PSYC1022: The Psychology of Addiction

Topic 9: Biological mechanisms of reward

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Outline:

- Dependence liability
  - Dose
  - Rate of absorption
  - Route of administration
  - Solubility
- Dopamine revisited
  - Dopamine & surprise
  - Dopamine & pleasure

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Dependence liability

Why are some substances more addictive than others?

Dependence liability of different drugs depends upon their *bioavailability* in the brain (concentration of the drug within brain tissue able to bind to receptors).

- Bioavailability is determined by:
  1. dose level,
  2. the rate of absorption,
  3. the route of administration,
  4. the solubility of the drug.

Drug	Dependence score
Heroin	3
Cocaine	2.39
Tobacco	2.21
Street methadone	2.08
Barbiturates	2.01
Alcohol	1.93
Benzodiazepines	1.83
Amphetamine	1.67
Ketamine	1.54
Cannabis	1.51
Methylphenidate	1.25
LSD	1.23
GHB	1.19
Ecstasy	1.13
Khat	1.04
Solvents	1.01
Anabolic steroids	0.88

(Nutt et al., 2007)

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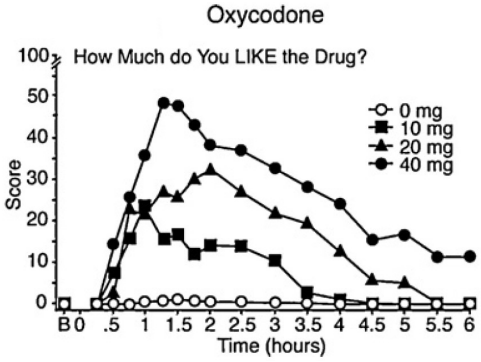
Dependence liability: Dose

The bioavailability of the a drug is most obviously determined by the dose administered.

- Larger doses produce greater subjective reports of "liking"

Walsh et al. (2008):

- 3 different doses of Oxycodone
- liking increased as a function of dose
- liking is linked to the peak or maximum drug bioavailability.



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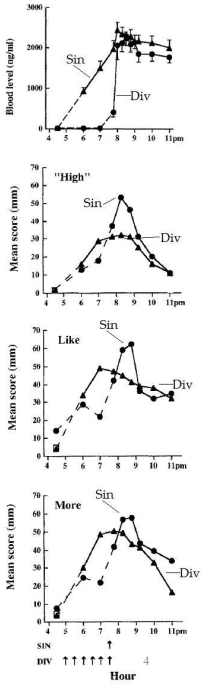
Dependence liability: Rate

The rate (or speed) of increase of drug bioavailability determines drug liking (even when dose is fixed)

- Infuse the same dose of a substance at different speeds & participants self-report "liking", "high" or "wanting"

De Wit (1992): Pentobarbital (GABA agonist). Two groups: 150 mg as a single dose (Sin) vs. 180 mg divided into six cumulating doses 30 mg/30 min (Div).

- doses produced similar max. peak blood levels but a different rate in incline (top figure)
- Ratings of drug high, liking & wanting were greater for the Sin compared to the Div dose.
  - Thus, rate of increase of the drug's bioavailability, independent of its peak or max. availability, is an important determinant of its abuse liability.
- Similar effects found for Diazepam (De Wit et al., 1993).



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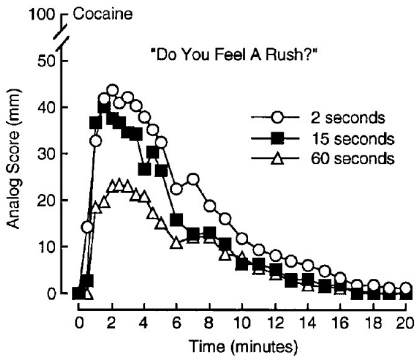
Dependence liability: Rate

Abreu et al. (2001): administered cocaine users with a fixed i.v. dose of cocaine at an infusion rate of 2, 15, & 60 seconds.

- Subjective ratings of rush, high & liking were all greater when cocaine was infused more rapidly at 2 seconds compared to 15 & 60 seconds.

- Confirms that abuse liability is enhanced by increasing the rate of the infusion, independent of the drug's peak bioavailability.



