

Stress causes the brain to increase subsequent responses to both threatening and pleasurable stimuli.

Mary F Dallman  
for:

Susan F Akana, Norman C Pecoraro, Hani Houshyar, and Abigail B Ginsberg at UCSF

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### Glucocorticoids (& stress):

- rapidly, non-transcriptionally, inhibit HPA activity & increase "comfort food" intake
- Slowly, via transcriptional mechanisms recruit a CRF stress-response network that sensitizes HPA responses to novel stress and increases "comfort food" intake

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### Stressors: Acute or Chronic?

- Acute stressors stimulate the HPA axis briefly, but are self-limited by GC feedback
- Chronic stressors activate a limbic stress-response network:
  - GC-dependent increase in limbic CRF
  - Activation of all monoaminergic cell groups via CRF
  - Sensitization of HPA responses to new stimuli
  - Altered behaviors, autonomic and neuroendocrine outflows

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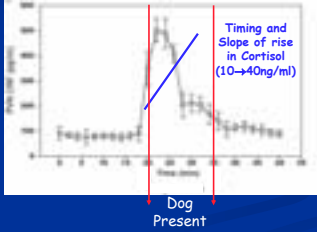
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Rapid endogenous response of cortisol in sheep to dog stress may limit duration of maximal CRF secretion from the PVN



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C J Cook Physiol Behav 2004

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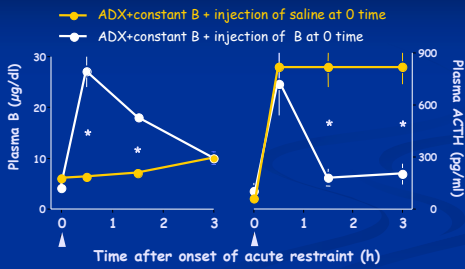
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Acute GC response to stress limits the duration of ACTH responses



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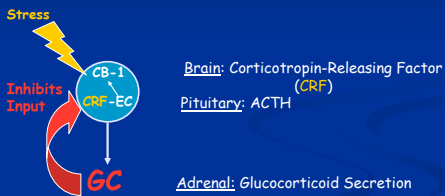
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Acute GC Feedback is Non-Transcriptional. Mediated by Endocannabinoids? Tasker lab, 2003



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What are the effects of an Endocannabinoid-receptor (EC-1) Antagonist administered systemically on:

- Acute ACTH & B responses to Restraint?
- Sucrose ingestion after restraint?

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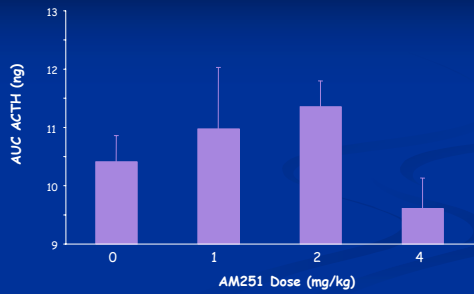
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An endocannabinoid-receptor antagonist increases and then decreases the ACTH responses to restraint



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A Ginsberg, 2005

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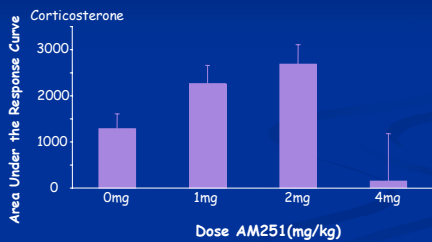
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An endocannabinoid-receptor antagonist increases and then decreases the B responses to restraint



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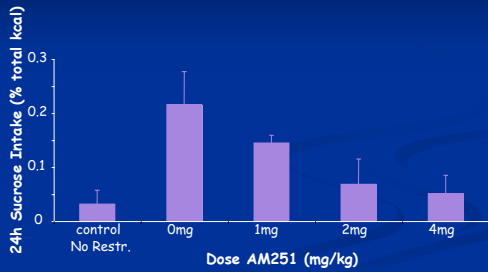
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An endocannabinoid-receptor antagonist decreases Sucrose drinking during the 24hr after restraint



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At lower doses, the CB-1 receptor antagonist AM251:

1. Stimulates ACTH and corticosterone responses to acute restraint stress, and,
2. Inhibits pleasurable sucrose ingestion after the restraint stress.

Does the CB-1 blocker interfere with the effects of the Glucocorticoid agonist RU362?

