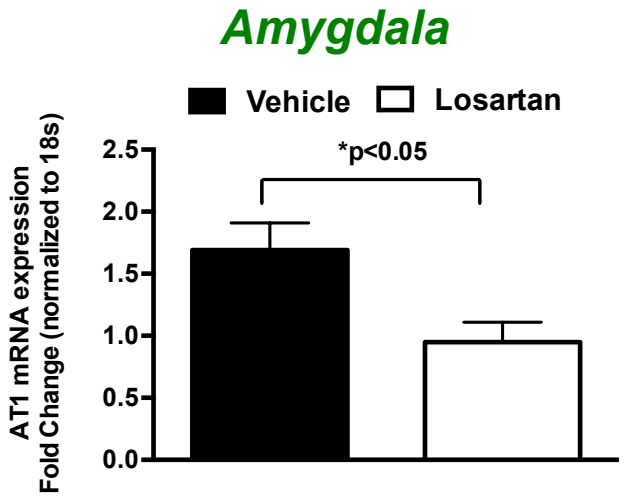
Amygdala and Fear

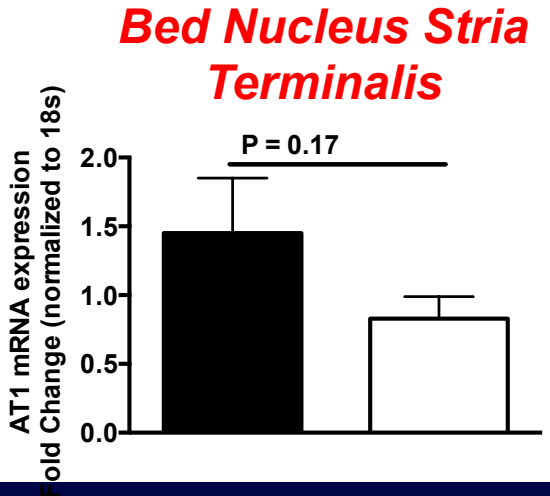
- Required for both the acquisition of classically-conditioned fear, and the extinction of conditioned fear
- Lesions in the BLA in animal models lead to an inability to extinguish conditioned fear responses

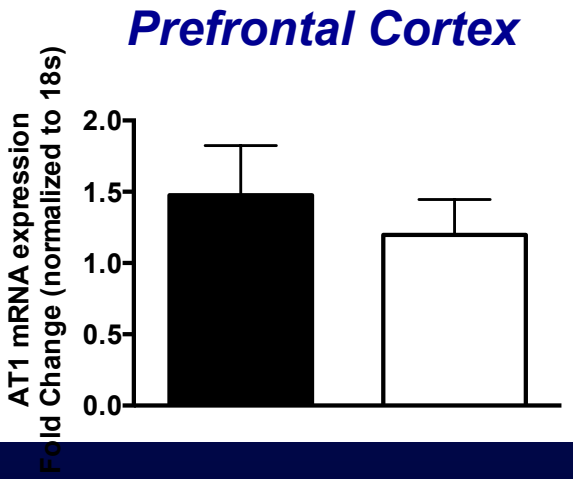


Chronic inhibition of angiotensin type 1 receptor enhances extinction of learned fear





