

## Sensitization to Cocaine's Toxic Effects

- Cardiovascular effects
  - coronary vasoconstriction and myocardial sensitization (Jaffe, 1990)
- Convulsive effects
  - a sub-lethal dose of cocaine produced seizures that showed an increased frequency and severity (Post & Kopanda, 1975)
  - restraint stress can augment the toxic effect of cocaine (Pudlak & Bozarth, 1994)

## Sensitization to Cocaine's Behavioral-Activating Effects

- Behavioral sensitization
  - low-dose stimulants produce a progressive enhancement in stimulated LMA across successive days of testing
  - moderate to high doses produce an intense focusing of behavior called stereotypy
    - characterized by excessive rearing, grooming, sniffing, and gnawing
  - robust & enduring phenomenon

## Factors that Influence the Development Sensitization

- Strain differences (Glick et al., 1986)
- Age (Fujiwara et al., 1987)
  - all ages show enhanced LMA to methamphetamine
  - after 22 days of age show sensitization
- Gender differences
  - more robust sensitization in intact & ovariectomized females, and castrated males rats (Robinson, 1984)
- Conditioning of environmental stimuli

## Environmental Stimuli and Conditioned Drug Effects

- Context-dependent sensitization
  - animals injected with stimulants display enhanced LMA in the environment (i.e., test environment) paired with the drug
  - behavioral sensitization does not develop when cocaine is administered in an environment other than the test environment
- Conditioned activation: Enhanced LMA to a SALINE injection in the test environment

## Conditioned Euphoria

- Environmental stimuli repeatedly paired with a drug elicit CR's that are drug-like
  - report intense urges to resume cocaine use, feelings of arousal, and experience palpitations
  - report feelings of a cocaine high prior to drug administration or when in close proximity of the drug
  - innocuous stimuli become triggers of arousal
- Conditioned responses show specificity

## Conditioned Changes in Neural Activity & SPECT Imaging

- Description
  - inject radioactive tracer and SPECT scanner images the brain
  - brightly lit colors on a photo image correspond to brain areas containing high concentrations of the radioactive tracer
- Hypothesis of drug craving
  - drug-related stimuli increase brain DA concentrations
  - DA pushes the tracer off the receptor causing the photo image to fade in that area of the brain

## Conditioned Changes in Neural Activity & PET Imaging

### ■ Description

- radioactive tracer (e.g., 2-deoxy-glucose) is taken up and accumulates in metabolically active cells
- activated brain regions show increased metabolic activity that is displayed by brightly lit colors on a photo image

### ■ PET image of a normal and cocaine brain

- darkened areas represent decreased activity
- cocaine reduces brain activity

## Dopamine Involvement in Stimulant-Induced Sensitization

### ■ In vivo microdialysis studies

- description
  - implant animals with a dialysis probe
  - measures NT activity in an intact & behaving animal
- Kalivas and Duffy (1993)
  - DA enhancement in the VTA 24 hrs after cocaine ceased
  - DA enhancement in NAS 14 days after cocaine ceased
- Post et al. (1992)
  - cocaine environment produced increased DA in NAS compared to saline or cocaine in a different environment

## Brain Regions Critically Involved in Stimulant-Induced Sensitization

### ■ I. VTA is critically involved in the development of sensitization

- microinjections of amphetamine into the VTA
  - do not elicit behavioral activation
  - are sufficient to sensitize an animal's Locomotor response to a systemic or intra-accumbens injection of amphetamine
- sensitized response shows cross sensitization with other stimulant drugs

## Brain Regions Critically Involved in Stimulant-Induced Sensitization

### ■ II. NAS is critically involved in the expression of sensitization

- intra-accumbens injections of DA and DA agonists elicit LMA
- repeated microinjections fails to produce further increases in LMA
- repeated microinjections do not sensitize an animal's locomotor response to a systemically administered stimulant challenge injection

## Molecular Mechanisms Mediating Stimulant-Induced Sensitization

### ■ Proposed hypotheses

- development of sensitization
  - subsensitivity of DA autoreceptors allows extracellular DA to effectively stimulate D1 receptors in VTA (Kalivas, 1995)
- expression of sensitization
  - increased DA release in the NAS (Kalivas, 1995)
  - D1 receptor supersensitivity in NAS (White et al., 1995)