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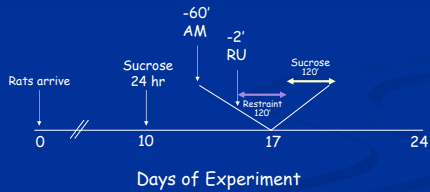
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Partial Design of Expts to test interaction Between CB-1 Antagonist and GR Agonist:



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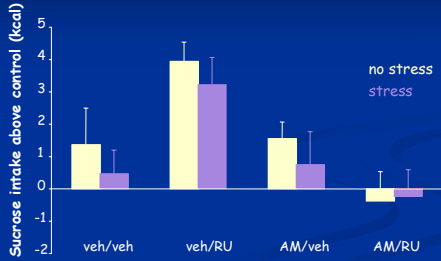
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The CB-1 antagonist blocks the effect of the GR agonist on 2 hr sucrose ingestion



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### Preliminary Conclusions:

- ✓ Endocannabinoids may be mediators of Fast Feedback by B on CRF
- ✓ GR agonists rapidly increase Sucrose ingestion (rapid B feed-forward?)
- ✓ Rapid GR-dependent sucrose ingestion may be mediated by endocannabinoids

Stay Tuned!

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### Chronic Stressors Appear to Recruit a Chronic Stress Response Network

- In the BRAIN outputs are *biased toward*:
  - Increased HPA axis responsiveness
  - Increased Comfort Food Intake
  - Decreased Chow Intake
  - Anxiety
  - Increased Sympathetic responsiveness
- In the BODY autonomic and endocrine outputs are *biased toward*:
  - Shifts of energy stores to the center
  - Elevated muscle tone
  - Increased arterial blood pressure
  - Insulin resistance

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### All of these are Acute &/or Chronic Stressors for People:

- Natural Catastrophes (earthquakes, famine, drought, tsunamis, hurricanes)
- Unnatural Catastrophes (War, Torture, 9/11, Iraq, Madrid, London, New Orleans)
- Lower Socioeconomic Status
- Job loss, Company down-sizing, Job control
- Bereavement, Caretaking
- Chronic Illness
- Loneliness
- Addiction, depression, anxiety
  - BUT, these may result from activation of the brain chronic stress response network

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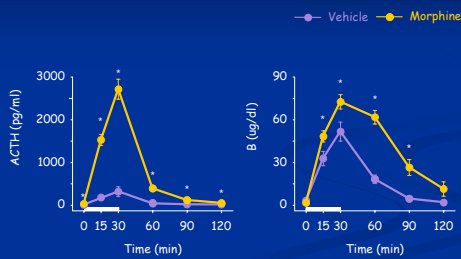
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### During Acute Morphine Withdrawal Rats Are Sensitized To Novel Restraint



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Houshyar, 2004

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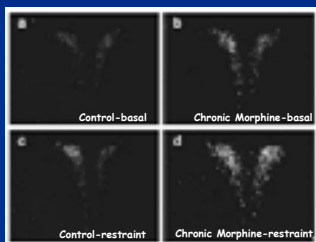
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### Sensitized CRFmRNA after acute novel stress in chronically stressed intact rats



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Houshyar et al. 2003

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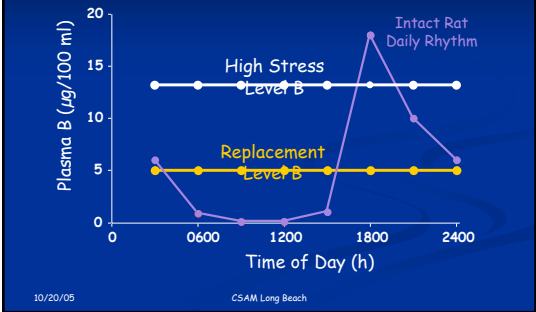
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Plasma B after ADX and B pellets s.c.




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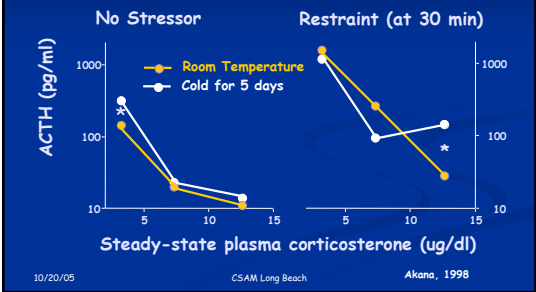
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Sensitized ACTH responses to acute stress require high B in chronically stressed ADX rats




