Preclinical Assessment of Abuse Potential

Roger D. Porsolt Ph.D.
President
Porsolt & Partners Pharmacology
Plan

- Definitions

- Drug abuse
  - Drug tolerance
  - Similarity to drugs of abuse
    - Overt behavior
    - Drug discrimination
  - Positive reinforcing properties
    - Conditioned place preference
    - Self-administration

- Conclusions
Dependence Liability

- Psychological
  Drug craving: difficulty in stopping drug use or sustaining abstinence

- Physical
  Occurrence of withdrawal symptoms on drug cessation
Abuse Liability

- Likelihood that a drug with psychoactive or CNS effects will sustain patterns of non-medical self-administration that result in disruptive or undesirable consequences.
Dependence does not predict abuse

<table>
<thead>
<tr>
<th></th>
<th>Abuse</th>
<th>Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>U50488</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>(\Delta 9)-THC</td>
<td>✔</td>
<td>✗</td>
</tr>
</tbody>
</table>
Substance characteristics leading to abuse potential

- Central action
- PK parameters (rapid onset, short duration of action)
- High solubility
- High safety margin
- Tolerance after prolonged use (dose escalation)
- Similarity to other drugs of abuse (drug discrimination)
- Positive reinforcing properties (conditioned place preference, self-administration)
Drug Classes Associated with Abuse Liability and Scheduled by DEA

- Opioids
- Sedative hypnotics
- Cocaine, amphetamine and other CNS stimulants
- Hallucinogens, phencyclidine and similar agents
- Cannabinoids (marijuana and related compounds)
- Nicotine-like drugs
- Chemical precursors of controlled substances
- Anabolic steroids
## Drug Schedules

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
</table>
| I        | No current accepted medical use  
          | High abuse potential          | Heroin, methaqualone,  
          |                         | psylocybin, marijuana |
| II       | Current accepted medical use  
          | High abuse potential          | Cocaine, PCP, morphine,  
          |                         | fentanyl, methadone |
| III      | Current accepted medical use  
          | Medium abuse potential        | Opium, acetaminophen +  
          |                         | codeine, amphetamine,  
          |                         | barbiturates |
| IV       | Current accepted medical use  
          | Low potential for abuse       | Benzodiazepines, zolpidem,  
          |                         | modafinil, barbital, pemoline |
| V        | Accepted medical use  
          | Very low abuse potential      | Codeine preparations,  
          |                         | promethazine, opium  
          |                         | preparations |
Preclinical Abuse Liability: Advantages of Studies in Non-Humans

- Relatively inexpensive
- Can occur early in drug development
- Broad range of dosing conditions
- Different routes of administration
- Compare a wide variety of drugs
- Mechanism studies
DRUG TOLERANCE
Hot Plate Test in the rat: Tolerance after repeated morphine treatment

![Graph showing foot-licking latency (s) across different treatments.](image)

- Pretreatment (bid: Days 1-9)
  - 0 mg/kg i.p.
  - 0 mg/kg i.p.
  - 8 mg/kg i.p.
  - 16 mg/kg i.p.
  - 32 mg/kg i.p.

- Treatment (Day 10)
  - 0 mg/kg i.p.
  - 8 mg/kg i.p.
  - 8 mg/kg i.p.
  - 8 mg/kg i.p.
  - 8 mg/kg i.p.
SIMILARITY TO DRUGS OF ABUSE

Overt Behavior
## Irwin Test in the Mouse

### MK 801 (p.o.)

<table>
<thead>
<tr>
<th>0.125 (mg/kg)</th>
<th>1 (mg/kg)</th>
<th>4 (mg/kg)</th>
<th>32 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>Excitation +++ Straub</td>
<td>Excitation +++ Straub</td>
<td>Sedation ++ Straub</td>
</tr>
<tr>
<td></td>
<td>Stereotypies Convulsions Hyperthermia +</td>
<td>Stereotypies Convulsions Hyperthermia +</td>
<td>Stereotypies Convulsions Hyperthermia +</td>
</tr>
<tr>
<td></td>
<td>Motor incoordination</td>
<td>Muscle tone</td>
<td></td>
</tr>
</tbody>
</table>

### Phencyclidine (p.o.)

<table>
<thead>
<tr>
<th>1 (mg/kg)</th>
<th>4 (mg/kg)</th>
<th>16 (mg/kg)</th>
<th>64 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Reactivity</td>
<td>Excitation ++ Tatart</td>
<td>Excitation +++ Stereotypies Convulsions</td>
<td>Convulsions Death (3/3)</td>
</tr>
<tr>
<td>↓ Traction</td>
<td>↓ Reactivity to touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Fear</td>
<td>↓ Traction</td>
<td>Motor incoordination</td>
<td></td>
</tr>
<tr>
<td>↓ Muscle tone</td>
<td></td>
<td>↑ Respiration</td>
<td></td>
</tr>
</tbody>
</table>
SIMILARITY TO DRUGS OF ABUSE

