

SUBSTANCE MISUSE OPTION LECTURE 5

“HOW DRUGS AFFECT THE BODY: A GENERAL INTRODUCTION”

Illustrative figures in this lecture are from the
National Institute on Drug Abuse (USA) web site

WHAT IS A DRUG?

“any chemical entity or mixture of entities, other than those required for the maintenance of normal health (food), the administration of which alters biological function and possibly structure”

World Health Organisation (1971)

- A psychoactive drug is a drug that affects the brain to produce alterations in mood, thinking, perception and behaviour.

WHAT IS A DRUG?

- Drugs can exert their effects on biochemical systems in a wide variety of target tissues in the body.
- Many drugs have been designed as therapeutic agents, to rectify imbalances in chemical systems which have been induced by disease, e.g. L-dopa is used for the management of the symptoms of Parkinson's disease.
- However, other drugs (e.g. cocaine) are not used for therapeutic purposes, whilst others (e.g. morphine) have both a therapeutic use (as an analgesic) and non-therapeutic use (for altering mood).

PSYCHOACTIVE DRUGS

“the desire to experience some altered state of consciousness seem to be an intrinsic part of the human condition ... we are surrounded by drugs ... the cup of tea and coffee, the glasses of beer, wine and whiskey, the cigarettes, the snorts of cocaine, the joints, the tablets of acid, the fixes of heroin, and the ubiquitous tranquillisers and sleeping pills.”

Mike Gossop (1993)

PSYCHOACTIVE DRUGS

- There are a wide variety of psychoactive drugs that are used in society.
- These can be broken down into a number of different classes.
- There are important differences between these drugs in relation to their use, legal status and potential harmful effects.

PSYCHOACTIVE DRUGS

- Opiates: Morphine, heroin, methadone, prescription analgesics
- Stimulants: Amphetamine, cocaine, crack, methylamphetamine, methylphenidate, ecstasy
- Hallucinogens: LSD, mescaline, psilocybin, magic mushrooms
- Cannabinoids: Marijuana, hashish

PSYCHOACTIVE DRUGS

- Barbiturates: Pentobarbitone (nembutal), amylobarbitone (amyta)
- Benzodiazepines: Diazepam (valium), chlordiazepoxide (librium), temazepam
- Over-the-counter medications: Contain weak stimulants, weak analgesics, scopolamine, atropine
- Volatile substances: Glues, aerosol sprays, gas lighter fuels, amyl nitrites (poppers)

PSYCHOACTIVE DRUGS

- Miscellaneous substances: Phencyclidine (PCP), ketamine, khat, gammahydroxybutyrate (GHB), anabolic steroids
- Nicotine: In form of cigarette, cigar, snuff, chewing tobacco, nicotine, patch
- Alcohol

DRUG, SET AND SETTING

Zinberg (1984) first argued that in order to understand what impels someone to use an illicit (and licit) drug, and how that drug affects the user, three determinants must be considered:

- The drug (the pharmacological action of the substance itself)
- The set (personality, attitudes and expectancies, physical condition of the user)
- The setting (the influence of the physical and social setting within which the use occurs)

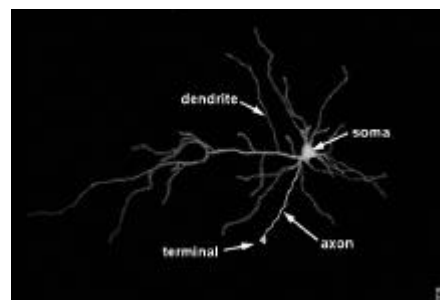
EFFECTS OF PSYCHOACTIVE DRUGS

- In this lecture, we will look at "the drug" and consider briefly the way that psychoactive drugs affect the brain and other parts of the body.
- We will also consider how the body, and changes in body function produced by drugs, can exert an influence on the effects of further drug administration.
- All psychoactive drugs affect the brain or the central nervous system (CNS).
- The effects of psychoactive drugs are mediated through a number of different endogenous chemical substances (neurotransmitters) acting through a vast complex of intercellular communications that strike a balance between excitatory and inhibitory function.