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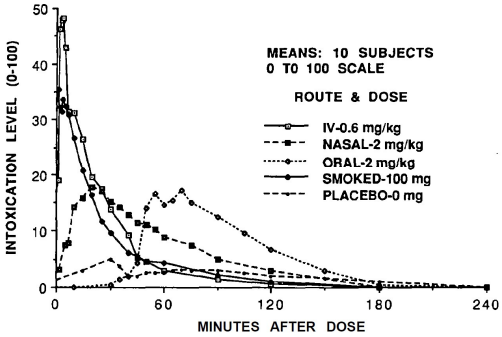
Dependence liability: Route

Route of administration is a crucial determinant of how quickly the drug enters or is absorbed by the body, and thus the peak effect, and the rapidity with which the peak is reached.

Jones (1990): Time-course of the subjective effects of various cocaine doses taken through different routes of administration

- smoking is fastest, followed by intravenous, nasal, oral.



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Dependence liability: Route

Volkow et al., 2000: studied timeframe of cocaine's subjective effects more closely

- confirmed that the rate to peak effect was faster for smoked (1.4min) than intravenous (3.1 mins), which were substantially faster than intranasal (14.6+).
- Smoking may be faster because delivery of drugs to the brain from lung has a shorter distance & high volume flow compared to peripheral veins.
- Differences in the rate of bioavailability may be responsible for the differential dependence liability of the various routes of administration

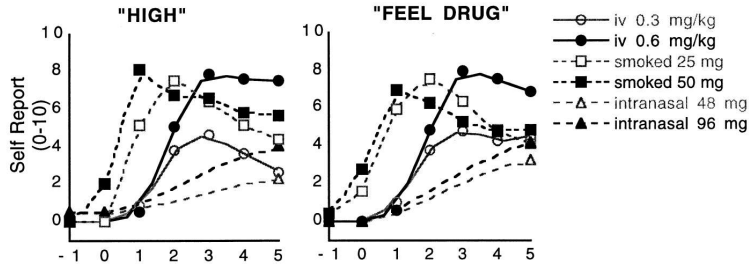

Fig. 4. Temporal course for the self reports of "high" for the first 5 minutes after cocaine administration for the low and large doses of intravenous, smoked and intranasal cocaine.

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Dependence liability: Route

Benowitz (1990): rise & fall of plasma nicotine following administration via different routes

- smoking a whole cigarette
- oral (intranasal) snuff
- oral chewing tobacco
- nicotine gum

Smoking the cigarette produces a faster time to peak concentration (≈8mins) than oral snuff, chewing tobacco & nicotine gum (all ≈30mins). Yet the peak concentration was comparable for smoking, oral snuff & chewing tobacco.

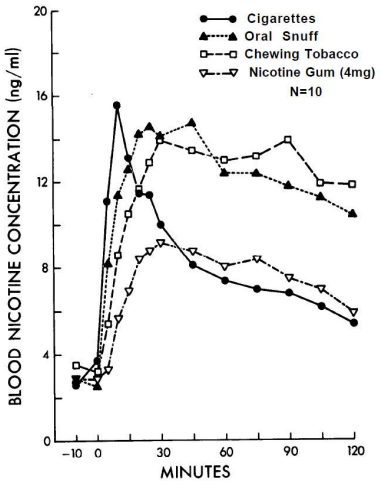

FIGURE 1. *Blood concentrations &ring and after cigarette smoking for 9 minutes (one and one-third cigarettes) and use of oral snuff (2.5 g), chewing tobacco (average 7.9 g), and nicotine gum (two 2-mg pieces) for 30 minutes*

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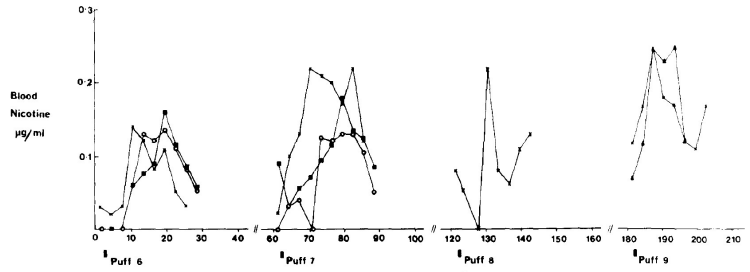
Dependence liability: Route

Isaac & Rand (1969): anaesthetised dogs were given intrapulmonary infusions of tobacco smoke. Each puff had identical parameters which were set to estimate the average human puff.

