SPOTLIGHT 2A
INDIVIDUAL DIFFERENCES IN DRUG RESPONSES

KEY ISSUES AND CONTROVERSIES

- Why do individuals vary in their responses to a drug dose?
- How do expectations about the effects of drugs alter drug-related responses?
- Why might someone respond differently to a drug dose depending on the context in which it is taken?
- Why do people respond to placebo pills and is it ethical to prescribe placebos?
INTRODUCTION

In Chapter 2 we considered the effects of psychoactive drugs on behaviour, emphasising the population effects of drugs. In reality, the specific effects experienced by individuals vary quite a lot; the way in which one person responds to a drug may be very different from another person’s reaction. Imagine two friends are out drinking beer. At the end of the evening one friend may be feeling much more intoxicated than the other even though they have consumed the same amount of alcohol. Let’s say one of the friends goes out again but this time to another friend’s house where they have never been before. They may drink an amount of alcohol that they think will not be overly intoxicating but they end up feeling a little more drunk than they had intended. In this spotlight we will find out why this might be the case. We will investigate differences between people in how they handle and respond to drugs and how environmental factors have an impact on drug responding both across and within individuals. Understanding individual differences in drug responding can help us figure out why some people do not respond well to therapeutic drugs and why some people may experience unexpected or adverse responses to drugs.

INDIVIDUAL DIFFERENCES IN DRUG RESPONDING

For the same dose of a drug, two people might experience different effects because different amounts of the drug reach the receptor sites; in other words they differ in drug pharmacokinetics. People also differ in pharmacodynamics, for example the number of drug receptors they have or their physiological response to a particular concentration of drug at the site of action. Some of these differences are inherited and relate to the genetics of drug metabolising enzymes or receptor types and some are acquired as a person ages or suffers from a disease.

A major influence on drug responding is body size. Large people have a bigger vascular system than smaller people. This means that a particular dose of drug will be distributed in a greater blood volume and will therefore be more diluted in the blood stream of a large person versus a small person. Less of the drug will be available at the target site to have its effects and so the drug effect will be smaller. This is why drug doses are usually scaled for body weight. Body composition (the amount of fat versus muscle a person has) is also a factor and this is becoming more of an issue with increasing numbers of obese people in many countries. The effect of body composition depends upon the drug. Obese people may respond more strongly to a drug than leaner people of a similar size if that drug is not very fat soluble. This is because fat is less richly supplied with blood than muscle and so a drug that is not taken up into fat will be more concentrated in the blood plasma of the obese than the muscular person. On the other hand, fat soluble drugs, including most psychoactive drugs, will be taken up into the body fat. This can extend the duration of action of a fat soluble drug in obese relative to lean people.

Age is another major factor affecting drug responding. In general, older people tend to need lower doses of drug than younger people to achieve the same effects and drug effects are prolonged in older people. One of the changes that occur with age is an increase in fat relative to lean tissue and this change in body composition may in part explain why older people respond differently to drugs than younger people. Aging is also associated with changes in drug metabolism and excretion. The size and effectiveness of the liver is reduced with age and the kidneys are less able to excrete drugs into urine. Older people may also be more sensitive to effects of drugs due to changes in receptor sensitivity. For example, much smaller doses of benzodiazepines are
required in elderly than young people to achieve sedative effects (Albrecht et al., 1999). Aging is also associated with greater likelihood of chronic disease that can affect drug metabolising and excreting organs.

Men and women respond differently to drugs for various reasons. On average, men are bigger than women and they have a lower proportion of body fat than women. As we know, these factors affect the distribution of drugs in the body. Men and women also differ in the way in which they metabolise some drugs. Alcohol is a good example of sex differences in drug pharmacokinetics. Even allowing for size, women have higher blood alcohol content than men after consuming the same amount of an alcoholic beverage because women have a lower amount of an enzyme that breaks down alcohol. Alcohol is converted to acetaldehyde by the enzyme alcohol dehydrogenase. Alcohol dehydrogenase is present in the stomach and so some alcohol is metabolised in the stomach before it can enter the bloodstream. Women have less gastric alcohol dehydrogenase than men and so ingestion of the same amount of alcohol will result in greater blood levels of alcohol in women than men (Frezza et al., 1990).

Changes in female sex hormones across the menstrual cycle can also affect response to drugs via interactions between hormones and neurotransmitter systems like dopamine. For example, responses to stimulant drugs like amphetamine and cocaine are similar in men and in women who are in the follicular phase of the menstrual cycle, but men report stronger drug effects than women who are in the luteal phase of the menstrual cycle (Justice and de Wit, 1999).