NEUROTRANSMITTERS

- A number of chemical substances, known as neurotransmitters, act as communicators between different neurons.
- When an action potential reaches the end of a neuron, or the presynaptic terminal, there is a release of neurotransmitter (e.g. dopamine) into the synapse (the space between two neurons).
- This neurotransmitter interacts with receptors (which are proteins) located on the postsynaptic neuron to exert a functional effect, e.g. an excitation or inhibition of action potential generation in the postsynaptic neuron.
- The neurotransmitter is then broken down into an inactive metabolite - part of this process occurs when the neurotransmitter is taken back into the presynaptic terminal.

A SINGLE DOPAMINE NEURON



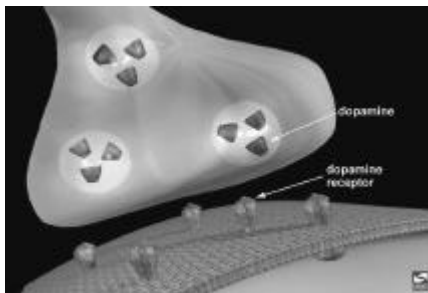
SHOWS HOW ONE NEURON CAN INFLUENCE ANOTHER



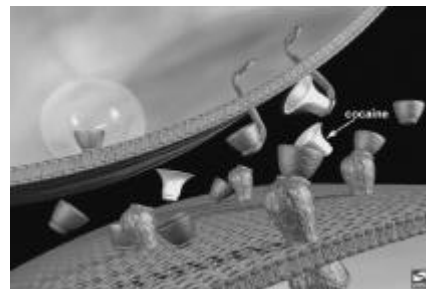
DRUGS AND NEUROTRANSMITTERS

- Certain drugs can increase the release of a neurotransmitter, resulting in enhanced synaptic levels of the endogenous substance, an increase in postsynaptic receptor activity and, therefore, a greater functional effect. Amphetamine is known to increase release of the neurotransmitter dopamine.
- Other drugs can retard the re-uptake of transmitter into the presynaptic terminal (where it is metabolised), thereby increasing synaptic levels of neurotransmitter, increasing receptor activity and therefore functional effect. Cocaine prevents the re-uptake of dopamine.

DOPAMINE PRESYNAPTIC TERMINAL AND POSTSYNAPTIC DOPAMINE RECEPTORS



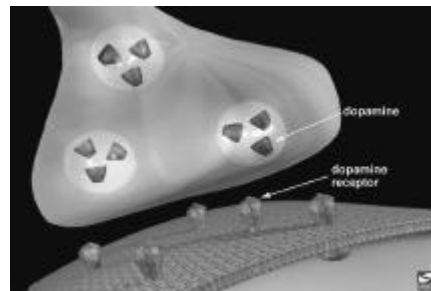
COCAINE RETARDING UPTAKE OF DOPAMINE MOLECULES



DRUGS AND NEUROTRANSMITTERS

- Certain other drugs can mimic the effects of neurotransmitters by "binding" to the same receptor sites as the endogenous transmitter and producing the same functional response. These drugs are known as **agonists**.
- Another group of drugs bind to the same receptor sites as neurotransmitters but do **not** trigger the series of events that lead to a functional response. However, since they bind to receptors, they can prevent the functional effects of the endogenous neurotransmitter. These drugs are called **antagonists**. An example of receptor antagonists are antipsychotic drugs, which block dopamine receptors.

DOPAMINE PRESYNAPTIC TERMINAL AND POSTSYNAPTIC DOPAMINE RECEPTORS



DRUGS AND NEUROTRANSMITTERS

- Since the brain is organised in circuits, a drug exerting direct effects primarily on one neurotransmitter system in a specific brain region will indirectly influence the activity of other neurotransmitter systems in other parts of the brain.
- Drugs of abuse cause a cascade of events in the brain which underlie their psychological effects, e.g. euphoria produced by cocaine or amphetamine.
- Of course, trying to understand the way that pharmacological effects at a cellular level are translated into psychological experiences is extremely complex and fraught with difficulties.
- And remember: drug, set and setting (Zinberg, 1984)

PHARMACOKINETICS OF DRUG ACTION

- When looking at how psychoactive drugs produce their pharmacological effects, and in trying to understand the individual variations in drug effect, we need to consider a number of different events and factors.
- For a drug to exert its effects in the brain it must reach its site of action. Thus, it will travel from the site of administration into the body to its target organ(s) or tissue(s).
- This process can be influenced by absorption, distribution, metabolism and elimination of the drug.