- successive infusions produced a phasic peak increase in plasma nicotine within ≈10 seconds, which tended back towards baseline within 30 seconds.
- Such rapid micro peaks may account for the particular dependence liability of smoking as a route of administration generally.



The concentration of nicotine in arterial blood following the administration of 2 or 4 successive puffs of cigarette smoke into the respiratory tract (at ▮). The figure is a composite of the results obtained from 4 cigarettes in 3 dogs. Dog 7, ▲; Dog 9, ×; Dog 11, ■, ○.

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Dependence liability: Route

Substances which are primarily administered orally have a slower time to peak concentration

Helmlin et. al. (1996): MDMA plasma concentration peaks about 2 hours after ingestion

- May account for the relatively low abuse potential ascribed to this drug.

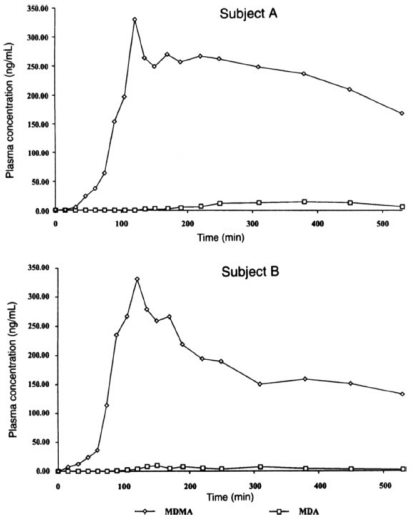

Figure 5. Plasma profiles of subjects A and B after an oral dose of 1.5 mg/kg 3,4-methylenedioxymethamphetamine (MDMA).

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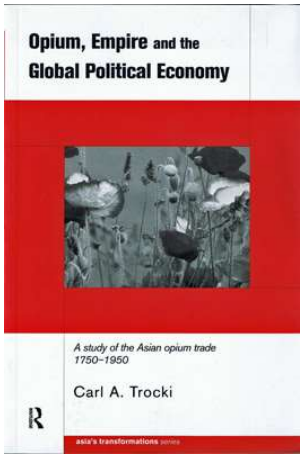
Dependence liability: Route

For centuries in China, opium was taken orally for medical purposes without any dependence epidemic

- 1700s: British East India company introduced mixing opium with tobacco for smoking which precipitated an epidemic of dependence
- Chinese state enforced increasingly severe penalties for opium smoking, which ultimately culminated in the opium wars.

The differential dependence liability produced by different routes of administration can have crucial implications for the resulting dependence epidemic & the following economic & political ramifications.

- Biopsychosocial effects of substance use



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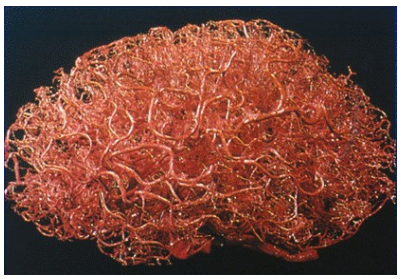
Dependence liability: Solubility

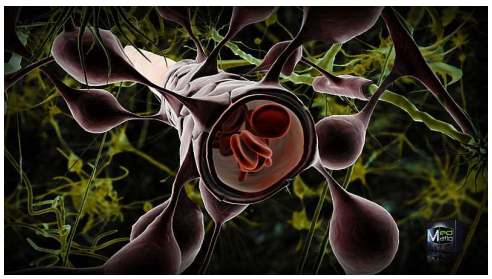
Blood Brain Barrier

An extensive network of blood vessels supply the brain with blood, carrying oxygen, nutrients & chemical signals.

- Blood vessels have a specialised barrier/lining (endothelium), which restricts the passage of microscopic particles
- Cells of the barrier actively transport metabolic products such as glucose across the barrier with specific transporter proteins.
- Astrocyte cells surround the endothelium & provide biochemical support.

Blood Brain Barrier (BBB): the brain's special protective barrier.