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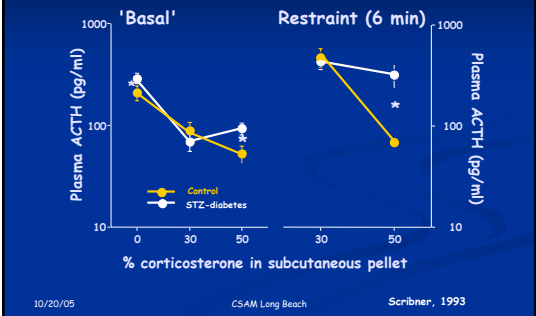
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Sensitized ACTH responses in diabetics require high, stress levels of B (ADX rats)




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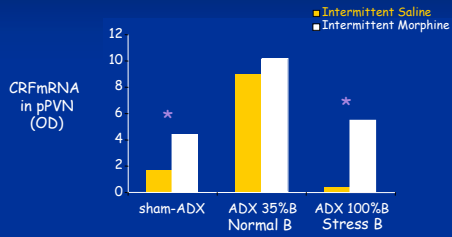
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Sensitized CRF responses also require high B in chronically stressed ADX rats



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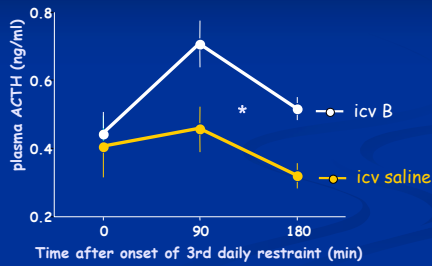
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B directly into brain Sensitizes ACTH Responses to Repeated Restraint (ADX)



10/20/05 CSAM Long Beach Laugero et al. 2002

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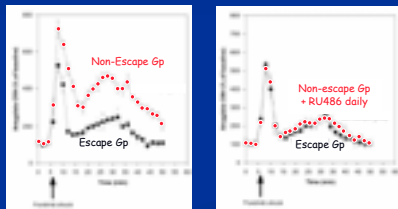
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Sheep exposed to 7 days of dog stress for 5 min/d sensitize Amygdala CRF responses to novel stimulus on d 8. This depends on glucocorticoid action



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## Chronic Stress Response Network

A central brain stress-response network that requires both elevated GC and limbic CRF is recruited under conditions of chronic stress:

- ✓ GCs become stimulatory rather than inhibitory on HPA axis - sensitize responses to new stimuli
- ✓ Elevated GCs augment limbic CRF synthesis and secretion
- ✓ Change behaviors, and neuroendocrine activities

All of these are initially GC-dependent

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## "Comfort foods" and Glucocorticoids

High GCs promote:

- ✓ Searching for lost "comfort foods" &
- ✓ Disappointment with degraded "comfort foods"
- ✓ Ingestion of "comfort foods" more than chow

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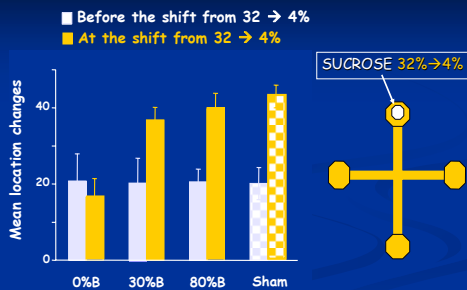
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## Appetitive searching is B-dependent

(ADX + sham rats)



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Pecoraro, 2005

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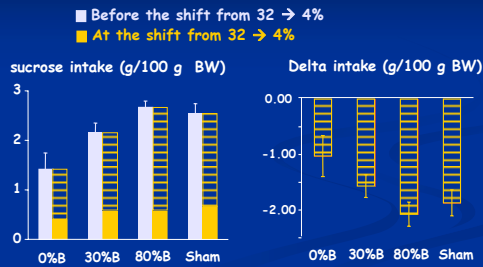
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## B dose-dependent sucrose intake & "contrast" (ADX & Sham rats)



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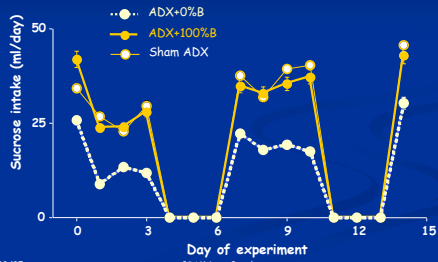
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## High B is required for normal levels of 30% sucrose ('comfort food') intake



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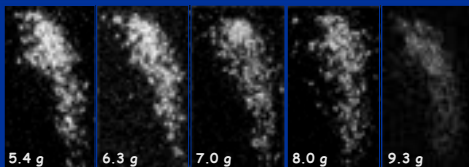
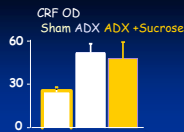
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## CRF mRNA in the PVN is Significantly and Inversely Related to Sucrose Intake in ADX Rats



