Alcohol, Stress and the Brain

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Koob GF, A Role for Brain Stress Systems in Addiction, Neuron 59 (2008) 11-34

Stress – definition

"Stress is the nonspecific (common) result of any demand upon the body"


"Stress is anything which causes an alteration of psychological homeostatic processes"

from: Burchfield SR, Psychosom Med, 1979, 41:661-672.
I saw Kazak out of the corner of my right eye. His eyes were pinwheels. His teeth were white daggers. His slobber was cyanide. His blood was nitroglycerine. He was floating toward me like a zeppelin, hanging lazily in the air. My eyes told my mind about him. My mind sent a message to my hypothalamus, told it to release the hormone CRF into the short vessels connecting my hypothalamus and my pituitary gland. The CRF inspired my pituitary gland to dump the hormone ACTH into my bloodstream. My pituitary had been making and storing ACTH for just such an occasion. And nearer and nearer the zeppelin came. And some of the ACTH in my bloodstream reached the outer shell of my adrenal gland, which had been making and storing glucocorticoids for emergencies. My adrenal gland added the glucocorticoids to my bloodstream. They went all over my body, changing glycogen into glucose. Glucose was muscle food. It would help me fight like a wildcat or run like a deer. And nearer and nearer the zeppelin came. My adrenal gland gave me a shot of adrenaline, too. I turned purple as my blood pressure skyrocketed. The adrenaline made my heart go like a burgler alarm. It also stood my hair on end. It also caused coagulants to pour into my bloodstream, so in case I was wounded, my vital juices wouldn’t drain away. Everything my body had done so far fell within normal operating procedures for a human machine. But my body took one defensive measure which I am told was without precedent in medical history. It may have happened because some wire shortcircuited or some gasket blew. At any rate, I also retracted my testicles into my abdominal cavity, pulled them into my fuselage like the landing gear of an airplane. And now they tell me that only surgery will bring them down again.

Breakfast of Champions by Kurt Vonnegut
Brain Actions of Corticotropin-Releasing Factor (CRF)

Corticosteroids → Pituitary Gland → CRF → Amygdala → Behavioral response to stressors → Behavioral activation

ACTH → β-Endorphin → Medulla Oblongata → Sympathetic Activation

Cardiac output ↑
Stroke volume ↑
Peripheral vascular resistance ↑
Blood glucose ↑
Heart rate ↑
Blood pressure ↑

Adrenal Medulla → Epinephrine → Gastric acid secretion

HCl → Gastric emptying
Major CRF-Immunoreactive Cell Groups and Fiber Systems in the Rat Brain

CRF Produces Arousal, Stress-like Responses, and a Dysphoric, Aversive State

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>CRF Agonist</th>
<th>CRF Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acoustic startle</td>
<td>Facilitates startle</td>
<td>Blocks fear-potentiated startle</td>
</tr>
<tr>
<td>Elevated plus maze</td>
<td>Suppresses exploration</td>
<td>Reverses suppression of exploration</td>
</tr>
<tr>
<td>Defensive burying</td>
<td>Enhances burying</td>
<td>Reduces burying</td>
</tr>
<tr>
<td>Fear conditioning</td>
<td>Induces conditioned fear</td>
<td>Blocks acquisition of conditioned fear</td>
</tr>
<tr>
<td>Cued electric shock</td>
<td>Enhances freezing</td>
<td>Attenuates freezing</td>
</tr>
<tr>
<td>Taste / Place Conditioning</td>
<td>Produces place aversion</td>
<td>Weakens drug-induced place aversion</td>
</tr>
</tbody>
</table>
Theoretical Framework Relating Addiction Cycle to Motivation for Drug Seeking

Positive and Negative Reinforcement—Definitions

**Positive Reinforcement** — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (non dependent drug taking paradigms).

**Negative Reinforcement** — defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking).
Stages of the Addiction Cycle

- Preoccupation Anticipation
  - Preoccupation with obtaining persistent physical or psychological problems
- Persistent desire
  - Larger amounts taken than expected
- ADDICTION
- Tolerance
- Negative Affect
- Withdrawal
- Compromised social, occupational or recreational activities
- Binge Intoxication
1. Addiction is a reward deficit disorder
2. Addiction is an S-R perseveration disorder
3. Addiction is a stress surfeit disorder
4. Addiction is a self-regulation disorder
Neurobiology of Addiction