ABSORPTION

- The absorption of a drug is in part dependent upon its route of administration.
- Drugs can be applied topically for a localised response, e.g. drops into the eye, or cream for an abrasion. Drugs administered in this manner are not normally absorbed into the body as well as other forms of administration.
- Since psychoactive drugs must enter the bloodstream to reach their site of action, the most common route of administration for this purpose is orally, in either liquid or tablet form.

ABSORPTION

- When a drug is required to act more rapidly, or is known to be broken down in the gastrointestinal tract, the preferred route of administration is by injection. Drugs of abuse are often administered intravenously (directly into a vein).
- Drugs of abuse (e.g. cocaine or amphetamine) are also taken by the intranasal route.
- Certain drugs are smoked, e.g. marijuana, cocaine, heroin. This is a route of administration that is more socially acceptable, requires less paraphernalia, and is a less of a risk than intravenous injections, where sharing of needles may occur (possibly resulting in HIV).

DISTRIBUTION

- When a drug is administered a significant proportion of it reaches the bloodstream.
- Most drugs are dissolved in the water phase of blood plasma. Within this phase, some of the drug molecules will be bound to proteins and may therefore not freely diffuse out of the plasma.
- The drug is then transported around the body and can cross capillary walls to reach their target tissue(s).
- Drugs acting in the brain most also pass the "blood-brain" barrier.

METABOLISM

- Metabolism is a process whereby enzyme systems in the body transform drugs into safer molecules which can then be excreted by various routes of elimination.
- These enzyme systems are primarily located in cells in the liver, but can be found in other cells.
- There are a number of consequences of metabolism:

METABOLISM

- An active drug is converted into an inactive form - this is largely responsible for termination of drug action.
- An active drug may be metabolised into another active drug, which may or may not have the same pharmacological action of the parent drug.
- An active drug may be converted into a toxic compound.
- An inactive drug may be converted into pharmacologically active metabolites.

EXCRETION

- The most common route for drug excretion is through the kidneys into the urine. Drugs and their metabolites are filtered out from the plasma through the capillaries within the glomeruli of the kidneys. Drug testing in sport involves urine sampling.
- Drugs and metabolites can also be eliminated by the body in other ways, e.g. salivary glands, sweat glands.

INDIVIDUAL DIFFERENCES IN DRUG PHARMACOKINETICS

- There are genetically determined individual differences in pharmacokinetics through individual variations in the amount and characteristics of enzymes involved in metabolism and the amount of binding protein.
- Obviously, these individual differences will result in individual differences in drug response.
- One important factor influencing drug pharmacokinetics is age. Growing older is associated with a reduction in total drug clearance for many drugs, in particular CNS depressants.

INDIVIDUAL DIFFERENCES IN DRUG PHARMACOKINETICS

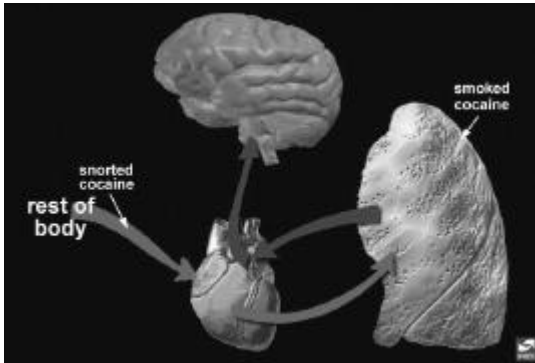
- Over 90% of alcohol is metabolised in the liver.
- The major metabolic pathway is oxidation by alcohol dehydrogenase (ADH) to acetaldehyde, which in turn is oxidised by aldehyde dehydrogenase (ALDH) to acetate, which is metabolised into carbon dioxide and water. It should be noted that acetaldehyde is highly toxic.
- Women have less ADH than men are therefore likely to have higher blood alcohol concentrations when they drink because less alcohol is metabolised before it is distributed around the body in the blood.

INDIVIDUAL DIFFERENCES IN DRUG PHARMACOKINETICS

- There are at least four isoenzymes of ALDH in humans. ALDH2, the isoenzyme largely responsible for the oxidation of acetaldehyde exists in two forms, one of which is virtually inactive.
- As many as 50% Orientals (Japanese, Chinese and Korean men and women) have a low activity of ALDH2 and this results in a flush reaction when these people drink.
- This reaction is unpleasant, and individuals with low activity ALDH2 are less inclined to drink and are less vulnerable to developing alcohol dependence.