Genetic differences between people can affect drug metabolism. The genes coding for the enzymes that metabolise drugs can exist in slightly different forms known as polymorphisms and these polymorphisms can affect the activity of the enzyme. In most cases, the polymorphisms result in slight changes to the activity of the enzyme but in some cases the enzyme may be inactivated (Evans and Johnson, 2001). Drug enzyme polymorphisms often differ in frequency among ethnic and racial groups. One example is polymorphisms in the alcohol metabolising enzyme aldehyde dehydrogenase, which converts the first product of alcohol metabolism, acetaldehyde, into acetic acid. Some Asian groups of people have a polymorphism that results in the production of aldehyde dehydrogenase with reduced activity (Cook et al., 2005). This means that when alcohol is consumed, acetaldehyde builds up because it is not metabolised properly. Acetaldehyde is a pretty nasty compound and an unpleasant reaction is associated with a build-up of acetaldehyde that includes nausea and flushing of the skin (Wall et al., 1992). If you have not experienced this effect then to give you an idea, acetaldehyde build up is thought to be partly to blame for the unpleasant effects of an alcohol
hangover. A treatment for alcoholism, called antabuse, also has a similar effect because it blocks the actions aldehyde dehydrogenase.

There are also ethnic differences in other enzymes that metabolise drugs (Bertilsson et al., 2002). A small proportion of Caucasians have a polymorphism of a liver enzyme that means they metabolise some drugs very quickly and so therefore have a poor clinical response (Johansson et al., 1993). On the other hand there are genetic variants that result in poor metabolism of some drugs and a higher likelihood of an adverse drug reaction (Bertilsson et al., 2002).

There is similar genetic variation in the genes that encode drug receptor targets. Polymorphisms in the dopamine transporter are associated with differences in response to amphetamine (Hamidovic et al., 2010) and polymorphisms of the adenosine receptor affect responses to caffeine (Yang et al., 2010). Treatment response to antidepressant drugs is also affected by genotype (Serretti et al., 2006). Patients with a particular variant of the serotonin transporter respond better to treatment with serotonin re-uptake inhibitors like Prozac.

Whether or not a patient experiences side effect of drugs is also influenced by genotype. Antipsychotic medication is more likely to induce the side effect of weight gain in individuals who have a particular variant of a gene that is associated with the control of food intake (Malhotra et al., 2012). Variations in dopamine genes may be associated with a motor side effect of antipsychotics, tardive dyskinesia (Bakker et al., 2006).

Implications

Research into genetic differences in drug responding is leading to a new approach to prescribing psychiatric drugs. The idea is that with genetic testing, health professionals can avoid prescribing drugs that patients are unlikely to respond to or may be likely to induce an adverse reaction. This approach to treatment is known as pharmacogenomics and is part of a wider move towards personalised medicine. At the moment many people are prescribed drugs like antidepressants that are not effective for them and it is only after several medications have been tried out that the right drug is found. With pharmacogenomics, this process will be speeded up greatly. Patients will not even have to take the drug to see if it works because doctors will be able to perform a simple and quick DNA test that will let them know how they are likely to respond.

PERSONALITY AND DRUG RESPONSES

Personality can influence placebo responding as it has been reported that people with a more optimistic disposition show a greater pain relieving response to a placebo than people with a more pessimistic outlook on life (Geers et al., 2010).
Acute responses to stimulant drugs vary according to personality traits. People differ in their reports of arousal and euphoria after taking amphetamines, with some people expecting stronger effects than others (White et al., 2005). One reason for this has been suggested to relate to similarities in neurochemical mechanisms that underlie drug effects and personality traits. (Depue and Collins, 1999; Drevets et al., 2001). For example, individuals who score high on a personality measure of reward sensitivity experience much greater effects of amphetamine on ratings of euphoria, vigour, arousal, elation and friendliness (White et al., 2005). One reason why this might be is that dopamine neurotransmission underlies both the subjective responses to amphetamine and trait reward sensitivity (Depue and Collins, 1999; Drevets et al., 2001). This may be significant because it is possible that individuals who respond more strongly to the acute effects of drugs like amphetamine are more likely to end up abusing them (Gabbay, 2003).

Variations in the response to alcohol have been linked to high rates of alcohol use disorders. In one study, young men with bipolar disorder reported less intoxication after alcohol than healthy controls even though they had similar breath alcohol levels. The authors suggest that the lower response to alcohol may contribute to the increased rates of alcohol misuse in young people at-risk for bipolar disorder (Yip et al., 2012). Evidence from animal models suggests that a low response to alcohol may be related to variation in serotonin genes but may also depend on early life experiences (Barr and Goldman, 2006).

