Relationship Between Stress and Substance Use Disorders: Neurobiologic Interface

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Traumatic Exposure Common in the Lives of Individuals with SUDs
Clinical Evidence for Stress-Relapse Connection

• Intuitive appeal, but methodologic issues
  – Definition of stressor
  – Causal relationship difficult to establish

• Childhood adverse events strongly associated with SUD’s

• PTSD, mood/anxiety disorders strongly associated with SUD’s
PTSD and Substance Use Disorders

- Treatment seeking individuals
  - PTSD - 30-40% have substance use disorders
    - maybe higher in combat-related PTSD
  - Substance use samples - 20-60% have PTSD - higher in women, cocaine/opiate users

- Epidemiologic data
  - Significantly increased odds ratios
Non-Random Association
Neurochemical Response to Stress

- Hypothalamic-Pituitary-Adrenal axis
- Extra-Hypothalamic CRH systems
- Locus Coeruleus-Norepinephrine
- Dopamine Systems
- Serotonin Systems
- GABA Systems
- Glutamate Systems
Adaptive Allostatic Response

McKewen, B. *NEJM* 1998; 338:171-79
Stress Response

Allostasis vs. Homeostasis

• Homeostasis - tightly controlled physiology parameters

• Allostasis - Adaptive response to stress
  – Recruitment of all available physiological, psychological and behavioral resources

McKewen, B. NEJM 1998;338:171-79
Homeostasis versus Allostasis

[Diagram showing a graph with axes labeled 'Approach' and 'Avoidance'. The graph includes a circle labeled 'Healthy Homeostatic Balance' and another labeled 'Trauma', connected by an arrow. There is a larger circle labeled 'PTSD' with a sub-circle labeled 'Altered Homeostatic Steady State'.]
Animal Models of Relapse: Reinstatement (Relapse)

- Resumption of previously drug-reinforced behavior by non-contingent exposure to drug or non-drug stimuli
  - Self-administration training
  - Extinction
  - Test for reinstatement under various conditions

» deWit and Stewart, 1981;
» Psychopharmacology (2003), Volume 168
Reinstatement Models

- Drug-primed reinstatement: low dose drug administration
- Cue-induced reinstatement: environmental cues associated with drug use
- Stress-induced reinstatement: foot shock, forced swim, isolation, immobilization, etc.
Stress-Induced Reinstatement: Pharmacologic and Surgical Manipulation

- Blocked by CRF antagonists
- Induced by CRF agonists
- Blockade of B-receptors in amygdala and BNST blocks stress-induced reinstatement
- Increased by amount of previous drug exposure
- Cue-induced reinstatement increased by stress
Stress Response in Drug Dependent Individuals

• Acute withdrawal from all drugs of abuse - activation of HPA axis
• Dysregulation of HPA axis/abnormal stress response persists for weeks to months
• ? Dysregulation associated with early life trauma
• ? Role of dysregulation in drug craving/relapse

» Kreek and Koob, 2006
Human Laboratory Studies

• Stress Exposure
  – Psychological - Trier
  – Physical – Cold Pressor
  – Pharmacologic – CRF, Yohimbine

• Drug-cue Exposure

• Measurement
  – Craving (proxy for use)
  – ACTH/cortisol
  – Physiologic parameters
Craving and Stress Increase in Response to CRF

![Graphs showing craving and stress increase over time for different groups: Cocaine Dependent Males, Cocaine Dependent Females, Control Males, and Control Females. The x-axis represents assessment time in minutes, ranging from -20 to 120. The y-axis represents the craving and stress levels, ranging from 0 to 4. Each group shows distinct patterns of increase and decrease over time.](image-url)
Heart Rate Responding to CRF

(Cocaine x Gender: $P = 0.05$)
Correlation Between ACTH and Cortisol in Cocaine Dependence

Control Males

Cocaine Dependent Males

Control Females

Cocaine Dependent Females
Relationship Between Stress Response and Relapse???
Relationship Between CRH-induced Craving/Stress and Relapse

Back et al., 2010
Probability of Relapse Based on % Cortisol Change from Baseline
CONCLUSIONS

• Elevated craving and stress to CRH and drug cues associated with relapse

• Attenuated ACTH/cortisol response to CRH associated with relapse
Impact of Early Trauma on Stress Reactivity/Addiction
Childhood Sexual Abuse and Psychiatric Disorders in Women

- Abuse positively associated with a number of disorders
- Strongest relationship with alcohol/drug use
- More severe abuse increases risk
- Not explained by background/familial factors

Kendler et al., 2000
Adverse Childhood Experiences (ACE) and Illicit Drug Use (n = 8603)

ACE account for one half to two third of serious problems with drug use.

PEDIATRICS 111: 564-572, 2003
Does Stress Alter Reward Sensitivity before Development of Addiction?
Effects of Childhood Trauma on Reward Sensitivity (Jia et al.)

