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**I = Interviewer**

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*Welcome to IFL Science – The Big Questions, the podcast where we invite the experts to explore the biggest mysteries of science with your host, Dr Alfredo Carpineti.*

**I: Since the dawn of our species, humans have been using chemicals to alter our state of mind. Drugs and alcohol have been used in rituals and medication, for inspiration and escapism, as well as a way to cope with the happenings of the world. Only in the more recent decades have we begun to appreciate the physiological effects that substances have on our brain through science. A discipline that continues to intrigue us with its mysteries and its potential to unlock new therapies that can help those who need it.**

**We are joined by neuropsychopharmacologist, Professor David Nutt. Professor Nutt thank you so much for joining us today.**

R: Thank you Alfredo, it's a pleasure to be on with you.

**I: So, the question that we are tackling today is all about how drugs and alcohol affect the brain and what we know, but before we start that, can you tell us a little bit about yourself?**

R: So, I am a psychiatrist, a psychopharmacologist, I treat patients with medicines, drugs, and I study how drugs work in the brain, and I use drugs to help me understand how the brain works.

**I: Fantastic. So let's start with the big question immediately. How do alcohol and drugs affect our brain?**

R: Well different drugs, including alcohol, work in different ways. So, for instance, alcohol works on a number of different neurotransmitters, chemical messengers in the brain whereas other drugs work on different ones. For instance, cocaine works on dopamine, psychedelics work on serotonin, opiates, heroin works on opiate systems, but alcohol works pretty much on everything.

**I: Is that the reason why they make us feel good at first? So, there are a lot of drugs and there are a lot of chemicals that we enjoy, caffeine for example, that are not classed as traditional drugs but what is the mechanism that makes us feel good, for example, when drinking alcohol or taking other drugs?**

R: Well, that's a complicated question. It depends on what you mean by good. So, I think there are two main directions that we can discuss this. The first is, if you want to get high, then the drugs that get you high are drugs like cocaine, amphetamine, alcohol to some extent and they

largely work through releasing dopamine. Dopamine gives you energy, drive, they make you become loud, chatty, over-active etc. But if you're using drugs to deal with distress and a lot of people do that, particularly drugs like heroin and to some extent, lower doses of alcohol are used by people to dampen down distress and they work differently. So, alcohol dampens down distress through the GABA system in the brain, the inhibitory system whereas opiates dampen down distress by increasing the endorphins system, which is an anti-stress, anti-pain system in the brain. So, different drugs work on different systems. There is some very interesting work done recently showing that in fact, where you take a drug has a big effect on whether you enjoy it or not. So, for instance, people usually take cocaine when they're out socializing and if you take cocaine by yourself in front of the TV it has not much effect, whereas if you take it out at a party it has an effect because you're actually doing things useful with it. The opposite is true of opiates, most people don't go to a party and take heroin because they just fall asleep in the corner, but they do take it at home where it chills them out and keeps them calm and deadens the pain of their lives. So, the location and the environment has a big impact as well as the pharmacology of the drugs.

**I: So, there is not just a chemical but also a psychological and social kind of factor?**

R: Absolutely. We call that "set and setting" and that's of course, extremely important for drugs like psychedelics where if you're going to take a psychedelic you need to be in a very safe, secure environment where you're protected and so you don't feel threatened or run the risk of being traumatized whereas other drugs, to some extent, alcohol is similar. One of the interesting discoveries with alcohol is that if you go into a pub expecting to drink alcohol and you're given a non-alcoholic drink, but you think it's alcohol, you start to get a bit high. Your brain can actually remember what it is like to drink alcohol and kind of reinitiate that state even if you're not given alcohol.

**I: Fascinating. Also, let's discuss some of the negative consequences such as hangovers and addictions. How do they present themselves?**

R: So, the general principle is you take a drug, you change your brain. The brain adapts, the brain doesn't like to be changed. The brain is a very sophisticated organ, like other organs in the body it likes to maintain equilibrium. If you change it, it tries to reset itself and that resetting process is a chemical process and it offsets the effect of the drug, but when the drug has disappeared from your system when you've washed out the alcohol or the cocaine, then your brain is set in the opposite state. So, whereas when alcohol was calming you, your brain turns on noradrenaline to keep you awake. When alcohol disappears from your system, when you've slept it off, you've got too much noradrenalin, so you have withdrawals, you have shakes and you have anxiety. With cocaine, the opposite happens. With cocaine, you blast the dopamine system for hours and then the dopamine system gets depleted until the next day you feel knackered because you haven't got enough dopamine going, so the effects of the drug lead to the consequences.

