Dopamine Neurotransmission

- Frontal cortex
- Nucleus accumbens
- VTA/SN

**AMPHETAMINE**

% of Basal Release vs. Time After Amphetamine

**FOOD**

% of Basal Release vs. Time (min)

Di Chiara et al.
DA and Drug Reinforcement

1. **Reward Circuit**

- In laboratory animals repeated exposure to the drug results in enhanced responses to it (sensitization) that have been hypothesized to underlie addiction.

- Here we tested if, in humans addicted to cocaine, there is an enhancement of DA release and of the reinforcing effects of the drug.

*For this purpose we compared the changes in DA and the behavioral effects of intravenous MP between cocaine abusers (n=20) and controls (n=20)*
Self Reports of Drug Effects After iv MP in Controls and in Cocaine Abusers

Cocaine abusers showed decreased drug induced increases in rewarding responses and enhanced drug craving

Methylphenidate-induced Increases in Striatal DA in Controls and in Cocaine Abusers

Cocaine abusers showed decreased DA increases and reduced reinforcing responses to MP.

2. Memory circuit

- In rats when a neutral stimulus is repeatedly paired with the drug (conditioned), it elicits DA increases and reinstates drug self-administration.

Here we tested if conditioned stimuli increase DA in addicted subjects and its relationship to drug craving.

Philipps et al. Nature 422, 614-618

In training the cue was paired with cocaine

In training the cue was not paired with cocaine
Viewing a video of cocaine scenes decreased specific binding of $[^{11}\text{C}]$raclopride presumably from DA increases

Cue-induced increases in DA were associated with craving.

Relationship between Cue-Induced Decreases in [11C]raclopride Binding and Cocaine Craving


Cue-induced increases in DA were associated with craving.
We assessed the relationship between DA markers and frontal activity in cocaine (n = 20) and in methamphetamine abusers (n = 20) and controls.

3. Motivation & Executive Control Circuits

DA is involved not only with reward and prediction of reward but also with motivation and executive function via its regulation of frontal activity.

Here we tested if, in addicted subjects, changes in DA function were linked with disruption of frontal activity as assessed by brain glucose metabolism.
Anatomy

Dopamine Synapse

Dopamine Measures Obtained

Effect of Cocaine Abuse on Dopamine D2 Receptors


normal subject

cocaine abuser (1 month post)

cocaine abuser (4 months post)

DA D2 Receptors in Controls and in Cocaine Abusers (NMS)

Volkow et al., Neuropsychopharmacology 14(3):159-168, 1996.
Dopamine D2 Receptors are Lower in Addiction

Reward Circuits

Non-Drug Abuser

Drug Abuser

Adapted from Volkow et al., Neurobiology of Learning and Memory 78:610-624, 2002.
Effects of Tx with an Adenovirus Carrying a DA D2 Receptor Gene into NAc in DA D2 Receptors

Overexpression of DA D2 receptors reduces alcohol self-administration

Brain Glucose Metabolism in Cocaine Abusers (n=20) and Controls (n=23)

Volkow et al., AJP 156:19-26, 1999.
Correlations Between D2 Receptors in Striatum and Brain Glucose Metabolism

DA D2 Receptors and Relationship to Brain Metabolism in Subjects with Family History for Alcoholism

DA D2R were associated with metabolic activity in OFC, CG and dorsolateral prefrontal cortex

Correlations between Metabolism and D2R

P <0.005

DA D2R were associated with metabolic activity in OFC, CG and dorsolateral prefrontal cortex

Volkow et al. Arch Gen Psychiatry 2006.
Medications for Relapse Prevention

Non-Addicted Brain

- Control
- Drive
- Memory

STOP

- Strengthen reinforcing effects of non-drug reinforcers
- Strengthen inhibitory control
- Strengthen prefrontal-striatal communication
- Interfere with conditioned memories (craving)
- Counteract stress responses that lead to relapse

Brookhaven PET Group

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