EFFECTS OF DIFFERENT FORMS OF ADMINISTRATION OF COCAINE

- Once absorbed, the pharmacokinetics of cocaine are quite similar irrespective of the route of administration. The pharmacological effects of the drug are also the same regardless of route.
- However, the rate of onset, intensity and duration of effects are dependent on the route of administration.
- Oral ingestion, not usually used for illicit purposes, achieves maximal plasma levels the most slowly, followed by the intranasal route.
- Intravenous and smoked cocaine achieve maximal blood (and therefore brain) concentrations most rapidly. Maximal plasma levels occur in seconds.



DOSE-RESPONSE EFFECTS

- As would be expected, the magnitude of effect exerted by a drug depends on the amount of drug administered and which eventually reaches the target tissue.
- The larger amount of drug administered the larger the effect and the longer-lasting the duration of effect.
- In research studies, we sometimes study a drug's effects at a number of different doses, to determine a dose-response relationship.

DOSE-RESPONSE EFFECTS

- The situation is not always so simple.
- For example, certain doses of a drug might produce a stimulation of behavioural activity, whilst other doses produce a sedation.
- An example of this is alcohol. Many of you will have been stimulated by a certain number of drinks, but sedated after consuming further drinks.
- This situation may arise in the following way: lower doses of alcohol produce effects on certain neurotransmitters (and/or brain regions), whilst higher doses eventually affect other chemical systems (and/or brain regions) which lead to the opposite behavioural response, i.e. sedation.

ACUTE vs. REPEATED DRUG

- The effects of drugs on the body when they are administered repeatedly are not necessarily the same effects as those produced by the first (acute) drug administration.
- The body tries to achieve equilibrium, or homeostasis, when systems are altered.
- Thus, for example, when a drug is administered and produces a certain effect in the brain, the body will tend to react in the opposite direction in an effort to maintain or restore the normal conditions.
- The body "adapts" to changes produced by drugs.

DRUG TOLERANCE

- One form of adaptation to drugs is known as tolerance.
- Drug tolerance is defined either as the decreased effectiveness of a drug following the continued presence of the drug in the body, or:
- as the necessity of increasing the dose of a drug to maintain its effectiveness after repeated administrations.

DRUG TOLERANCE

- One of the most dramatic forms of tolerance is to the subjective effects of LSD; there is reportedly little or no effect by the fourth consecutive day of exposure.
- Some effects of a drug may develop tolerance very slowly, whilst others may take a much longer time, e.g. for benzodiazepines, there is rapid tolerance to the sedative effects, but not to anxiolytic properties.
- Once tolerance develops, it does not last indefinitely. It disappears over time, with variation between drug effects.
- Prior administration of one drug may well reduce the effectiveness of another drug, i.e. cross-tolerance can occur between drugs (e.g. benzodiazepines and alcohol), particularly those of the same class.

DRUG TOLERANCE

- There are several forms of tolerance, the best known being physiological tolerance.
- **Physiological tolerance** arises from some adjustment made by the body to compensate for an effect of the continued presence of the drug.
- These adjustments may involve entire physiological systems, or occur at a synaptic level (e.g. reduction in receptor number or sensitivity after administration of an agonist or arising from an increased release of neurotransmitter caused by drug).

DRUG TOLERANCE

Tolerance can be manifested in two ways. Firstly:

- If a drug enhances neurotransmitter release, or directly activates receptors, there is an increased functional response.
- When such drugs are given repeatedly, the system may try to compensate by a reduction in receptor sensitivity.
- This means that if the drug is given again, the functional response will be less enhanced than after acute administration.

DRUG TOLERANCE

Secondly:

- Once the drug has left the body, there is a period when receptor sensitivity is still diminished.
- The functional response produced by normal levels of transmitter will now be diminished.
- Therefore, drugs which increase brain function produce the opposite effects when they disappear from the body.
- This opposite effect may be viewed as a withdrawal symptom.

DRUG TOLERANCE

- Amphetamine increases alertness, energy and feelings of pleasure.
- With repeated administration, tolerance develops such that higher doses of amphetamine must be administered to achieve the same subjective effects.
- Moreover, after the effects of amphetamine have dissipated, the user may start to feel opposite effects, such as a reduced energy and alertness, and feelings of dysphoria or lack of pleasure.
- Normal pleasures, such as food and sex, may not produce the same enjoyment.