- Prefrontal Cortex
- Dorsal Striatum
- Nucleus accumbens
- Orbitofrontal Cortex
- Thalamus
- Globus Pallidus
- Hippocampus
- Insula
- Amygdala
- Bed Nucleus of the Stria Terminalis

Binge/Intoxication
Withdrawal/Negative Affect
Preoccupation/Anticipation
Binge/Intoxication Stage

Preoccupation/Anticipation
"Craving"

Prefrontal Cortex: orbital, medial, and cingulate
Subjective effects – craving

Executive Control

Hippocampus
Contour

BLA
Conditioned Fear

Insula
Interosceptive Contour

Hypothalamus & brainstem
effectors (autonomic,
somatic, neuroendocrine)

Withdrawal/Negative
Affect

Binge/Intoxication

From: Koob, G. F. and Volkow, N. D. Neurocircuity of Addiction,
Neuropsychopharmacology reviews 35 (2010) 217-238
Converging Acute Actions of Drugs of Abuse on the Ventral Tegmental Area and Nucleus Accumbens

Withdrawal/Negative Affect Stage

Types of Withdrawal

- Somatic ("physical") withdrawal - bodily signs
- Motivational ("psychic") withdrawal - emotional signs
Somatic Withdrawal

Different Somatic Signs for Different Drugs of Abuse

- Flu-like state, pain - Opioids
- Tremor, hyperthermia, seizures - Alcohol
- Increased appetite, Sleep disturbances - Nicotine
Motivational Withdrawal

Common Elements Negative Emotional State Signs

- Anxiety
- Irritability
- Dysphoria
- Malaise
- Everything is gray
- Alexithymia- inability to express one’s feelings
- Hyperkatifiea- hyper-negative emotional state
Standard Pattern of Affective Dynamics Produced by Novel and Repeated Unconditioned Stimulus

Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

<table>
<thead>
<tr>
<th>Positive Hedonic Effects</th>
<th>Negative Hedonic Effects of Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Dopamine</td>
<td>↓ Dopamine ... “dysphoria”</td>
</tr>
<tr>
<td>↑ Opioid peptides</td>
<td>↓ Opioid peptides ... pain</td>
</tr>
<tr>
<td>↑ Serotonin</td>
<td>↓ Serotonin ... “dysphoria”</td>
</tr>
<tr>
<td>↑ GABA</td>
<td>↓ GABA ... anxiety, panic attacks</td>
</tr>
</tbody>
</table>
Anti-Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

↑ Dynorphin … “dysphoria”
↑ CRF … stress
↑ Norepinephrine … stress
Sampling of Interstitial Neurochemicals by *in vivo* Microdialysis

- Allows sampling of neurochemicals in conscious animals (correlate brain chemistry with behavior).
- Implanted so that semi-permeable probe tip is in specific brain region of interest.
- Substances below the membrane MW cutoff diffuse across membrane based on concentration gradient.
- Both neurochemical sampling and localized drug delivery are possible.

Collaborators: Dr. Friedbert Weiss, Dr. Larry Parsons, Dr. Emilio Merlo-Pich, Dr. Regina Richter
Withdrawal-induced Increases in Extracellular Levels of CRF

Ethanol Withdrawal
- Basal
- 2-4 h
- 6-8 h
- 10-12 h

Cocaine Withdrawal
- Basal
- 12 h
- Cocaine SA Session
- Cocaine Withdrawal Session

Cannabinoid Withdrawal
- HU-210
- HU-210 + SR 141716A
- Injection

Opiate Withdrawal
- Morphine
- Morphine + Naltrexone
- NTX

Nicotine Withdrawal
- Non-dependent
- Nicotine-dependent
- Vehicle
- Nicotine

References:
Rodent Model of Excessive Drinking During Withdrawal

**Self-administration training**

Sweetened solution fading used to train animals to lever press for:

10%w/v EtOH vs Water

**Dependence induction**

Chronic intermittent alcohol vapors (4+ wks)

Target blood alcohol levels (BALs): 0.125-0.250 g%

**Withdrawal from alcohol vapors**

Negative emotional state:
- Anxiety-like behavior
- Reward threshold deficits
- Increased CRF release in the extended amygdala

Excessive drinking:
- 2-3 fold higher alcohol intake
- Increased progressive ratio breakpoints
- Relapse following prolonged abstinence

Methods from:
CRF$_1$ Antagonist R121919 Decreases Excessive Ethanol Self-administration during Withdrawal

(30 min session 2 h into withdrawal)

CRF Antagonist D-Phe-CRF$_{12-41}$ in Central Nucleus of the Amygdala Decreases Ethanol Self-Administration During Withdrawal in Wistar Rats (30 min session 2 h into withdrawal)

CRF$_1$R Antagonist Blocks *Transition* to Dependence-induced Drinking

From: Roberto, Cruz, Gilpin, et al., Biological Psychiatry, 67 (2010) 831-839
Protracted Abstinence

- State of protracted abstinence in subjects with addiction or alcoholism weeks after acute withdrawal.