- 36 light to moderate social drinkers.
- Two risk groups (HR vs LR) on the basis of high and low ratings on Childhood Trauma Questionnaire (CTQ, Bernstein et al., 1998).
- Exposed to 2 stress, 2 alcohol cue and 2 neutral relaxed trials presented during fMRI
Individuals with greater childhood trauma (HR) showed greater nucleus accumbens/striatum (reward) activity with stress and with neutral relaxing stimuli compared to LR group. CTQ scores correlated positively with this NAcc activity (p<.01).
Significant Correlation between NAcc Activity (right) during Stress with Age of First Substance Use

- Left NAcc Activity under Stress
  \[ R^2 = 0.21, \ R = -0.46, \ p < 0.01 \]

- Right NAcc Activity under Stress
  \[ R^2 = 0.28, \ R = -0.53, \ p < 0.01 \]
How do early experiences produce long-lasting changes in vulnerability to the development of addictions and other disorders?
Mean Stress-Induced Changes in Dopamine Signals in Core Region of Nucleus Accumbens of Maternally Separated & Handled Animals

Brake et al., 2004
Mean Changes in Locomotor Activity following Injection of Saline or Cocaine

Brake et al., 2004
Epigenetics

- Environmentally-induced changes in DNA expression
- Methylation, acetylation of histones impacts transcription
- Gene-by-environment interactions – CRF polymorphisms
Impact of Negative Life Experience on Alcohol Consumption Depends on CRF Polymorphism

Percentage of lifetime heavy drinking adjusted for sex in adolescents grouped by genotype and exposure to negative life events.

Blomeyer, et al., 2008
Biol Psychiatry
Mean Alcohol Consumption by H1/H2 haplotype and CSA status

Comparisons by CSA status
H2 carriers  p > 0.77
H1 homozygotes p < 0.0006

Nelson et al., 2010
Addict Biol
OXYTOCIN

- Regulates lactation
- Promotes affiliative behavior
- Anxiolytic, released in response to stress
- Decreases HPA and “fight or flight” response
OXYTOCIN AND MARIJUANA/COCAINE CRAVING

• Pilot human laboratory studies

• Intranasal administration of oxytocin versus placebo

• Trier Social Stress Task
  – Decreased stress response
  – Decreased craving
Marijuana: Craving

Administration of Oxytocin
TSST

Group x (TSST) P = 0.245
Post TSST Group Difference p=0.025

- Oxytocin
- Placebo
Marijuana: Cortisol

Administration of Oxytocin

TSST

Group x (TSST) P = 0.328
Post TSST Group Difference p= 0.066
PTSD and SUBSTANCE USE DISORDERS

Little empirical evidence to guide treatment:

• Traditional substance use programs defer treatment of trauma related issues

• PTSD programs don’t accept individuals with active substance use disorders
Psychotherapeutic Treatments

• Cognitive-behavioral therapies efficacious in both PTSD and substance use disorders

• Manualized integrated treatments promising
  – Relapse prevention + stress inoculation + exposure (Triffleman et al., 1999)
  – Imaginal exposure + relapse prevention (Brady et al., 2002)
Exposure Therapy for PTSD

• Strongest empirical evidence compared to other PTSD treatments
• “Contraindicated” in individuals with substance use disorders
• No empirical evidence to support this widely-held clinical belief
Concurrent Treatment with Prolonged Exposure (COPE)

- 12 sessions, manual guided, individual therapy
- First 4 sessions CBT for cocaine - education re: trauma response/ PTSD
- Sessions 5-12 exposure

Brady, Back, Foa, Carroll
Impact of Events Scale

Brady et al., 2001
COPE Clinical Trials

• University of New South Wales: 120 individuals with drug dependence/PTSD, compared to treatment as usual
• Columbia University: 120 individuals, compared with Relapse Prevention CBT
• MUSC: OEF/OIF Veterans
Severity of PTSD symptoms

A reduction of 15 points on the CAPS total score is considered clinically significant.
Severity of dependence

Mean

Baseline  6 wks  3mths  9 mths

Control  Treatment

5.6  5.3  2.1  1.6  1.0  1.8  1.5  2.9  1.8  2.4  1.5

Baseline 6 wks 3mths 9 mths
Effects of Stress/Trauma On Substance Use Disorders

1. Facilitate initiation
2. Increase risk of developing addiction after initiation
3. Trigger relapse
Stress and Substance Use Disorders: Clinical Considerations

- Careful assessment/aggressive treatment of co-occurring stress sensitive disorders
- Importance of social support in mediating effects of stress
- Careful attention to environmental factors – ongoing stress/abuse
- Coping Skills/Stress Management Techniques
CONCLUSIONS

• Relationship between stress and substance use/relapse, development of dependence
• Mechanistic studies important
• Identification of new avenues for treatment development