DRUG TOLERANCE

- **Metabolic tolerance** arises from an increase in the rate at which the body is able to metabolise and get rid of a drug. Repeated drug may increase the action of an enzyme the body uses to destroy the drug.
- **Behavioural tolerance** arises when an animal, through experience with a drug, learns to decrease the effect that the drug is having. This learning can involve both instrumental learning and conditioning processes.

BEHAVIOURAL SENSITISATION

- There is another neuroadaptatory change that can occur with illicit drugs.
- Repeated, intermittent administration of illicit drugs (e.g. amphetamine, heroin), in the laboratory animal produces an enhancement in some behavioural responses.
- This effect, known as behavioural sensitisation, is paradoxical since we would expect these drugs, which enhance dopamine function, to produce tolerance.
- In fact, they also show tolerance to some of their behavioural and physiological effects.
- In man, there may be sensitisation to the psychosis-producing effects of stimulants like amphetamine.

TOXIC DRUG EFFECTS

- There are many different receptor types throughout the body through which drugs can interact and produce pharmacological effects.
- The same receptor may exist in various tissues or organs in the body.
- Therefore, even doses of a drug that only interact with one specific receptor type can produce a wide variety of effects.
- Drugs often exert direct effects on more than one receptor type and this becomes more evident as dose is increased, i.e. specificity of drug action is lost as dose is increased.

TOXIC DRUG EFFECTS

- Clinical drugs are prescribed for their therapeutic effects.
- However, it is recognised that drugs can also produce toxic effects or unwanted side effects.
- Toxicity trials during drug development allow us to determine the ratio between the minimum dose which produces a therapeutic effect and the minimum dose which produces unwanted side effects.
- Ideally, this ratio should be high.
- However, it must be remembered that no drug is completely safe - they can all produce toxic reactions when given in a high enough dose.

TOXIC DRUG EFFECTS

- Toxic effects are observed when a person overdoses, either intentionally or accidentally. This toxicity is predictable, in the sense that we would expect this reaction given knowledge of the dose administered.
- However, there is also an unpredictable toxicity which can occur at therapeutic or even sub-therapeutic doses.
- This form of toxicity may occur for two reasons:

TOXIC DRUG EFFECTS

- **Idiosyncrasy** is where a drug produces an unusual reaction. This effect is normally genetically determined and is often due to some biochemical deficiency, resulting in an over-reaction to a drug, e.g. person may not metabolise drug in proper manner.
- An **allergy** is an acquired, qualitatively altered reaction of the body to a drug.
- An initial exposure to the drug, or related drug, can sensitise a person by producing an allergic response. This allergic reaction can manifest itself in various ways.
- For example, the acute reaction anaphylaxis, which normally occurs within one hour, frequently involves respiratory and cardiovascular systems and is often fatal.

DRUG RELATED HARM

Psychoactive drugs can produce various forms of physical and psychological harm:

- possibility of misuse leading to drug addiction
- higher risk of premature death (e.g. overdose)
- risk of acquiring blood-borne viruses
- other physical health problems
- psychological and psychiatric problems
- possible obstetric complications among pregnant drug users.

POTENTIAL PHYSICAL AND PSYCHOLOGICAL HARM

- Hepatitis B and C, and HIV, via sharing of injecting equipment and unsafe sex.
- Overdose, respiratory failure, deep vein thrombosis, serious infections.
- Liver disease, pancreatitis, cardiovascular problems, seizures.
- Psychotic symptoms, anxiety and panic disorder depressive symptoms, Korsakoff syndrome.
- Organic brain syndrome (confusion, disorientation, and decreased intellectual functioning).

DRUG RELATED HARM

- However, there are marked variations between different types of drug in the problems which are considered to lead to death.
- According to estimates of the ONDCP in the US, about 25,000 Americans die each year from using illicit drugs
- Approximately 100,000 people die each year from adverse reactions to prescription medications.
- The estimates with alcohol are more controversial, but all exceed 100,000 people per annum.
- At least 430,000 die each year because of tobacco.
- As a comparison, the Centre for Disease Control and Prevention in the US reports that obesity accounts for about 300,000 deaths a year.