Psychomotor stimulants

Large class of diverse compounds

- Stimulate alertness, arousal ("psycho-")
- Stimulate motor activity ("-motor")

Major ones:
- Amphetamines and related compounds
- Cocaine
Amphetamines

History and basic pharmacology
- β-phenylethylamine derivatives
- sympathomimetic amines

Naturally-occurring compounds
- cathinone
- ephedrine

Cathinone
- active agent in Khat (shrub)
- chewed
- synthetic version (meth-cathinone)
Ephedrine

- from Ma Huang (herbal tea)
- isolated in 1920's
- bronchodilator for asthma
- pseudoephedrine is an isomer of ephedrine
- structure similar to epinephrine

Amphetamine

History
- synthetic
- identified in search for substitute for ephedrine (Alles, 1927)
- structurally-related to catecholamines
- 1932, Benzedrine inhaler
- widespread adoption
- peak use in early 1970's ("speed")
- new West Coast popularity ("tweakin")
Forms of amphetamine

**Amphetamine (racemic)**
- mixture of d- and l-isomers
- Benzedrine®, Adderall®
- bennies, speed

**d-Amphetamine**
- dextroamphetamine
- Dexedrine®
- dexies, hearts, speed

**l-Amphetamine**
- levoamphetamine
- less potent

**Methamphetamine**
- dl-methylamphetamine
- Methedrine®, Desoxyn®
- meth, crystal, crank, speed
- most potent
- l-methamp = "desoxyephedrine" (Vicks inhaler)

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Ice, Crank, Crystal Meth


A new drug gallops through the West

Mexicanos make in van methamphetamine
Ice, Crank, Crystal Meth

Pure d-methylamphetamine HCl
(can be smoked because of purity)

Traditional synthesis
- amalgam method > not very pure dL-methamphetamine
- 1981 main ingredient made illegal

Synthesis from ephedrine
- pure dL-methylamphetamine HCl

“Ice” or “Crystal”

Smoked vs. Oral Amphetamine

Blood level (ng/ml)

Smoked vs. Oral

Amphetamine-related drugs

- methylphenidate
  - Ritalin®
  - attention deficit disorder
- fenfluramine
  - Redux®
  - anorectic
- phenmetrazine
  - Preludin®
  - anorectic
- subitramine
  - Meridia®
  - anorectic
Medical uses of amphetamine

- Obesity (anorexic effects)
  once major use - no longer
- Narcolepsy
- Attention deficit disorder
**Major effects - amphetamine**

Humans

**Autonomic functions**
- increase blood pressure
- increase body temperature
- bronchodilation
- (sympathomimetic effects)

**Effects on CNS**

Analeptic (awakening)
Anorexia
Psychomotor stimulant effects
- decreased fatigue, increased alertness
- arousal
- elevated mood
- euphoria

**Effects: non-human animals**

Autonomic effects
- same as humans
Psychomotor stimulant effects
- complex dose-effect relations
- low doses - locomotor hyperactivity
- higher doses - stereotyped behavior
Reinforcing effects
- self-administration and place preference
Effects of repeated administration

Tolerance
- most autonomic effects
- anorectic effects

Sensitization
- psychomotor stimulant effects
- rewarding effects
- psychotomimetic effects
  (amphetamine psychosis)

Sensitization to the psychomotor stimulant effects of amphetamine
- Rats given 2.0 mg/kg of d-amphetamine once per day for 10 days
- Measure amount of drug-induced rotational behavior each day

Cocaine
Source and history
- Naturally-occurring alkaloid in leaves of shrub Erythroxylon coca
- first reported use by Europeans - 1499
- active agent extracted in 1859 by Niemann
- widely used in late 1800’s, early 1900’s
- local anaesthetic effects - 1884 procaine (1905)
Cocaine - history of use

Cocaine - history of use

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Cocaine - history of use
Forms of cocaine

**Raw leaves**
- chew
- alkaloid content low (0.6 - 1.8 %)
- not stable

**Coca paste**
- initial extraction
- smoked
- around 80% cocaine

**Cocaine HCl**
- purified & converted to HCl salt
- crystalline form, water soluble
- pure if not diluted
- snorted or i.v.