Grams of Sucrose ingested during the previous 24 h period (All Rats ADX with no B)

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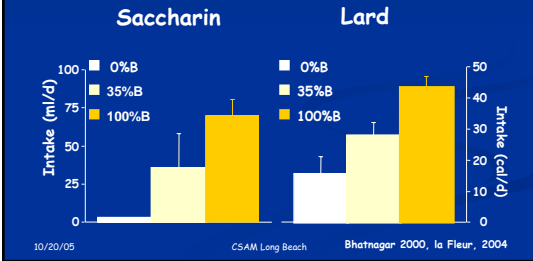
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Corticosterone (B) also stimulates intake of other "comfort foods" (ADX rats)




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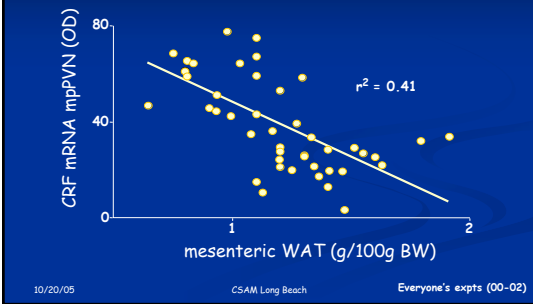
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Is Abdominal Fat Mass a Surrogate for the Metabolic Feedback Signal?




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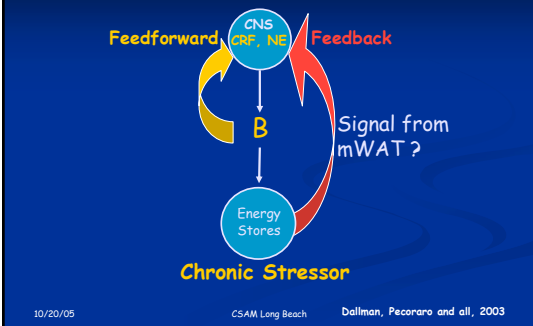
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Working Model:




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## Test of the working model:

Intact rats eat a greater proportion of  
"comfort foods"  
During repeated restraint

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Pecoraro, 2004

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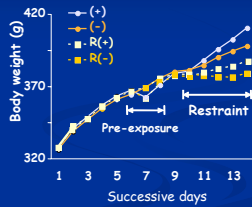
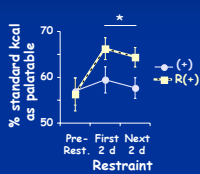
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Eating more "comfort foods" yields  
greater metabolic well-being in chronic stress



"comfort foods" (+)

Proportion ingested increases with stress & helps metabolism

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Pecoraro et al. 2004

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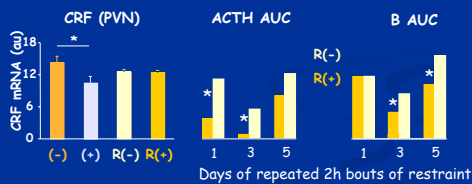
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"Comfort foods" also decrease CRF, and ACTH  
& B responses to Restraint  
(male SD rats From Harlan-Bantin & Kingman, Fremont, CA)



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Pecoraro et al. 2004

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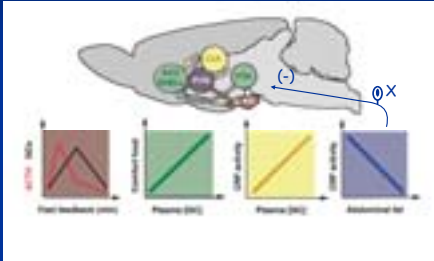
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## Model: Direct and Indirect effects of GCs



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## Development of stress-induced Metabolic Syndrome?

Stress & high glucocorticoids (GC) change behavior, autonomic outflow, neuroendocrine activity  
 High GC stimulate insulin and Comfort Food eating  
 In 'rich' societies Comfort Food is always accessible  
 There is a metabolic feedback signal that damps the Chronic Stress-Response Network in Brain  
 This probably makes stressed people "feel better"



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The Economist 12/5-12/03

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## Who Is Responsible for our Current Thinking?

### Current Lab Members

Norm Pecoraro  
 Susan Akana  
 James Warne  
 Abby Ginsberg

### Influential, not in Lab

K C Berridge (MI)  
 Christian J Cook (NZ)  
 J D Shepard (OK)

### Previous Lab Members

Susanne Ia Fleur  
 Hani Houshyar  
 Paqui Gomez  
 Beth Bell  
 Seema Bhatnagar  
 Kevin Laugero  
 Karen Scribner  
 Alison Strack

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