**STRESS AND DRUG RESPONSES**

There are links between stress and drug responses. A strong association has been noted between early life stress and later alcohol abuse (Pilowsky et al., 2009). There is supporting evidence from studies of laboratory animals in which exposure to a stressor can be carefully controlled. A stressful environment increases the reinforcing effects of drugs of abuse whereas exposure to a stimulating environment reduces the reinforcing effects of drugs like cocaine (Stairs and Bardo, 2009). The effects of harsh environments early in life can have long lasting effects on drug responses (Kosten et al., 2000). However, social status is also important and is likely to interact with stressful conditions to determine drug responses. Animals of low social status within a group hierarchy are more likely to self-administer drugs of abuse (Miczek et al., 2008). In addition, social context modifies the propensity of monkeys to self-administer cocaine and this is related to changes in dopamine D2 receptors (Morgan, Grant et al., 2002). The effects of manipulating environmental conditions on drug responses has been conducted mainly with laboratory animals but there are implications for individual differences in responses of people to drugs of abuse.

**Implications**

Research into the role of personality, stress and social environment suggests that these factors interact to affect drug responding. Perceptions of stress that are mediated by individual differences in personality traits affect responses to drugs, especially drugs of abuse, and this may be exacerbated by the effects of poor social environment. High levels of anxiety combined with early life stressors might affect how a person first responds to taking a drug and then whether they carry on taking that drug. Understanding how different people respond to drugs and what makes some people more sensitive to the effects of drugs of abuse is likely to be helpful in predicting if someone is at risk of substance abuse and in designing more effective treatments for drug abuse.
ENVIRONMENTAL FACTORS THAT AFFECT DRUG RESPONSES

Genes are an important factor influencing drug responding and some but not all genetic effects map onto ethnic group status. However, some differences between ethnic groups in drug responding may be due to environmental factors such as diet. We will next discuss the role of these kinds of factors in drug responding. Let’s take two people who are very similar in body size, age, sex and ethnicity. These two people might still respond very differently to a drug. Why is this? There are many factors such as diet, drug taking history, the setting in which the drug is taken and the expectations they have about the drug, which will affect how they react.

Drug–drug and drug–food interactions

People usually do not take just one type of drug. This is often the case for patients who are being prescribed more than one type of psychiatric medication. For example, patients with depression often suffer from anxiety too and may be taking both antidepressant and antianxiety drugs. Recreational drug users also rarely take just one substance. Indeed, poly-drug use is the norm. This means that how a person responds to a drug may be influenced by interactions between drugs. Drug interaction is defined as the modification of the effects of one drug by the prior or concomitant use of another drug. Drugs can also interact with food constituents and herbal preparations in a similar way. Such interactions may occur accidentally or due to lack of knowledge about substances being taken.

There are three types of interaction that can occur. The effects can simply add together so that the total effect is the sum of the individual effects. This kind of interaction has been noted with alcohol and some benzodiazepine drugs that are used to treat anxiety (Linnola, 1990). Taking alcohol on top of a benzodiazepine may be dangerous for driving because both drugs impair motor coordination and the combination can result in increased likelihood of an accident (Maxwell et al., 2010). Some interactions are synergistic: the presence of a drug or food constituent actually potentiates the effect of another drug. In other words the effect of the drugs add up to more than the sum of their parts. Synergistic: drug reactions occur between antidepressant medications and an amino acid found in some foods called tyramine. Tyramine increases levels of noradrenaline in the body but these increases are normally dealt with by the enzyme monoamine oxidase that breaks down dietary tyramine in the gut. However, when someone is taking monoamine oxidase inhibitors as a treatment for depression, their ability to handle tyramine in the diet is vastly reduced and a small amount of tyramine can induce harmful increases in blood pressure (Da Prada et al., 1989). This is why people taking a monoamine oxidase inhibitor are advised to monitor their diet and avoid foods that are high in tyramine such as aged cheese and Marmite. Another type of interaction is where one drug reduces the effect of another, which is an antagonistic interaction. For example, the memory impairing effects of the main active constituent in cannabis, THC, are inhibited by another compound found in cannabis, cannabidiol (Morgan, Schafer et al., 2010).

