

Brain Reward Circuitry

- Directs and motivates behavior
- Consists of two fiber pathways
 - descending fiber pathway
 - ascending fiber pathway
 - mesolimbic DA is a critical component
 - increases the incentive value of appetitive stimuli (e.g., sexual, maternal, and feeding behavior)
 - can be either electrically or chemically activated

Mesolimbic Reward System

- Electrical activation
 - surgically implant animals with electrodes
 - stimulates the descending fiber system and transsynaptically activate A10 cell bodies in VTA
 - DA mediates the rewarding effects of BSR
 - first stage neurons are not DA neurons
 - conduction velocity estimates: 1-8 meters/sec
 - suggesting that myelinated fibers are being activated

Mesolimbic Reward System

- Pharmacological activation
 - cocaine
 - binds to the DA transporter
 - blocks DA reuptake at the NAS terminal fields
 - amphetamine
 - stimulates DA release in the NAS
 - blocks DA reuptake in the NAS terminal region
 - inhibits the degrading enzyme monoamine oxidase (MAO)

Dopamine Mediation of Psychomotor Stimulant Reward

- I. Response-pattern analysis from IVSA
 - regulated drug-intake (Yokel & Pickens, 1973)
 - dopamine antagonists (Yokel & Wise, 1975)
 - low dose: overcome pharmacological blockade
 - high dose: produce an extinction-like pattern
 - noradrenergic blockers: motor-impairing effects

Dopamine Mediation of Psychomotor Stimulant Reward

- II. Psychomotor stimulants enhance the rewarding effectiveness of BSR
 - increased lever-press rates for fixed parameter stimulation
 - lowering of current intensity or frequency thresholds
- III. DA blockers attenuate the rewarding effectiveness of BSR
 - elevated current and frequency thresholds

The Brain Region Critical for Psychomotor Stimulant Reward

- I. DA-depleting lesions & IVSA studies
 - NAS: disrupt stimulant self-administration (Roberts et al., 1977; Roberts et al., 1980; Lyness et al., 1979)
 - VTA: disrupt cocaine self-administration (Roberts & Koob, 1982)
 - lesions in other DA-containing areas or in noradrenergic areas do not disrupt stimulant self-administration (Roberts et al., 1977)

The Brain Region Critical for Psychomotor Stimulant Reward

- II. ICSA studies
 - rats will self-administer amphetamine into the NAS terminal fields (Hoebel et al., 1983; Philips et al., 1981)
 - animals will self-administer DA into the NAS
 - cf. rats will not self-administer cocaine into the NAS region (Goeders & Smith, 1983)

Neuroadaptive Effects Produced by Psychomotor Stimulants

- Tolerance
 - a diminished responsiveness to the drug
 - is not well documented with the stimulants
 - produced by continuous drug delivery
- Sensitization (reverse tolerance)
 - an increased responsiveness to the drug
 - occurs predominately with stimulant drugs
 - produced by intermittent drug administration

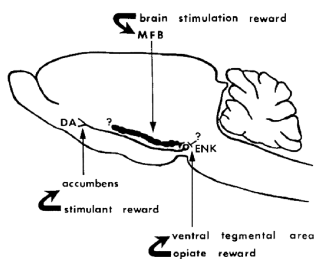
Stimulant-Induced Tolerance

- Acute tolerance documented in humans
 - addicts report tolerance to the "rush" but not to the "high" following continuous IV cocaine infusions (Sherer, 1988)
 - tolerance develops to cocaine's subjective & cardiovascular effects (Ambre et al., 1988; Fischmann et al., 1985)
 - tolerance to cocaine's effects dissipate within 24 hrs of drug termination (Ambre et al., 1988; Fischmann et al., 1985)

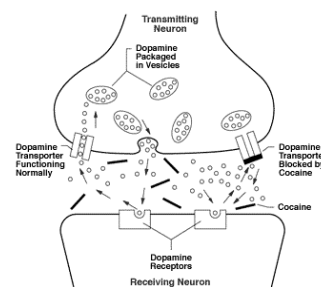
Stimulant-Induced Tolerance

- Pre-clinical studies
 - minipumps deliver drug continuously
 - may mimic high plasma levels of drug typically maintained during a binge
 - tolerance to cocaine's locomotor-stimulating effect (King et al., 1992; Pudiak et al., 1995)
 - tolerance to cocaine's threshold-lowering effect in BSR (Pudiak et al., 1995)
 - tolerance to cocaine's reinforcing effect in IVSA (Emmett-Oglesby & Lane, 1992)

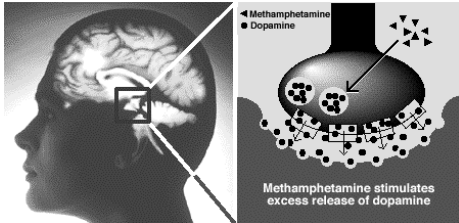
Brain Reward Circuitry



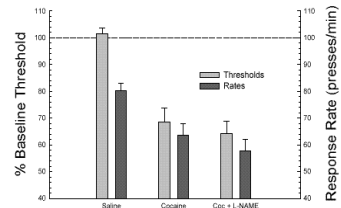
The Effect of Cocaine in the Nucleus Accumbens



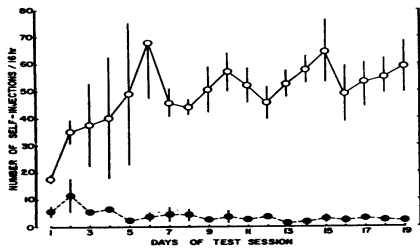
The Effect of Methamphetamine in the Nucleus Accumbens



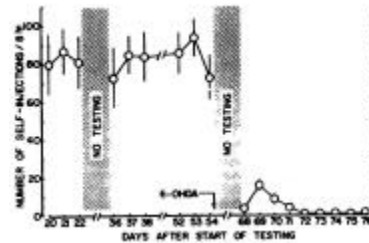
Cocaine Facilitation of BSR



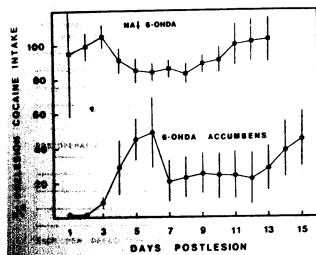
The Effect of 6-OHDA Lesions on Amphetamine Acquisition



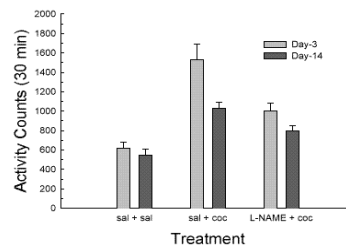
The Effect of 6-OHDA Lesion on Amphetamine Self-Administration



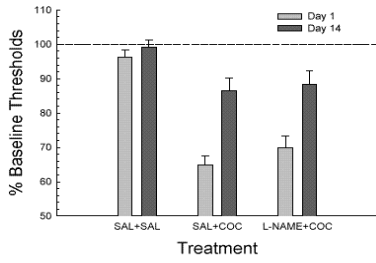
The Effect of 6-OHDA Lesions in DA and NA Containing Areas



Tolerance to Cocaine's Locomotor-Stimulating Effect



Tolerance to Cocaine's Threshold-Lowering Effect in BSR



Tolerance to Cocaine's Reinforcing Effect in IVSA