## Summary: The Neural Mechanisms of Stimulant-Induced Sensitization

- DA activation is essential for the development and expression of sensitization
- The development of sensitization has been localized to the VTA
- The expression of sensitization has been localized to the NAS

## Theoretical Models of Drug Craving

- Dopamine-Depletion Model (Dackis & Gold, 1985)
- Incentive-Sensitization Model (Robinson & Berridge, 1993)

## The Dopamine-Depletion Model

- Proposed by Dackis & Gold (1985)
  - euphoric effects result from blockade of DA re-uptake
  - chronic cocaine use produces prolonged blockade of DA re-uptake & this may subsequently result in DA depletions
    - may be the physiological trigger of drug craving
    - may produce the dysphoric state commonly associated with cocaine abstinence

## Data Supporting the Dopamine-Depletion Model

- Following IV cocaine SA animals displayed elevated BSR thresholds (Markou & Koob, 1991)
- Following unlimited access to cocaine basal DA levels in the NAS were reduced (Weiss et al., 1992)
- Continuous cocaine via osmotic minipump markedly reduced brain DA concentrations (King et al., 1993)

## The Incentive-Sensitization Model

- Proposed by Robinson and Berridge (1993)
  - drug craving is due to drug-induced sensitization that results when the neural system is repeatedly activated by stimulant drugs
  - repeated activation renders the neural system hypersensitive to the drug and to the stimuli associated with its activation
  - conditioned activation of the DA system underlies drug craving

## Data Supporting the Incentive-Sensitization Model

- Pre-clinical studies showing psychomotor stimulants produce context-dependent sensitization
- Addicts showing conditioned euphoria to drug-related stimuli and generalizing the CR's to innocuous stimuli
- Conditioned changes in DA activity following exposure to drug-related stimuli

## Potential Medications and Treatments for Cocaine Addiction

- Pharmacological agonists
- Pharmacological antagonists
- Antidepressants
- Neuroadaptive blocking or reversing agents
- Cue-extinction procedure
- Cocaine vaccine
- Catalytic antibodies

## Pharmacological Agonists

- Dopamine agonists functionally reverse potential DA depletions
- Enhanced DA activity may abate or alleviate drug craving induced by severe depletions
- Based on the Dackis & Gold Model (1985)
- Depletions may be more prevalent during a binge (i.e., continuous drug administration)

## Dopamine Agonists

- Bromocriptine
  - effectively suppresses cocaine withdrawal in humans (Dackis et al., 1987; Kumor et al., 1989)
- Amantadine
  - attenuates cocaine self-administration (Sannerud & Griffiths, 1988)
  - fails to maintain self-administration (Sannerud & Griffiths, 1988)

## Limitations of Dopamine Agonists

- Bromocriptine
  - unsuccessful in alleviating or reducing the “rush” produced by cocaine
  - self-administered by laboratory animals
- Amantadine
  - conflicting results of the effectiveness on suppressing cocaine withdrawal
  - addicts displayed enhanced physiological reactivity to cocaine-related stimuli

## Pharmacological Antagonists

- Dopamine antagonists prevent dopamine from binding to and subsequently activating dopamine receptors
- Pharmacological agents that block dopamine receptors offer two advantages:
  - may block cocaine’s reinforcing effects
  - may block the effects of conditioned dopamine release elicited by drug-associated stimuli

## Limitations of Dopamine Antagonists

- Pre-clinical data: Dopamine antagonists may enhance responsiveness to stimulants
  - low to moderate doses of DA antagonists increase rates of cocaine self-administration
  - block the development but not the expression of cocaine sensitization
  - chronic neuroleptic administration produces supersensitivity to a cocaine challenge injection
    - enhances cocaine’s locomotor-stimulating effect
    - following neuroleptic treatment animals show an increased number of DA receptors

## Limitations of Dopamine Antagonists, cont.

- Clinical data: Dopamine antagonists may enhance responsiveness to stimulants
  - addicts complain of increased urges for cocaine following neuroleptic administration
  - increased incidence of stimulant abuse in schizophrenics
- Other potential limitations
  - development of extrapyramidal side-effects
  - may exacerbate already existing DA depletions and enhance dysphoria effects during abstinence

## Antidepressants

- Following the termination of a cocaine binge users display a syndrome that resembles a depressive disorder
  - anhedonia
  - anergia
  - dysphoria
- Relieving the dysphoric effects might abate drug craving and decrease relapse rates