**Cocaine free base**
- extract (volatile solvents)
- smoked

**Crack**
- free base made with baking soda & ammonia
- crackles when heated
Effects of cocaine

Very similar to amphetamine (generalize in drug discrimination), but some major differences:

Duration of action
Cardiovascular effects
- danger of CVA much higher
Convulsive properties
- these sensitize
Local anaesthetic effects
- Lidocaine, novacaine, benzocaine are related drugs

Psychostimulant actions

Mechanisms of action
- Primary actions on monoamine neurotransmission

Monoamines
(compounds with one amine group, $\text{NH}_2$)
- Epinephrine (E)
- Norepinephrine (NE)
- Dopamine (DA)
- Serotonin (5-HT)

Catecholamines (CA; catecholaminergic)
(compounds with catechol nucleus and amine)
- Epinephrine (adrenergic)
- Norepinephrine (noradrenergic)
- Dopamine (dopaminergic)

Indolealkylamines (indole and amine)
- Serotonin (serotonergic)
NE synapse

8.2
Inactivation & degradation

Receptors

Distribution of NE

8.30

Distribution of NE

Locus coeruleus
Distribution of DA

Nigrostriatal

Mesolimbic

8.19

Serotonin (5-hydroxytryptamine)

Receptors
5-HT_{1A}

Raphe

9.1

Primary neurochemical effects

Increase synaptic concentrations of monoamines (DA, NE, E & 5-HT)
Primary site of action

Monoamine transporter
(both amphetamine and cocaine)
- actions on DA, NE & 5-HT transporters

Actions of cocaine

Cocaine and amphetamine have different actions on monoamine transporters

Cocaine
- Blocks transporter
  - prevents reuptake
  - requires calcium

Actions of cocaine

Human PET Scans

Normal

Cocaine
Actions of cocaine

Time course of cocaine uptake into brain - (C)cocaine

Fowler et al. (2001)

Actions of cocaine

Time course to peak cocaine after i.v. administration mirrors times course of subjective effects

Fowler et al. (2001)

Actions of cocaine

Self Report of High (0-10)

 smoked
 intravenous
 snorted

Fowler et al. (2001)
**Actions of amphetamine**

**Release**
- calcium independent
- not blocked by reserpine
- blocked by TH inhibition
- requires transporter (blocked by reuptake blockers)

**Locus of action**

**Autonomic effects**
- sympathetic nervous system

**Psychomotor and rewarding effects**
- brain monoamine systems
- DA, NE and/or 5-HT?
- DA primary locus

**Role of DA**

Evidence that DA mediates the psychomotor stimulant and rewarding effects of psychostimulants
- Pharmacological studies
- Lesion studies
- Neurochemical studies
- Correlational studies
- Molecular biology studies
Pharmacological studies

Amphetamine self-administration

Response rate (% control)

Lesion studies

6-hydroxydopamine lesions

Neurochemical studies

Relationship between behavior and extracellular DA
Correlational studies

**DOPAMINE TRANSPORTER**

- **Cocaine & analogs**
- **Relative behavioral potency** vs. **relative binding potency**

- $r = 0.86$
- $p < 0.0001$

Molecular biological studies

The DA transporter knockout mouse

- Normal
- Knockout

DA sub-systems

- **Mesolimbic projections**
  - from VTA > nucleus accumbens
  - ventral striatum
- **Nigrostriatal projections**
  - substantia nigra > caudate-putamen
  - dorsal striatum
**Nigrostriatal DA system**

Psychostimulant-induced stereotyped behavior
- lesions
- local injections

**Mesolimbic DA system**

Locomotor hyperactivity and reward
- lesions
- local injections

![Cocaine into N. Accumbens](image)

**DA sub-systems**

Mesolimbic projections
- from VTA > nucleus accumbens
- locomotor activity and reward

Nigrostriatal projections
- substantia nigra > caudate-putamen
- stereotyped motor patterns
### Amphetamine neurotoxicity

Amphetamine and methamphetamine are potentially neurotoxic:

- Requires high doses
- 10 to 50 times normal street dose (in rats; primates may be more sensitive)
- High extracellular DA necessary

### d-Amphetamine

- Depletes DA
- Degeneration of DA terminals
- Primarily caudate (accumbens relatively spared)
- Cell bodies intact

### Methamphetamine

- Depletes DA and serotonin
- Degeneration of terminals
  - Caudate DA and cortical and hippocampal 5-HT
- Cell bodies intact
Amphetamine neurotoxicity

Does methamphetamine cause degeneration of striatal dopamine terminals in amphetamine addicts?

PET images from control subjects, Parkinson’s patients, and abstinent methamphetamine and methcathinone users (average period of abstinence, 3 years)

WIN-35,429 binding to DA transporter
Does methamphetamine cause degeneration of striatal dopamine terminals in amphetamine addicts?

