Pharmacology - Neuroadaptation

All drugs of dependence are associated with increased dopamine activity in the so-called reward pathway of the brain-- this pathway that gives us pleasure and tells us what's good for our survival. The overstimulation of the reward system when we use drugs of abuse, or develop an addiction, sets in motion a reinforcing pattern that teaches us to repeat the behaviour. Over time, as drug use and addiction continues and develops, the brain adapts to the overwhelming surges in dopamine. And it adapts by producing less dopamine, by reducing the number and activity of the dopamine receptors, and by essentially turning down the volume on the dopamine system.

Our brain strives for balance. In some respects, we can conceptualise it as constantly adapting and changing to function in a way that we can act and feel normal, a process called homeostasis. And when we talk about homeostasis occurring in the brain, we use the term neuroadaptation.

When we consume a drug, we alter the functioning of our brain. We upset the balance, and as a result, our brain tries to adapt. It tries to minimise the effect of the drug and get back to normal. If we use a drug frequently, then the brain will adapt to try and be in balance when the drug is present. But if we then stop taking the drug, our brain is no longer in balance, and it can take a really long time for the brain to re-adapt. In psychopharmacology, we refer to these processes as drug tolerance and physical drug dependence.

Tolerance occurs with the repeated administration of almost all drugs of abuse. However, it doesn't develop to all of the drug effects at the same rate or to the same level. Interestingly, tolerance often develops to the more unpleasant effects of the drug faster. So if a drug, when you first start using it, like heroin, for example, makes you feel nauseous and vomit-- you'll find that you develop tolerance to that rather quickly. You can develop tolerance quickly to one effect but slowly or not at all to another. For example, you may have developed tolerance to the nausea that occurs when you first use an opiate like heroin, but you'll never develop tolerance to the constipation or the pinpoint pupils that are also produced by heroin.

If tolerance is developed to one drug, then tolerance will develop to all of the drugs in the same drug class. What I mean by this is if you develop tolerance to heroin, you have also developed tolerance to the other opiates, such as morphine, codeine, and methadone. This is a phenomenon called cross-tolerance, and this phenomenon can be very useful for the medical treatment of physical dependence.

Tolerance to a drug has important implications for understanding drug use and addictive behaviour. The most obvious is that the user will have to keep increasing the dose to get that same effect that they had the first time they used. For example, in the case of heroin, experienced users may need to inject heroin as many as four or five times a day, and they'll need
to inject larger doses than they did originally, while a less-experienced heroin user may only need to inject once or twice a day with relatively small doses to achieve that same effect.

Once a high level of tolerance has developed and the individual needs to take more frequent and higher doses than initially, then it can be really difficult to come back down. Without tolerance, reducing the amount of drugs that are used and gradually stopping use altogether would be considerably easier and far more comfortable. Nevertheless, tolerance doesn't last forever, and it will drop down during periods of abstinence—periods when you're not using. So drug users will find that they need a smaller dose to avoid suffering an overdose.

Once we've developed tolerance to a drug, as the effects of that drug start to wear off, we may start to experience a range of uncomfortable symptoms—symptoms that may last from a few hours to a few days. We may start to feel depressed. We might feel some aches and pains. We might feel nauseous or experience flu-like symptoms. These feelings and these physical symptoms are known as the physical withdrawal syndrome. Now, this is an important concept, as it provides a source of motivation to keep using a drug. Because if we're feeling these rebound symptoms, these uncomfortable withdrawal symptoms, one way that we can stop them immediately is by taking the drug.

Withdrawal symptoms represent the unopposed consequences of neuroadaptation. That balance and normality that was achieved after the regular presence of a drug becomes unbalanced and dysfunctional when the drug is no longer present. So the signs and symptoms of the withdrawal syndrome are always the opposite of the effects of the drug. For example, if you use a drug that makes you feel euphoric or constipated or gives you pinpoint pupils, then the withdrawal syndrome will include depression, diarrhoea, dilated pupils.

If you take a drug that helps you sleep at night and makes you feel less anxious, once you've developed tolerance, the withdrawal symptoms are indeed not being able to sleep and feeling anxious. And we can stop that feeling by taking the drug.

An important factor affecting the severity of this physical withdrawal syndrome concerns the nature of the drug itself. Generally speaking, the longer a single dose of a drug produces an effect, then the less intense the withdrawal but the longer its duration. In pharmacology, we refer to a drug's half-life—that is, the amount of time it takes to eliminate half of the drug. The intensity or severity of the withdrawal syndrome is inversely related to the half-life of a drug. That is, the shorter the half-life, the more intense the withdrawal syndrome, but the shorter it will last. Whereas for drugs with a longer half-life, there will be a longer withdrawal syndrome, but they won't be as intense.

These characteristics of drug tolerance and withdrawal are important when we start to discuss the medical management of drug dependence, and we'll cover that topic in a later lecture. But let's sum up. Most drugs that are used and abused are done so because they produce a sought-after effect. All of the drugs of abuse have different chemical structures and different ways of working, but they share some factors in common.

And some of these factors include rapid and effective delivery to the brain, pleasurable activity and feelings associated with its presence in the brain, the release of dopamine in the reward pathway, neuroadaptation, and the development of tolerance, and the development of uncomfortable withdrawal symptoms when regular drug use is stopped. In the next few lectures,
we're going to look more closely at the structures in the brain that are associated with addiction, and we're going to ask ourselves, why do some people become addicted when others don't? We're going to look at some of the risk factors for addiction, and we're also going to discuss some of the factors that might protect us from developing addiction.