Drug interactions can occur due to pharmacokinetic effects. For example, a drug or food constituent can alter the effectiveness of metabolic enzymes. Some fruits such as grapefruit contain compounds that inhibit enzymes that metabolise drugs like caffeine and benzodiazepines. This means that if grapefruit is consumed alongside these drugs then their effects are greater because their metabolism is reduced (Bailey et al., 1994).
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There are also pharmacodynamic interactions. If two drugs interact with the same neurotransmitter system then toxicity can result because of the combined effects. An example is the serotonin syndrome that can result if antidepressant medications like serotonin re-uptake inhibitors (SSRIs) are taken with St. Johns Wort, an over-the-counter medication for depression that also increases serotonin neurotransmission (Fugh-Berman, 2000). Serotonin syndrome involves sweating, tremor, flushing, confusion and agitation and is potentially life threatening.

DRUG EXPECTATIONS AND PLACEBO EFFECTS

A person’s history of drug taking can affect responses due to processes of tolerance and/or sensitisation as we discussed in Chapter 2. But a history of taking drugs can also have effects to alter expectations about the effects of a drug. So how someone thinks they will be affected by a drug is important in determining how they actually respond. In addition, these drug expectancies can become dependent on the context in which a drug is taken, meaning that the same person can experience different drug effects depending on where they take the drug.

People bring to a drug experience ideas about how they will react. This may be based on prior experience with taking the drug or on folklore and cultural beliefs. One person may have an expectation that they will be happy and sociable after alcohol whereas someone else might believe that alcohol makes them reflective and subdued. These expectations can affect how a person behaves. Similarly, someone who believes that a pill is a pain killer will experience more of an analgesic effect than someone who does not have that same expectation. This is known as the placebo effect. Beliefs about expected drug effects can affect responses in a positive manner whereby the drug can produce a greater response if it is believed to be effective, but they can also be negative such that people will experience less of a drug effect if they have low expectations. For example, negative expectations can increase pain sensitivity and attenuate the effects of analgesic drugs (Tracey, 2010). This is known as a nocebo effect.

KEY STUDY


Placebo effects can explain individual variation in drug responding because the expectations about the drug add to the pharmacological effects of the drug and may even involve activation of the same pharmacological systems. A classic study on this topic is the report by Levine and colleagues on the role of opioids in placebo effects. To understand this study we need to first know that opioids are involved in pain relief. Brain opioids are important in natural responses to painful stimuli, and synthetic opioids are used medicinally as analgesics. Levine and colleagues were interested in whether the expectation that a pill will provide pain relief is due to activity in the brain opioid systems that mediate actual pain relief. To do this, they decided to study the effect of placebos on real pain. The (Continued)
patients in the study by Levine and colleagues certainly had a painful experience because they had a tooth removed! This was not done for the experiment of course: it needed to happen anyway. The experiment was actually about what the patients were given after the surgery. They were told that they might receive morphine, placebo, or naloxone. Two hours after the surgery, some of the patients were actually given morphine, some naloxone, and some placebo. All the doses were given double-blind so that neither the participants nor the experimenters knew who had what treatment. Then, another hour later, some of the placebo patients received naloxone and some of the naloxone patients received placebo. Most of the participants stayed the course of the study and what happened was very interesting. At first, the patients receiving the placebo reported less pain than those who received the naloxone. However, on closer inspection only some of the placebo patients experienced less pain than the naloxone group; in other words there were placebo responders and non-responders.

In the next phase of the study, when some of the participants who had received placebo in the first phase were given naloxone, those participants who were placebo responders reported an increase in pain. The placebo non-responders were not affected when they subsequently got naloxone. The critical findings from this study are: 1) that some participants report pain relief even though they have been given a placebo; and 2) that the placebo effect is blocked by an opioid antagonist. These results

Figure 2a.3 An interesting example of a placebo effect has been observed in Parkinson’s disease patients. Patients were given a placebo pill and told that it was an antiparkinsonian drug which would help with their movement control. The researchers found that when the patients took the placebo and expected their motor control to be improved, there was a release of dopamine in their striatum that was measured with PET scanning. In another study, the activity of single neurons in the subthalamic nucleus was recorded before and after a placebo was administered to patients. Patients who responded to the placebo showed a significant decrease of neuronal discharge and a reduction of bursting activity of subthalamic neurons, whereas the placebo non-responders did not. The figure shows the responses for two representative patients (a placebo responder and a non-responder). The reports of the patients correlated with both the clinical assessment of a neurologist, and the activity of single neurons. These results suggest that the expectation of a benefit affects brain reward mechanisms and this may underlie some of the effects of placebos.

Source: Benedetti et al. (2005)
tell us that the expectation of pain relief is pain relieving because it involves the release of endogenous opioids. In other words, the response to the placebo was exactly the same as the effect of a real analgesic: activation of the brain’s opioid system.