**I: You are actually working on a safer alternative to alcohol, can you tell us a little bit about that?**

R: Yes, what I've been trying to do is to pull together a team of people to help us find a functional alternative to alcohol. I like alcohol, most people like alcohol, most people like alcohol because it relaxes them and most people use alcohol in social situations, where there is a little bit of anxiety. You go to a party, you feel a bit tense, you don't know people, you're not quite sure what to do with your hands, so a drink is a way of calming yourself and helping facilitate social engagement. Now, we think, well, in fact, we know, we can mimic that using herbs. We have a drink called Sentia, which is an herbal drink containing herbs that have particular components in them that turn on the GABA system in the brain, which is the system in the brain which does reduce anxiety in social situations, which alcohol works on. What we're also now trying to do is invent an alternative molecule to alcohol that will only turn on the GABA system to enough extent to relax you and socialize you but won't have all the other consequences, because the thing about alcohol is the more you take, the more different systems it engages with. As I have already mentioned, alcohol in higher levels will start releasing dopamine but if you keep pushing the level of alcohol up it will also block other systems and that's why people have blackouts and terrible behavioral problems and also become addicted. So, if we just focus on the key elements of the desired effects of alcohol, which is sociability and conviviality, and relaxation, we can do that. We can invent molecules; we have done and we're now getting ready to put them through safety testing so we could potentially sell them as an ingredient so that drinks companies can then make their own cocktails that contain this alcohol alternative we call Alcarelle.

**I: So, you've just started testing. Can you tell us how far through this process is? Have you just started testing it on animals for safety or humans already?**

R: Well, we've obviously done some testing on ourselves because we needed to find out if it worked and now within the next few months we're going to have... currently we're looking at seven different molecules. By the end of this year, we will have decided on which molecule to manufacture in large amounts, because it's very expensive to make new molecules and to make enough to be safe, so we've got to be clear that we've got to put the best one through the safety testing and that's what...so by the end of the year we will have decided on our lead compound and then that testing will start next year, provided we raise money. We've still got to go out to investors.

**I: Fair enough. That sounds fascinating that we could have soon an alternative to alcohol that has all the social benefits but none of the drawbacks.**

R: Well certainly much less of the drawbacks. We can't say none, but absolutely, it would definitely be an advance because most people want to drink socially and we all know people who say, "Oh, I've just come for a couple of drinks." And then after the second drink, they lose control because something in the alcohol changes their brain and if we could stop that then there would be loads of people who don't binge and who go home at the right time and don't get into problems with their spouse because they've drunk more than they intended. So, if we could just help people drink the way they want to drink, that would be a massive advance.

**I: That sounds great. Do you think there is scope after you do alcohol to investigate this for other types of drugs? Something to get some of the interesting benefits but with less drawbacks?**

R: Well one of the models we're working on is a model that's been around for a long time in the field of opiate treatment. One of the pharmacological tricks we can use to minimize harm is to develop molecules which are called partial agonists. That means they have a ceiling effect. You take them and at a certain level of intake the effect plateaus out, it reaches a ceiling. Now, I got interested in this 30 years ago. I started working with a partial agonist called Buprenorphine and buprenorphine is now widely used as an alternative to methadone for heroin treatment. Why? Because it doesn't matter how much buprenorphine you take it will not stop you breathing and that's the safety benefit of buprenorphine is well proven, because it's a partial agonist. It was made for...so that concept is out there. One very well-known, well, this as a compound, although people don't know it's a partial agonist, is varenicline as an alternative to smoking. Varenicline is a safer way of taking nicotine, it's a partial agonist, it works on the nicotine receptor that allows you to stop smoking. It's an alternative to smoking so you avoid all the problems of burning tobacco etc. So, this concept is well established in other fields of pharmacology.

**I: That is fascinating. Thank you very much for taking the time and telling us a little bit about drugs and alcohol affect the brain and how there might soon be alternatives that can deal with the most negative aspects of those. Thank you very much.**

R: Thank you Alfredo.

*Thanks for listening to IFL Science, the Big Questions. Head over to [iflscience.com](http://iflscience.com) and don't forget to sign up to our newsletter so you don't miss out on the biggest stories each week. Until next time.*

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