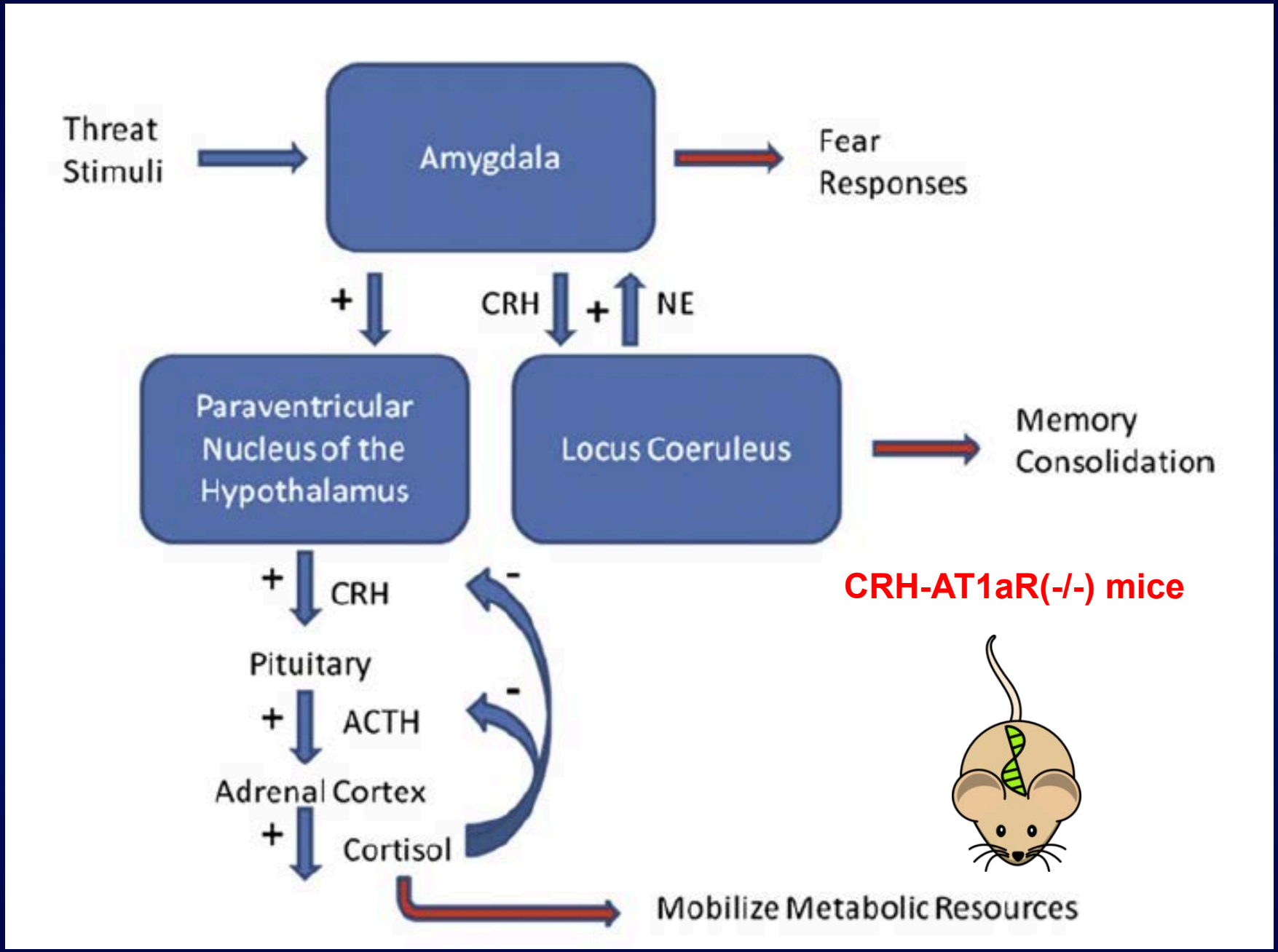




Marvar PJ, et al., Biol Psychiatry. 2014;75(11):864–872.

