Epigenetics and Drug Addiction

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• In the beginning was the....
• Sperm and ova
• 25,000 genes with 4% expression in the different cells – 1,000 genes.
• Very rigid life time shutdown of 96% genes.
• Of the remaining 4%
  – General requirements of a cell to be alive.
  – Remaining to express its unique properties and function.
• Seems that there are 3 aspects:
1) Lifetime lockdown of 24,000 or so genes.
2) Of the 1,000 genes majority are active in various housekeeping function, etc.
3) Minority genes expression can be altered and this cell specific.
Epigenetic Landscape

• 1957 Conrad Waddington
• How do the same genotypes produce different phenotypes?
• Environmental signals can cause stable alterations in chromatin structure.
Addiction

• Addiction
• Brain Reward circuit
• Dopamine
• Structural and functional changes
  – Dendritic changes
  – Synaptic function
• Epigenetic changes
  – Transcription factors
  – Transcription mechanism
Introduction

• Drug and alcohol dependence are debilitating psychiatric disorders.
• Addiction follows repeated exposure to an addictive substance
• Predisposing factors involve inherited (0.3-0.7) and environment
• The dynamic neurobiological changes that take place in response to chronic drug exposure is key to elucidating the aetiology of addiction.
The Central Problem

- Why do people become addicted to certain drugs and activities?
- There is nothing wrong with taking drugs or engaging in activities that make you feel good.
- We enjoy good food, activities like sports, gambling and sex that make us feel good.
- The problem is not that we enjoy them; the problem is we lose control of use.
What is addiction?

• Behavior that we engage in knowing that it is not good for our health (physical or mental), affects our job performance, and family and society.
• And even when we stop for sometime, many of us will revert to it
• Internet.
• What enduring changes in brain function has taken place that sustains this behavior?
The Brain Reward Circuit
Physical substrate for feeling good
Electrodes into rats' brains

The rats could press a lever themselves that would deliver a small current deep into its brain.

Electrical brain stimulation seemed to give the rats experience of pleasure and almost ecstasy at times.

They would perform complex and difficult tasks for another dose of stimulation, and would even press the lever up to 2,000 times an hour to the exclusion of eating or drinking.

Olds and Milner concluded that they had discovered the area of the brain responsible for reward – the happiness center.
Rats prefer auto-administration of electrical stimuli, which affect the dopamine reward circuit, over eating of a (normally) appetizing piece of cheese (drawing by Romain Giraud, student of SVI632 in 2010, University of Bordeaux).

http://www.cellbiol.net/layout image3/03%20figure1%20brain-reward%20stimulation%20Giraud.jpg
Brain Reward Circuits
Limbic Systems
Brain Reward Circuitry
Figure 2 | The neurocircuitry controlling palatable food and drug consumption.

Nucleus Accumbens
Dorsal Striatum
Nucleus Accumbens
• Each cell type exhibits different transcriptional responses and mediates distinct aspects of drug reward and addiction.

• Drug induction of ΔFOSB and the effects of ΔFOSB and G9a on cell morphology and behaviour, differ between D1-type and D2-type MSNs, and neuronal activity of these two cell types causes opposing effects on the rewarding properties of cocaine.
The Dopamine Hypothesis

Promotes reward-related activities.
Promotes “wanting” rewards; hence animals will work harder to obtain food rewards when dopamine signaling increases (bursts of release of the neurotransmitter).

Also postulated to promote learning associations between food rewards and the environments where they are found.

Berridge KC. The debate over dopamine’s role in reward: the case for incentive salience. Psychopharmacology (Berl.) 2006;191:391-431
Cocaine
Amphetamine
Cathinone

vesicles
Dopamine transporter

Dopamine receptor

Up and down regulation
Is dopamine required for natural reward?

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Abstract

Reward is fundamental to the organization of behavior, and the neurotransmitter dopamine (DA) is widely recognized to be critical to the neurobiology of reward, learning and addiction. Virtually all drugs of abuse, including heroin and other opiates, alcohol, cocaine, amphetamine and nicotine activate dopaminergic systems. So called “natural” rewards such as food, positive social interactions and even humor, likewise activate DA neurons and are powerful aids to attention and learning. Sweet solutions are a well-characterized natural reward. When a source of sugar is encountered, animals will consume substantial amounts, return to it preferentially, and will work to obtain access. Dopamine systems are activated in animals drinking sugar solutions, and lesions of dopaminergic neurons or pharmacological blockade of DA receptors seem to reduce the reward value of both sweet tastes and drugs of abuse. However, we have recently demonstrated that genetically modified mice that cannot make DA (DD mice) manifest normal sucrose preference. During preference tests, mutant mice initiated licking less frequently than did normal mice, but the rate of licking by DD mice for sweets was actually higher than that of normal mice, indicating that their motor ability to lick is intact. We conclude that DA is not required for the hedonic response to sweets nor for their discrimination. This brief and slightly humorous review discusses these findings in the context of current and historical answers to the question, ”What is the role of DA in reward?”