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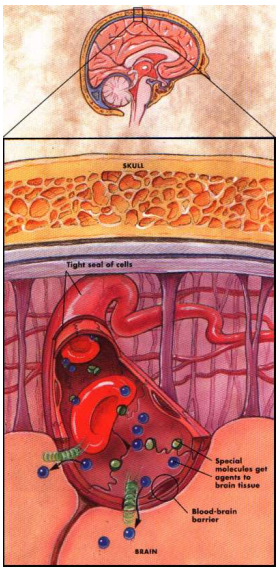
Dependence liability: Solubility

Blood brain barrier is selectively permeable: diffusion of ionized molecules is reduced. Diffusion of non-ionized molecules is not impeded.

- The more lipid soluble a drug is, the more readily it will pass through the BBB
- Non-ionized molecules can diffuse along a concentration gradient through the BBB (*passive transfer)*, until an equal concentration of the compound is established on both sides of the membrane.

Drug concentration in the brain is also determined by the rate of elimination

- The quicker the drug is eliminated the greater the addictive potential



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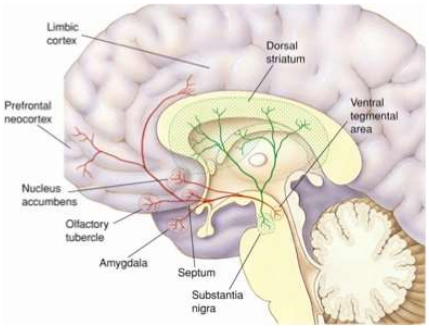
Dopamine revisited

Why does the absolute peak & the speed of onset of the peak influence DA in such a way as to enhance dependence liability?

- Early theorists labeled midbrain DA as the 'pleasure centre' (Olds and Milner, 1954) but this was later questioned because manipulations of DA function did not modify subjective pleasure reported by people (Wise, 2004) or hedonic facial reactions (Berridge, 2008).
- The implication was that through DA, drugs 'stamped-in' SA behaviour automatically, independent of subjective pleasure (Robinson & Berridge, 1993)



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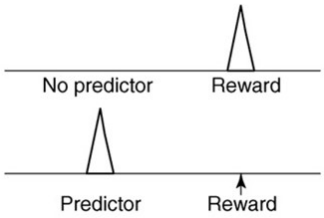
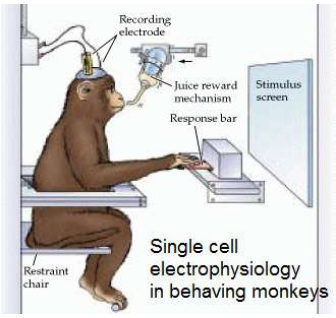
Dopamine & Surprise

Schulz (2011): *in vitro* single cell electrophysiological measurement of "burst" cell firing patterns of mesolimbic DA neurons

- monkeys were presented with a juice reward & DA cells fired.
- However, if a predictor stimulus (CS) was used to signal the juice, the DA cells came to fire in response to the CS & stopped responding to the juice reward itself
- Burst firing of DA cells encodes surprising rewards & surprising reward CSs, but not expected rewards or expected reward predicting stimuli
  - Thus dopamine can not simply be a pleasure centre.





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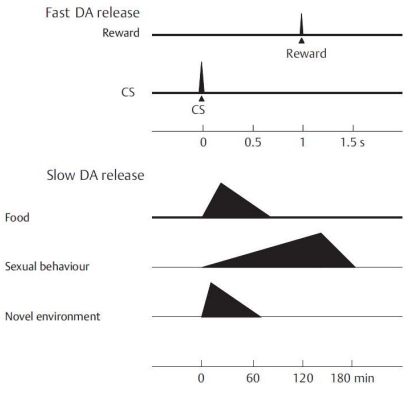
Dopamine & Pleasure

Hauber (2010): microdialysis measures slower changes in DA release over timescales of minutes

- Whereas surprising rewards & surprising reward paired cues produce a very sharp spike in DA activity, during consumption of those rewards, DA shows sustained released over a much longer timescale
  - consistent with a role for DA as a simple pleasure centre.

One speculation is that modes of drug administration which produce faster & higher peaks in bioavailability are especially dependence producing because they mimic both surprising rewards (fast DA) & reward consumption (high, sustained DA), and thus are more greatly valued than other modes of administration that produce slower or lower peaked bioavailability.



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Summary

- Knowledge of factors that influence dependence liability of a drug: dose, rate of absorption, route of administration & solubility.
- Understanding of empirical evidence for mesolimbic DA role in surprise & pleasure.

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