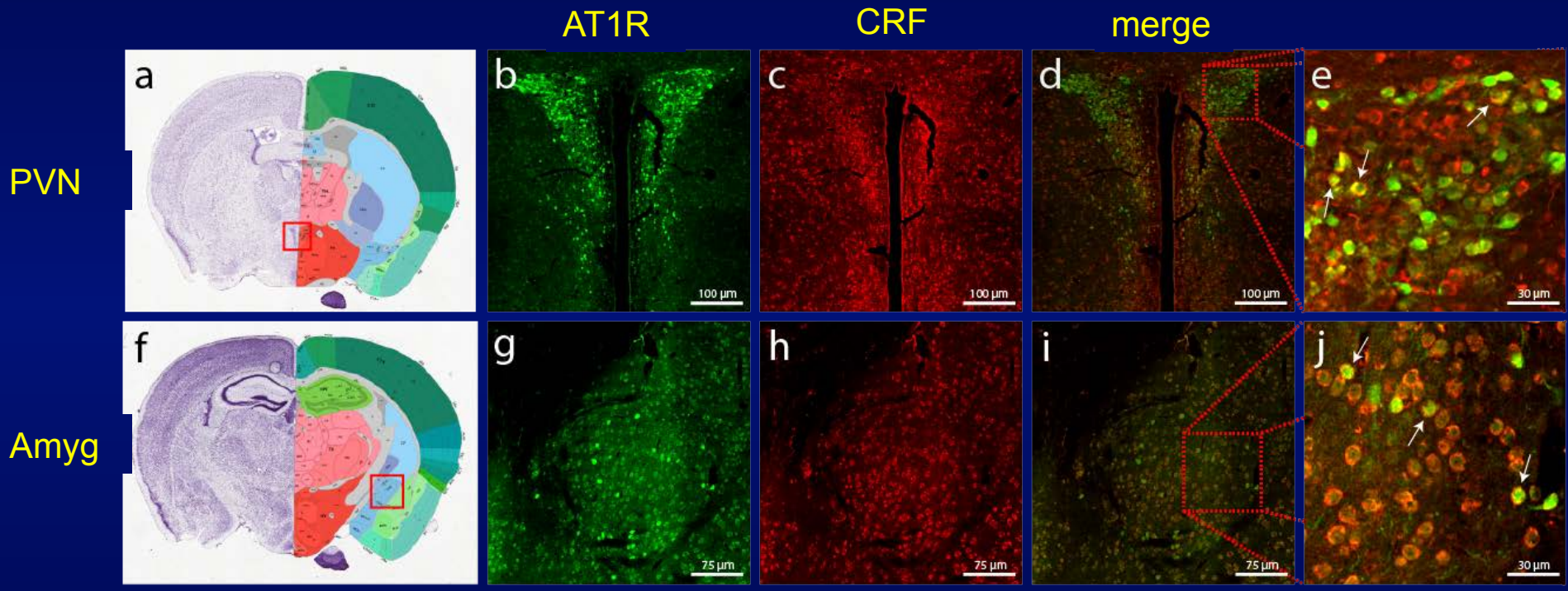
- Systemic administration of ARBs does not address whether ARBs are acting centrally and which cell types they are acting on?

- Determine whether AT1aR deletion from a genetically defined neural population—(corticotropin-releasing factor (CRF)-expressing cells) affects the expression of conditioned fear.



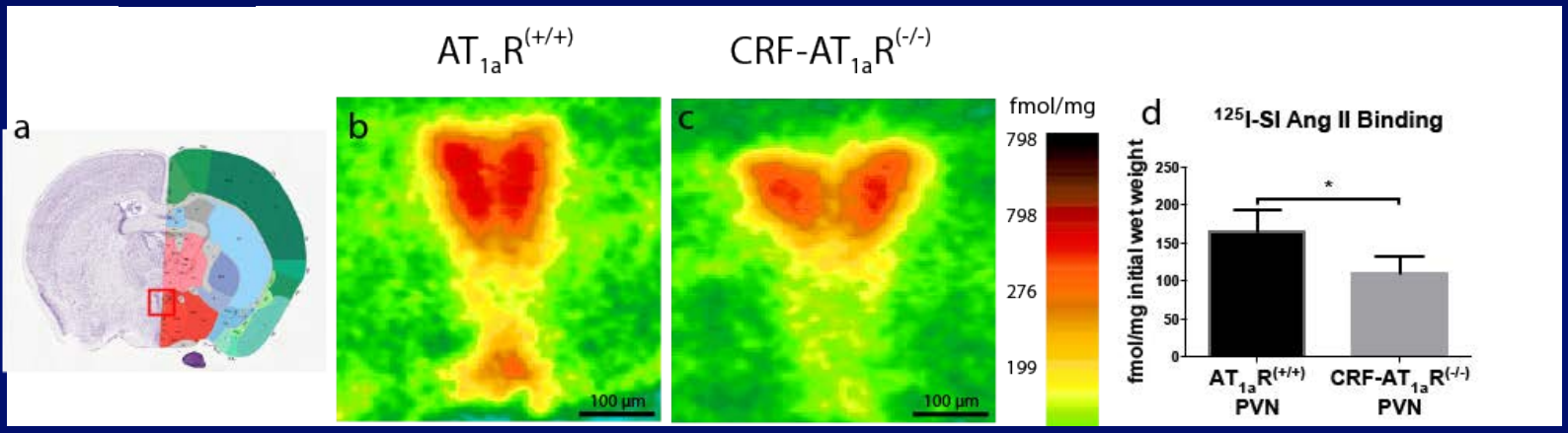
Skelton et al. Neuropharmacology, Volume 62, Issue 2, 2012, 628–637