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Structural Changes
Functional Changes

Synaptic changes: Long term potentiation (LTP), long term depression (LTD)
Intrinsic membrane excitability – ion channel function

How long time do these changes last – days, weeks, months, year?

Sensitizing regimens of (+/-)3, 4-methylenedioxymethamphetamine (ecstasy) elicit enduring and differential structural alterations in the brain motive circuit of the rat.
Transcriptional and Epigenetic Regulation
For all living cells, regulation of gene expression by extracellular signals is a fundamental mechanism of development, homeostasis, and adaptation to the environment. Indeed, the ultimate step in many signal transduction pathways is the modification of transcription factors that can alter the expression of specific genes.

Transcription initiation is the step in gene expression that is most highly regulated by extracellular signals.
• Transcription initiation involves two critical processes:
  1) Positioning of the appropriate RNA polymerase at the correct start sites of transcription
  2) Controlling the efficiency of initiations to produce the appropriate transcriptional rate for the circumstances of the cell.

• These control functions depend on regulatory elements that recruit appropriate transcription factors to the DNA
Main Transcription Factors

• ΔFosB
• CREB (Cyclic-AMP response element binding protein)
• NF-κB (nuclear factor)
ΔFosB

• Fos family proteins are induced transiently by acute drug exposure, chronic administration of virtually any drug of abuse induces the long-lasting expression specifically of Δ FosB.

• **Occurs only in the subtype of medium spiny neuron (MSN) that expresses D1 dopamine receptors (D1-type MSNs).**
  • Degron are spliced out and phosphorylation occurs.
  • Stabilizes the molecule for weeks.
Evidence

• Overexpression
  • Increased locomotor sensitivity to cocaine
  • Increased conditioned place-preference to cocaine and morphine
  • Increased cocaine self-administration

• Genetic or viral overexpression of Δ JunD

• Regulation of numerous genes related to dendritic spine architecture
  – (synaptotagmin, microtubule associated proteins, activity-regulated cytoskeleton-associated protein (ARC), actin-related proteins, cyclin dependent kinase-5 (CDK5), and kinesin)

• Activity of several other transcriptional and epigenetic regulatory proteins

• Master control molecule
CREB

- CREs were the first second messenger response element to be well characterized.
- Activation by cAMP on genes to which it is linked.
- Increased expression with cocaine, amphetamine, and morphine.
- Chronic nicotine and ethanol decrease pCREB
NF-κB

- Inflammation and immune responses
- Synaptic plasticity and memory
- Increased by cocaine and involved in increase in dendritic spines
- Nicotine dependence
- Induced through delta FOSB
Other transcription factors

- Myocyte enhancing factor 2 (MEF2)
- Glucocorticoid receptor
- Nucleus accumbens 1 transcription factor (NAC1)
- Early growth response factors (EGRs)
- Signal transducers and activators of transcription (STATs)
- And there will be many more!
Epigenetic and Structural Changes
Epigenetic Mechanisms

• Histone methylation, acetylation, and phosphorylation
• DNA methylation
• MicroRNAs
• Allow or prevent the interaction between the DNA strand and transcription machinery and get RNA polymerase II to start transcription
• The combinations provide wide range of epigenetic changes.
Cascades and Branches
Morphine Action.

Synaptic activity changes at locus coeruleus

- Acute decrease
- Chronic returns to baseline (tolerance)
- Withdrawal increases

Diagram showing the effects of morphine on synaptic activity and the activation of various signaling pathways.
Gene Priming and Desensitization

**Significantly upregulated genes**

- **Acute**: *Acute*  
  - Repeat + acute  
  - Repeat wd + acute

- **Repeated + acute**  
  - Repeat wd + acute

- **Repeated wd + acute**  
  - Acute  
  - Repeat + acute*  
  - Repeat wd + acute*

**Fold expression**

- $-2X$  
- $1X$  
- $+2X$
Inducibility – Molecular Scars

Chronic drug exposure

Primed gene

Desensitized gene

Drug challenge

Activated gene

Repressed gene

Nature Reviews | Neuroscience
Example of gene activation and repression

**a** Drug-activated gene

**b** Drug-repressed gene

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Summary

• Epigenetics has made inroads in the central question of the mechanism of addiction.
• As yet, does not provide the complete mechanistic answer.
• Facts are being gathered but the grand unifying theory is missing.
Reference