## Antidepressants and Neuroadaptive Effects

- Cocaine up-regulates  $\beta$ -adrenergic and dopaminergic receptor sensitivity
- Neuroadaptations within the DA system may underlie the dysphoria or drug craving experienced by addicts during drug abstinence (Proposed by Kleber & Gawin, 1984)
- Desipramine or imipramine given chronically down-regulate  $\beta$ -adrenergic and dopaminergic receptor sensitivity

## Therapeutic Effectiveness of Desipramine

- Conflicting studies
  - desipramine decreased cocaine craving in addicts who were unresponsive to psychotherapy (Gawin & Kleber, 1984)
    - attenuation of craving paralleled the time course for desipramine-induced neuroreceptor changes
  - Tennant & Tarver (1984) reported no differences between the desipramine and placebo group
    - shorter treatment trial
    - lower dose of desipramine

## Therapeutic Effectiveness of Imipramine

- Reported to be successful in facilitating cocaine abstinence in cocaine abusers
- Few studies have evaluated the therapeutic effectiveness of Imipramine
- A higher incidence of undesirable side-effects (e.g., dry mouth, blurred vision)

## Summary: The Therapeutic Effectiveness of Antidepressants

- Chronic administration of tricyclic antidepressants may reverse the withdrawal effects associated with cocaine abstinence
- More work needs to be done before an accurate assessment can be made

## Neuroadaptive Blocking or Reversing Agents

- Pharmacological agents that block or reverse the neuroadaptive changes induced by chronic stimulant administration
- Based on the premise that chronic stimulant use produces neuroadaptive changes in the brain mechanisms that mediate drug reward
- Consistent with the Incentive-Sensitization Model proposed by Robinson & Berridge (1993)

## Therapeutic Effectiveness of Neuroadaptive Agents

- A pharmacological agent that can reverse neuroadaptations has not yet been identified
- Compounds that block the development of stimulant-induced sensitization
  - NMDA antagonists (e.g., MK-801)
  - dopamine antagonists
  - NO synthase inhibitors (e.g., L-NAME)
- Not a viable treatment because compounds must be co-administered with the drug

## Cue-Extinction Procedure

- Focuses on extinguishing CR's to stimuli previously paired with drug-taking behavior
- Attempts to alleviate drug craving by repeatedly exposing an addict to drug-related stimuli in the absence of the drug
  - done in a safe laboratory setting
  - CR's to drug-associated stimuli gradually fade and show extinction
  - should diminish the likelihood of drug relapse

## Therapeutic Effectiveness of the Cue-Extinction Procedure

- Full-extinction of cue-elicited responsiveness was not accomplished in cocaine addicts
  - improved retention in out patient therapy
  - higher proportion of drug-free urines
  - relapses of drug use continued to occur but with a lesser frequency
- Clinical treatments that supplement the cue-extinction procedure may increase the likelihood of drug abstinence

## Cocaine Vaccine

- Uses the body's immune system to treat drug addiction
- Active immunotherapy
  - cocaine is metabolized so rapidly that it's not capable of generating cocaine-specific antibodies
  - altered cocaine molecule to create an analog that stimulates antibody production
    - change cocaine into a stable molecule
    - coupled to a carrier protein
    - stimulates production of cocaine-binding antibodies

## Initial Studies Using Active Immunotherapy

- Studies have shown that inoculated rats display:
  - significantly less drug-induced behavior (e.g., increased LMA) than control animals
  - brain cocaine concentrations were up to 77% lower than those measured in control animals

## Potential Limitations of Immunotherapy

- Addicts may compensate for counteractive effects of the antibody
- Repeated cocaine use may deplete the levels of circulating antibodies through degradation of antibody-cocaine complex
- Fails to target the core motivational and neurobiological features of drug addiction
- Specific to one drug
- "Booster" immunization is required

## Catalytic Antibodies

- Synthetic molecules that will target and break down cocaine into its by-products faster than the body's natural metabolizing enzymes
- Operational process
  - recognizes and binds the cocaine molecule
  - breaks down cocaine molecule into by-products
  - releases the by-products
  - free to bind another cocaine molecule