AT1 receptor and CRF co-localize in subsets of PVN and Amygdala neurons



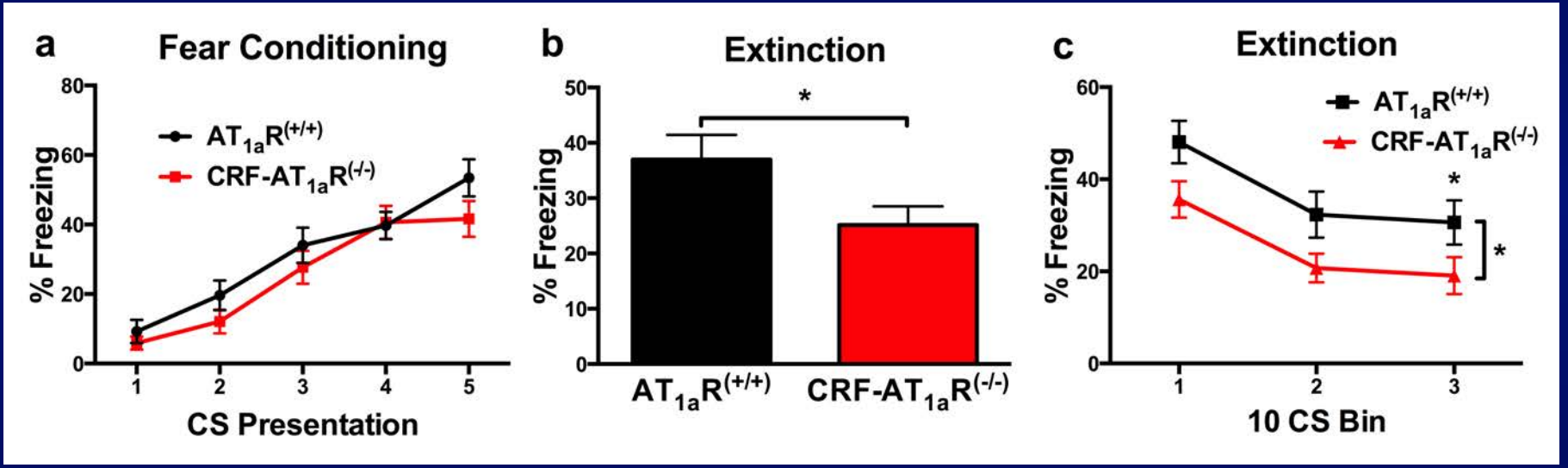
Hurt RC, Marvar et al.,. Genes Brain Behav. August 2015.