- Conceptualized as a state change characterized by anxiety and dysphoria or a residual negative emotional state that combines with drug or cue-exposure to produce relapse to excessive drug taking.

- Animal models of protracted abstinence include increased sensitivity to stressors and increased drug taking in animals during protracted abstinence.

- Neurobiological substrates include residual activation of brain stress systems including corticotropin releasing factor in the extended amygdala.
Effect of Mild Stress on Anxiogenic-Like Behavior in the Elevated Plus Maze In Animals with a History of Dependence

- EtOH No Restraint
- EtOH Restraint
- Control No Restraint
- Control Restraint

Percent Open Arm Time

Groups: 0.5x PBS, 10 μg D-Phe CRF

* Indicates statistical significance
CRF-1 antagonist selectively suppresses alcohol self-administration in post-dependent animals

(Hansson et al, PNAS 2006; Gehlert et al, J Neurosci 2007)
## Role of Corticotropin-releasing Factor in Dependence

<table>
<thead>
<tr>
<th>Drug</th>
<th>CRF antagonist effects on withdrawal-induced anxiety-like responses</th>
<th>Withdrawal-induced changes in extracellular CRF in CeA</th>
<th>CRF antagonist effects on dependence-induced increases in self-administration</th>
<th>CRF antagonist reversal of stress-induced reinstatement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Opioids</td>
<td>↓*</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ethanol</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Nicotine</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Δ⁹-tetrahydrocannabinol</td>
<td>↓</td>
<td>↑</td>
<td>nt</td>
<td>nt</td>
</tr>
</tbody>
</table>

* = aversive effects with place conditioning. nt = not tested. CeA = central nucleus of the amygdala.

From: Koob, G.F. 2008 Neuron 59:11-34
Chronic Glucocorticoid Receptor Blockade by Mifepristone Prevented Escalated Alcohol Intake and Motivation for Alcohol in Vapor-exposed Rats

Chronic Glucocorticoid Receptor Blockade by Mifepristone Decreased Escalated Alcohol Intake in Vapor-exposed Rats During Protracted Abstinence

Brain Arousal-Stress System Modulation in the Extended Amygdala

From: Koob, G.F. 2008 Neuron 59:11-34
Stress and Anti-stress Neurotransmitters Implicated in the Motivational Effects of Drugs of Abuse

- Corticotropin-releasing factor (↑)
- Norepinephrine (↑)
- Vasopressin (↑)
- Orexin (hypocretin) (↑)
- Dynorphin (↑)
- Substance P (↑)

- Neuropeptide Y (↓)
- Nociceptin (orphanin FQ) (↓)
Neurobiology of Addiction: Preoccupation-Anticipation ("Craving") Stage

Loss of Control Over Intake — Self-medication

Escalation of drug intake

Neuron/oligodendrocyte death

Prefrontal Cortex Abnormalities/ Hypofunction

PFC CRF/GABA interneurons Withdrawal

PFC DA/NE? Initial intake

Impairment of Executive Control

Cause

VTA CRF Neurons?
Neuroplasticity in Brain Circuits associated with the Development of Addiction - Revised
Acute reinforcing effects of drugs of abuse—depend on neurochemical substrates such as GABA, opioid peptides, serotonin, glutamate and dopamine in the ventral striatum of the basal forebrain.

Acute withdrawal from all major drugs of abuse—produces decreases in reward function, increases in stress-like responses and increases in CRF in the amygdala that are of motivational significance.

“Craving” (Preoccupation/anticipation stage of addiction cycle)—involves a significant cortical glutamate system dysregulation and a brain stress component also mediated by CRF systems in the extended amygdala.

Compulsive drug use associated with dependence—is mediated by not only loss of function of reward systems but recruitment of brain stress systems such as corticotropin releasing factor, norepinephrine and dynorphin in the extended amygdala.

Brain-arousal stress systems in the extended amygdala—may be key components of not only for the negative emotional states that drive dependence on drugs of abuse but also may overlap with the negative emotional components of other psychopathologies.