The controversy:
The DAT vs. VMAT as markers of dopamine terminal density

The DAT is highly regulated, the VMAT is not. Therefore, the VMAT and not the DAT provides a reliable indicator of DA terminal density.
Wilson et al. (1996)

Brain tissue from addicts show no change in VMAT binding, although is decrease in DAT

Suggest is no neurotoxicity in amphetamine addicts


Methylenedioxymethamphetamine

MDMA (extacy, E, X, XTC,Adam) and MDA
Synthesized in 1912, 1913 patent (Merck)
- anorectic in 1961
- not used clinically
- Dr. Shulgin
Street use
- early 1980’s; popular at “raves”
- also adjunct to psychotherapy (clin trials 1993)
- illegal since 1985 (1st Schedule I by DEA)
Several analogues

DOM - dimethoxyamphetamine
  - SF designer drug (late '60s)
  - "STP" (Serenity Transquility Peace)

DOB - 4-bromo-2,5-dimethoxyamphetamine

MDA - 3,4-methylenedioxyamphetamine

MDMA - 3,4-methylenedioxymethamphetamine

2-CB - 4-bromo-2,5-dimethoxyenethyllamine (NEXUS)
  (hallucinogen similar to LSD)

Synthesis

Safrole is distilled from sassafras or nutmeg oil (>1000 doses 1 kg of safrole)

MDMA

Percentage of 8th-, 10th-, 12th-Graders Reporting MDMA (Ecstasy) Use

<table>
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<th>1999 Males</th>
<th>1999 Females</th>
<th>2000 Males</th>
<th>2000 Females</th>
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<tr>
<td>8th-Graders</td>
<td>3.1 4.7 1.7</td>
<td>3.0 4.2 1.7</td>
<td>3.0 4.8 1.7</td>
<td>3.0 4.6 1.7</td>
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<td>5.6 5.6 5.6</td>
</tr>
<tr>
<td>12th-Graders</td>
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<td>5.6 6.2 8.2</td>
<td>5.6 6.3 8.2</td>
<td>5.6 6.4 8.2</td>
</tr>
</tbody>
</table>
Effects on behavior and affect

Low doses
- relaxation, serenity, emotional closeness

Moderate doses
- mild hallucinogenic effects
- intensification of feelings
- notorious memory impairment

High doses
- amphetamine-like effects
- hyperthermia (heat stroke)
- “hangover”

Distribution

Typical use is in pill form
- "love" "hug" "club" drug
- permasmile
- mostly recreational
- 60-120 mg per pill
  - LD50 = 50 mg/kg
  - (3000 mg)
- take 1-2 pills
- $20-30 per pill (whl=$5)

Different class than traditional drug users
Effects on behavior and affect

Can’t recognize content from pill

What is PMA?

- paramethoxyamphetamine
- "Death" "Mitsubishi Double Stack"
- "Killer" "Red Mitsubishi"
- substitute for MDMA
- cheaper to make
- slower longer effects
- more hallucinogenic
- incidence of toxic side effects much higher than MDMA (narrow safety margin)
Effects on behavior and affect

MDMA on the rise

1997 • 400,000 tablets seized
1999 • 3.3 million tablets seized
2000 • 9 million tablets seized
  • During a period of time when enforcement is very low.
2001 • dealers can unload >100,000 tablets per week in major cities
  • 1 in 4 teens in NYC say have tried.
**Neurochemical effects**

Monoamine neurotransmission
- Increase synaptic DA and 5-HT
- Blocks 5-HT transporter
- Enters neuron and causes Calcium-independent release of 5-HT

**Neurotoxic effects**
- Potent neurotoxin
- 1-2 times street dose
- Depletes forebrain 5-HT (not DA)

**MDMA & MDA neurotoxicity**

Degeneration of 5-HT terminals
- Fine axons from dorsal raphe
- Beaded axons from median raphe spared
- Can get 30% loss with single injection
- Up to 80% with repeated injections

Species differences
- Primates more sensitive
- Some evidence in humans (CSF 5-HIAA down)

McCann et al. (1997)
Normal PET image from 1 control and one MDMA user McN-5652, to label the 5-HT transporter


Cerebral Blood Flow


Amphetamine neurotoxicity

d-Amphetamine

- DA only

Methamphetamine

- DA and 5-HT

Methylenedioxymethamphetamine (and MDA)

- 5-HT only