Decreased AT1R expression in the PVNs of CRF-AT1aR(-/-) mice compared to controls



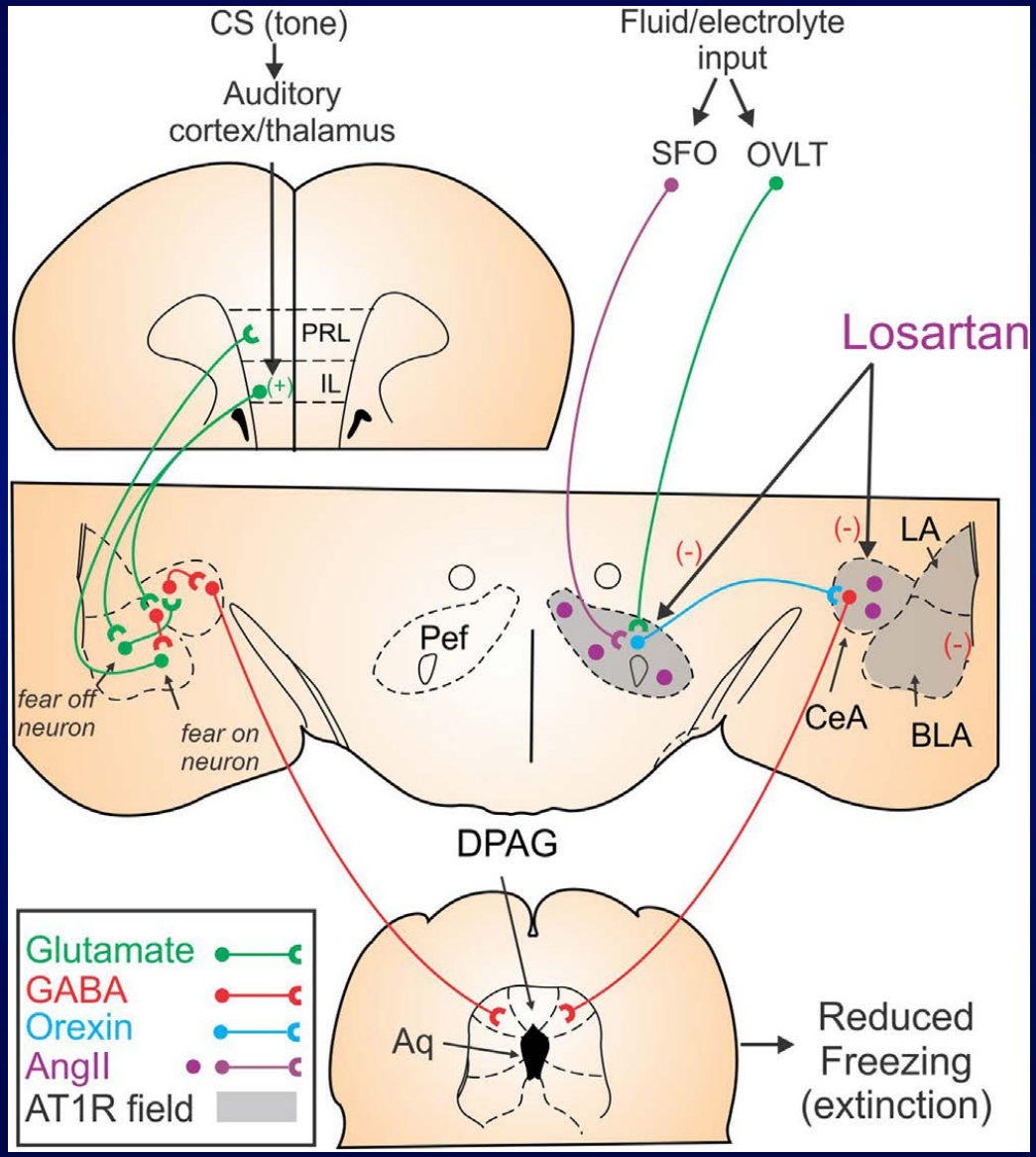
Hurt RC, Marvar et al.,. Genes Brain Behav. August 2015.

AT1R knockout from CRFergic cells decreases fear expression and enhances extinction retention



Hurt RC, Marvar et al.,. Genes Brain Behav. August 2015.