Drug Discrimination
Amphetamine (0.6 mg/kg i.p.) Discrimination Test in the rat

% responses on drug lever

<table>
<thead>
<tr>
<th>Amphetamine</th>
<th>Cocaine</th>
<th>Methylphenidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.075</td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td>0.15</td>
<td>4.4</td>
<td>1</td>
</tr>
<tr>
<td>0.3</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>0.6</td>
<td>***</td>
<td>**</td>
</tr>
</tbody>
</table>

mg/kg i.p.
Diazepam (2 mg/kg i.p.) Discrimination Test in the rat

% responses on drug lever

Diazepam

mg/kg i.p.

Alprazolam

Buspirone

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Drug Discrimination

**Strengths: pharmacologic specificity**

<table>
<thead>
<tr>
<th>Test Drug</th>
<th>Cocaine</th>
<th>Heroin</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>✓</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>✓</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Heroin</td>
<td>x</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>Morphine</td>
<td>x</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>Midazolam</td>
<td>x</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>x</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Test substance</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
POSITIVE REINFORCING PROPERTIES

Conditioned Place Preference
Place Preference Test in the rat
Place Preference in the rat
Morphine

% Time spent in Drug Compartment

Dose (mg/kg i.p.)

0 4 8 16

* **

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Place Preference in the rat
Cocaine

% Time spent in Drug Compartment

Dose (mg/kg i.p.)

0  8  16  32

*
Place Preference in the rat
Diazepam (from Gray et al, 1999)

Dose (mg/kg i.p.)

Time spent in initially least preferred Compartment (s)

0 2.5 5

* **
Place Preference in the rat
Nicotine

% Time spent in Drug Compartment

Treatment during training
days 8-11 (mg/kg i.p.)
0 0.8 0.8 0.8

Treatment before training
days 1-7 (mg/kg i.p.)
0 0 0.8 0.8 x 2
Place Preference in the rat
\(\Delta 9\)-tetrahydrocannabinol

% Time spent in Drug Compartment

Dose (mg/kg i.p.)

0
1
8
POSITIVE REINFORCING PROPERTIES

Self-Administration
Self-Administration Methodology

- **Substitution procedures**
  - established baseline (drug abuser)
  - reuse of animals (particularly primates)
  - high sensitivity (false positives ?)
  - possible negative contrast

- **Initiation procedures**
  - new animals per test substance (drug naive)
  - lower sensitivity (false negatives ?)
Intravenous self-administration of fluoxetine compared with saline and heroin in 3 monkeys

Number of i.v. infusions

Monkey 1

Monkey 2

Monkey 3

Fluoxetine

Heroin

0.1 0 0.1 0.3 1 0.1

0.1 0 0.1 0.3 1 0.1

0.1 0 0.1 0.3 1 0.1

Heroin

Fluoxetine

Heroin

(mg/kg i.v.)
Mean self-administration of cocaine and Substance X in 4 rhesus monkeys

- Infusions per session

- Saline
- 0.03
- 0.3
- 1
- 3

- Cocaine
- Substance X

(mg/kg/infusion)
Breaking points for some known or potential drugs of abuse in monkeys trained on an FR50 schedule

<table>
<thead>
<tr>
<th>Test Drug</th>
<th>Breaking point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>750</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>675</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>275</td>
</tr>
<tr>
<td>Bupropion</td>
<td>100</td>
</tr>
<tr>
<td>Modafinil</td>
<td>100</td>
</tr>
</tbody>
</table>

Data from Beardsley (2006)
Mean number of drug reinforcements received at each reinforcement ratio in 3 rhesus monkeys
## Weaknesses

- **False negatives**
  - GHB
  - LSD

- **False positives**
  - Buproprion
  - Modafinil
  - Nomifensine

<table>
<thead>
<tr>
<th></th>
<th>Rat</th>
<th>Monkey</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Heroin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>PCP</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>GHB</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>LSD</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Buproprion</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Modafinil</td>
<td>NT</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Nomifensine</td>
<td>✓</td>
<td>NT</td>
<td>✗</td>
</tr>
</tbody>
</table>
Conclusions

- Drugs for most CNS applications or with CNS mechanism of action will have to be assessed for abuse liability

- Drug discrimination a sensitive but indirect assessment of abuse liability

- Conditioned place preference is not a sensitive nor a direct assessment of abuse liability

- Self-administration, particularly in the primate, is the most direct and sensitive assessment of abuse liability
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