Operant Animal Models of Drug-Seeking Behavior

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Operant chamber a.k.a. Skinner box

- Infusion line for drug delivery
- Levers
- Stimulus lights
- Tone generator & loudspeaker
- Levers
- Floor bars can be electrified
- Computer (controls schedule contingencies and collects data)
Why study drug-seeking behavior?

– One of the characteristics of drug addiction
  • Recurring relapses even after years of abstinence

– Chronic drug or alcohol exposure leads to adaptive changes in the central nervous system
  • The mechanisms underlying drug seeking and relapse differ from those mediating the acute effects of drugs

⇒ Effective pharmacological treatment of addiction requires knowledge of the neurobiology of drug-seeking behavior
Drug seeking and relapse can be triggered by

- Stress
- Priming doses of the drug
- Drug-associated stimuli (cues)
Major neurotransmitters

- Dopamine
- Glutamate

Also
- GABA
- Noradrenaline
- Serotonin
- Endocannabinoids
- The endogenous opioid system
- ...
Operant models of drug-seeking behavior

- Progressive ratio schedules of drug self-administration
- Fixed-interval second-order schedules of drug self-administration
- Extinction/Reinstatement model
Progressive ratio (PR) schedules of drug self-administration

- Number of responses required for each reinforcer increases progressively during the session

- Session ends when no responding for a pre-determined time period (e.g. 1 hour; final response ratio = "break point")

- Measure the maximal effort (motivation) to obtain the drug
Progressive ratio schedules

- Increasing the drug unit dose increases the break point (increased motivation to work for the drug)
Effects of glutamate receptor antagonism on progressive ratio cocaine self-administration

- BL = Coc 0.25 mg/inf
- Sal i.p. + Coc 0.25 mg/inf
- Coc 0.5 mg/inf
- Non-Competitive NMDA antagonist MK-801 0.15 mg/kg + Coc 0.25 mg/inf
- Non-competitive NMDA antagonist memantine 10 mg + Coc 0.25 mg/inf

Progressive ratio (PR) schedules of drug self-administration

– Number of responses required for each reinforcer increases progressively within a session
  • Large changes in reinforcer magnitude may result in only small changes in breakpoint

– Session ends when no responding for a pre-determined time period (e.g. 1 hour; final response ratio = ”break point”)
  • Sessions end at unknown and varying times and may be long

– Measure the maximal effort (motivation) to obtain the drug
  • Measure drug seeking under the influence of the drug
  • Motor suppressant effects of medications must be controlled for
Fixed-interval second-order schedules of drug self-administration

- "Schedules within schedules" or "superimposed schedules"

- Fixed-ratio (FR) component
  - A stimulus (S; e.g. light or tone) is presented after a fixed number of responses (e.g. 10)

- Fixed-interval (FI) component
  - The first completed fixed-ratio component after a pre-determined interval delivers the reinforcer (e.g. FI 15 min)

- The stimuli become gradually conditioned to drug effects and support responding on their own
Fixed-interval second-order schedules of drug self-administration

- Typically 4-5 intervals
- 1\textsuperscript{st} interval measures drug seeking in the undrugged state
- 2\textsuperscript{nd} interval measures drug seeking under the influence of (a small dose of) the drug
Fixed-interval second-order schedules of drug self-administration

- Responding is influenced by
  - Conditioned reinforcing properties of the stimulus
  - Ability of the stimulus to guide behavior
  - Incentive value (strength) of the reinforcer
  - Motivation to respond for the reinforcer
A typical response pattern during a fixed interval second-order schedule

Rat #4
FI15min(FR10:S)
Stimulus omission decreases 1st interval responding for cocaine

![Bar graph showing comparison of 1st interval responses between two conditions: FI 15min(FR10:S) and FI 15min(FR10:S)].
Increasing the cocaine unit dose increases responding/drug seeking

**First Interval**

- Cocaine Unit Dose mg/inf: 0.25, 0.5
- Responses: 0, 10, 20, 30, 40, 50, 60, 70

**Second Interval**

- Cocaine Unit Dose mg/inf: 0.25, 0.5
- Responses: 0, 50, 100, 150, 200

Bäckström and Hyytiä Psychopharmacology 166 (2003)
Fixed-interval second-order schedules of drug self-administration

- Support high rates of responding
  - Response rates often variable from day to day

- No direct relationship between response rate and reinforcer delivery
  - Responding may be more habitual than goal-directed

- Responding is partly dependent on the conditioned reinforcing properties of drug-associated stimuli

- Effects of medications on stimulus perception, motor performance, perception of time etc.
AMPA/Kainate glutamate antagonist CNQX decreases 1st but not 2nd interval cocaine seeking
The extinction/reinstatement model

1. Training/conditioning (1-2 months):
   Drug (+ stimulus)

2. Extinction (2-3 weeks):
   Drug (+ stimulus)

3. Relapse test(s):
   Drug + stimulus (light, tone…)
   Drug + stress (foot shock)
   Drug + priming dose of drug
The extinction/reinstatement model
The extinction/reinstatement model

– Drug seeking induced by drug-conditioned stimuli, stress, and priming doses of the drug can be measured separately or in combinations

– Drug seeking is usually measured in the undrugged state and after withdrawal mimicking the human condition

– Laborious, weeks or months of training, extinction, and testing
The extinction/reinstatement model

– Not all animals meet stability criteria for training, extinction, and relapse; some animals may not relapse at all

– Variability in relapse response rates

– Usually no ability to consume the drug

– Compared to human addicts, animals have no motivation to stay abstinent
  • recently punishment models have been developed

– Possible motor suppressant effects of medications
The opiate antagonist naltrexone and the AMPA/Kainate glutamate antagonist CNQX attenuate cue-induced alcohol seeking.

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