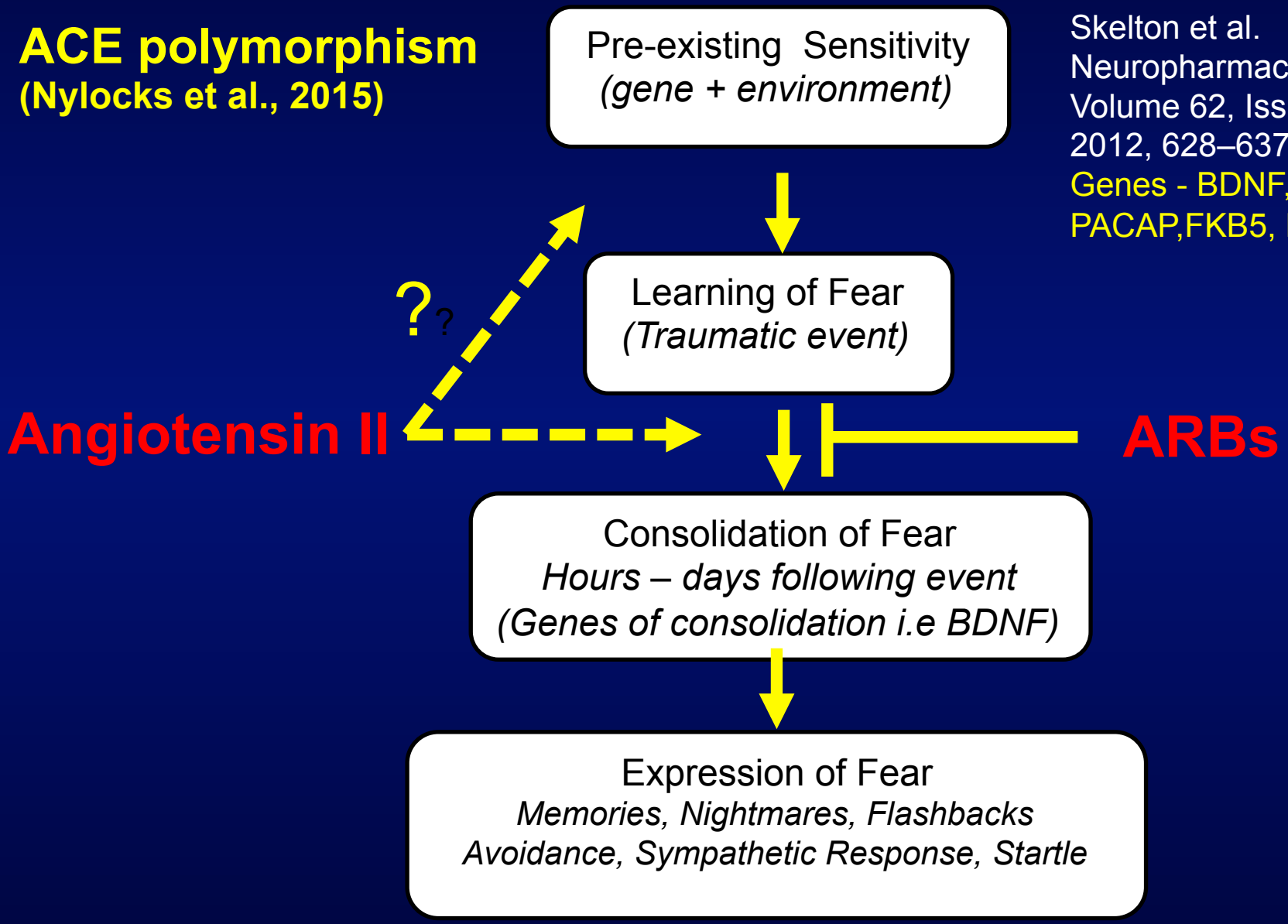
Fear Circuits and the Renin Angiotensin System a Therapeutic Target?



Shekhar et .
Biol Psychiatry. 2014 Jun 1;75(11):836-7.