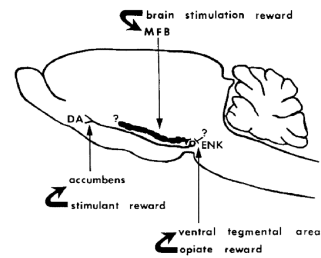
## Advantages Over Immunotherapy

- Catalytic enzymes bind cocaine, release its by-products and are free to bind another cocaine molecule
  - rapid turnover prevents the rapid depletion of the antibody that may occur in immunotherapy
  - should be more effective if attempts are made to compensate for the reduced subjective effects
    - free to bind more cocaine molecules
    - reduce toxic side-effects associated with increased doses of cocaine (e.g., seizures, cardiovascular problems)

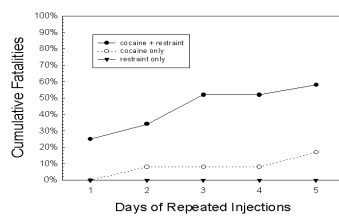
## Therapeutic Effectiveness of Catalytic Antibodies

- Still in the early stages of development
  - catalytic enzyme breaks down cocaine in a test tube (1993)
- Same limitations as immunotherapy
  - no effect on the motivational or neurobiological components of addiction
  - specific to one drug
- Could be used to treat cocaine overdose

## Brain Reward Circuitry



## Restraint Stress Enhances Cocaine's Toxic Effect



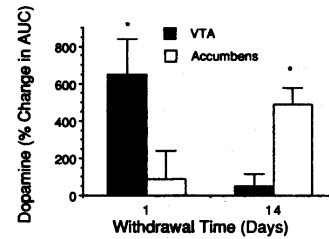
## Positron Emission Tomography (PET) Imaging



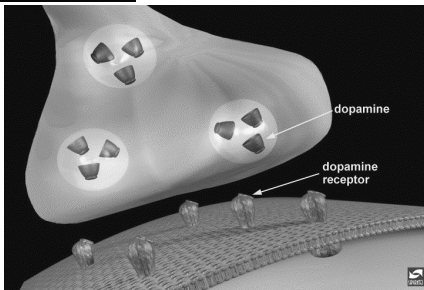
## PET Images of a Normal and Cocaine Brain



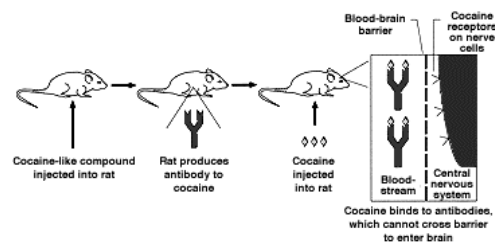
## Mesolimbic Dopamine and Behavioral Sensitization



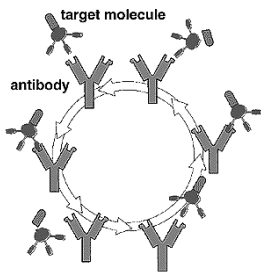
## Dopamine Neuron



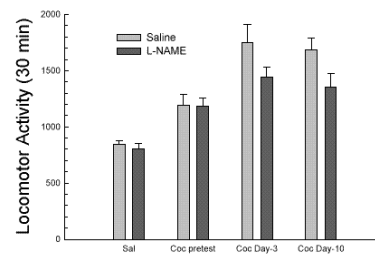
## Cocaine Vaccine



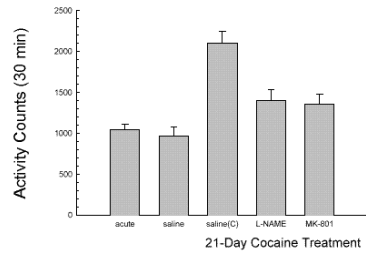
## Catalytic Antibodies



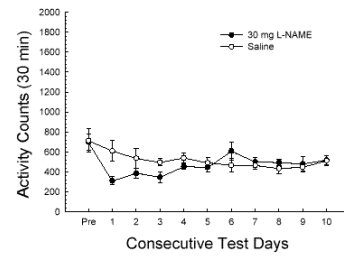
## Haloperidol-Induced Supersensitivity to Cocaine



## Pharmacological Agents that Attenuate Cocaine Sensitization



## The Effect of Repeated L-NAME on Spontaneous LMA



## Responsiveness to Cocaine Following Repeated L-NAME