More recently, brain imaging studies have confirmed that expectation of pain relief has effects in systems in the brain associated with pain responding (Wager et al., 2004; Zubieta et al., 2005). In addition, the expectation of receiving a stimulant drug enhances its effects, suggesting that expectations are likely to contribute generally to the effects of a variety of drug responses (Volkow et al., 2003). Furthermore, if a person has no expectations about the effects of the drug then the response may be reduced (Benedetti et al., 2011).

CONDITIONED DRUG RESPONSES

Learning about the effects of drugs on the body is one process that underlies placebo effects. When a person takes a drug they associate cues such as the sight of a pill or other drug paraphernalia, like needles, with the drug effects. After several pairings between the cues and the drug effects, the cues themselves can elicit drug-like responses. Pavlov was the first scientist to observe that stimuli that had been paired with morphine injections could elicit learned drug responses in dogs (Pavlov, 1927). Similar effects occur in cocaine addicts who experience cocaine-like effects when they have only received a placebo injection (Muntaner et al., 1989). This kind of effect may also explain why drug addicts often report craving in the presence of drug-related cues in real-world situations (Siegel, 1999). The cues trigger a drug-like effect that is experienced as a desire to take the drug. Seeing someone else taking a drug can also be a powerful cue and this makes it hard for people to give up drug taking if they are surrounded by others who are not abstaining (Childress et al., 1993). The importance of social context is also underlined by the finding that seeing someone else benefit from a pain relieving treatment increases placebo responses (Colloca and Benedetti, 2009).

Sometimes, exposure to drug-related cues does not elicit a response that is similar to the drug effect itself but triggers physiological responses that oppose the drug effect. In this case, when the drug is administered with drug-associated cues, its effects are reduced by the compensatory responses, and tolerance is observed (Siegel, 1977). An example would be compensatory response that develops to cues associated with alcoholic drinks. Most people are used to drinking alcohol in beverages like beer and the taste of the alcoholic drink elicits compensatory reactions that reduce the effects of alcohol. This means that when alcohol is served without these cues, say in a novel soft drink, the person is more affected by the alcohol than they would have been if they drank their usual beverage (Birak et al., 2010). This kind of
learned tolerance can also be specific to the context in which the drug is taken. Indeed the effects of alcohol on behaviour are stronger in a familiar drinking environment than an environment in which alcohol has not previously been consumed (Birak et al., 2011; Shapiro and Nathan, 1986). Learned tolerance may also explain some cases of overdose among drug abusers (Siegel, 2001). Taking a drug in an environment different from the one in which it is normally taken can lead to an overdose because the unfamiliar environment fails to elicit the compensatory responses that normally oppose the drug effect in the usual context.

Expectations about the effects of drugs are influenced by factors such as the colour, taste, and size of tablets. Red pills are associated with stimulant effects whereas blue pills are associated with tranquilising effects (de Craen et al., 1996). The more expensive a pill is thought to be then the more effective it is (Waber et al., 2008). This might explain why more expensive and invasive procedures are thought to be very effective placebos (Kaptchuk et al., 2006) and why people say that they get better pain relief from branded than non-branded pain killers (Branthwaite and Cooper, 1981).

**Implications**

Recent research on placebos suggests that expectations about a drug effect can bring about the same neurobiological responses as the drug itself. This suggests that drug-like effects can be elicited in the absence of any active pharmacological agent if the context suggests that a response will occur. This has implications for the clinical use of drugs because it suggests that the therapeutic context could enhance any patient response. So, having a positive interaction with a doctor and believing that a pill will offer symptom relief may result in changes in the brain that alter behaviour. The placebo effect also offers explanation as to why some people respond to magic charms and talismans. If someone expects to feel pain relief by following a ritual then it is likely that they will. An ethical dilemma that arises is whether doctors should be allowed to prescribe placebo pills without patients’ consent. Could placebo research be used to justify the existence of healing practice based on strange rituals? Some evidence suggests that the patient–doctor relationship is a more important part of certain placebo effects than the ritual of having an injection (Kaptchuk et al., 2008). So, even social interaction can have a powerful effect on drug responses. As we discover more about the nature of placebo effects and nocebo affects, the potential for the misuse of placebos and nocebos is obvious and is an important topic for debate.

**FURTHER READING**


This reviews the mechanisms underlying the placebo effect and discusses ethical issues associated with the use of placebos.


This provides evidence of the importance of social hierarchy in drug responding.

This presents a model to test the role of drug-associated environmental cues in drug responses.


This provides a comprehensive review of a range of evidence on the genetics of reponses to caffeine. It also provides a useful overview of the pharmacology of caffeine.