Modeling Fear Disorders

ACE polymorphism
(Nylocks et al., 2015)



Skelton et al. Neuropharmacology, Volume 62, Issue 2, 2012, 628–637
Genes - BDNF, PACAP,FKB5, Nk3

PTSD and Cardiovascular Disease

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

Boscarino et al. Prev Med. 2012 Jan 18;
Player et al., Int J Psychiatry Med. 2011;41(4):365-77.

* More likely to have hypertension, hyperlipidemia, obesity, and cardiovascular disease.

Ahmadi et al., Am J Cardiol. 2011 Jul 1;108(1):29-33.

Targeting the angiotensin system could provide an additional avenue for *treating co-morbid PTSD and cardiovascular disease?*

Acknowledgements

Emory University (2006-2010)
Division of Cardiology
Mentor: David G. Harrison, MD

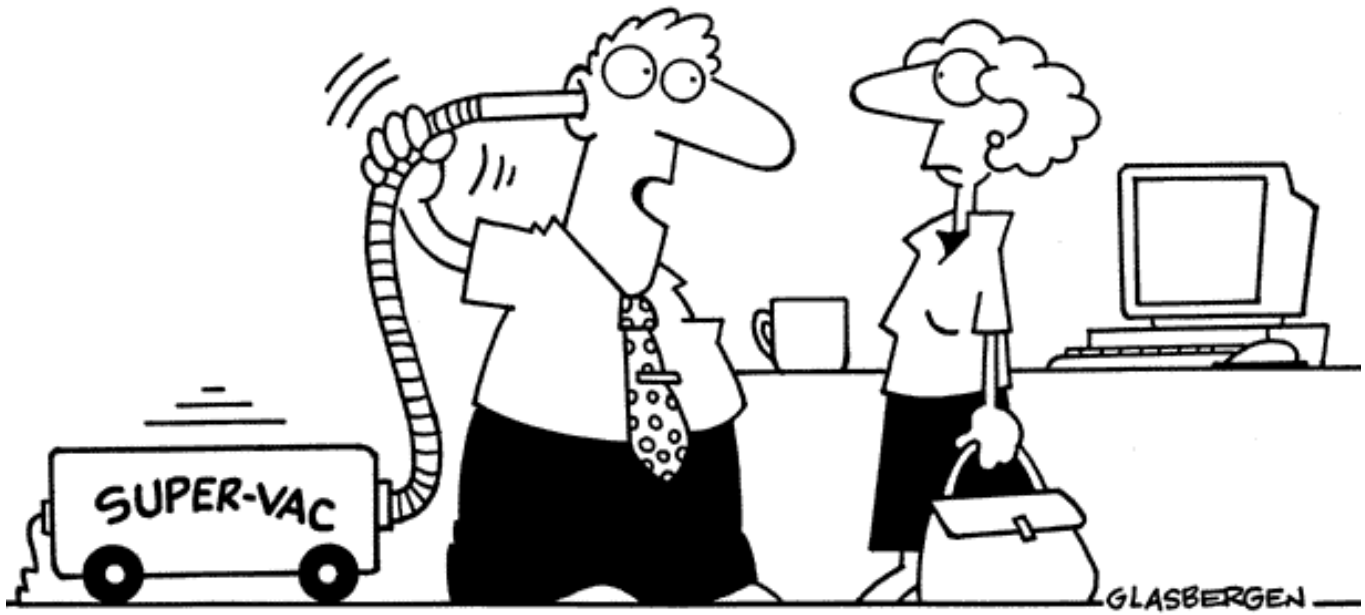
Emory University (2011-2013)
Behavioral Neurosciences
Department of Psychiatry
Mentor: Kerry J. Ressler, MD/PhD

University of Bristol, UK (2012-2014)
Department of Physiology
Mentor: Julian F. Paton, PhD

GWU **(2014-present)**

Funding: NIH NHLBI K99, NIH NHLBI R00, American Heart Association – Collaborative Sciences Award, Emory University Scholars Program in Interdisciplinary Neuroscience Research NIH NRSA F32

Thank you – Questions?



"It's just something I do every day at 5:00
to get rid of stress before I go home."