Episode 84: MDMA: Why Does Toxicity Differ Between People?

Transcript

Welcome back to the top sub I'm Rebecca and I'm Rob and this week we're going to be taking a look at MDMA. There's a lot of myths about MDMA. I thought we could maybe look at a few myths before we dive in and actually look at what the evidence says and what the science says. Sounds good.

So have you heard any myths about MDMA? None come to mind I probably have but... A classic one that I remember growing up in the 90s was that MDMA puts holes in your brain. Oh that's an interesting one.

That was definitely something that I'm sure even we may have been taught that at school. And it's not true. Yeah. It's not true.

It doesn't put holes in your brain. Other myths? Pure MDMA is safe. I think I've heard that one.

That's also a myth. Yeah. MDMA has actually got a relatively narrow recreational dose versus toxic dose. Everyone reacts in the same way.

That I've heard and that's definitely not true. That's definitely not true and we're going to be looking at that this episode. And how about the come down is just because you've used all your serotonin? I mean that's false, right?

It's sort of partly true. There is some evidence that supports this. You do have with MDMA this huge serotonin release. But it's not just that your serotonin has been depleted.

You then get receptor downregulation. So there's a little bit more to it than that. But it is a partly true myth. And finally water fixes everything.

I mean I don't think water fixes everything. With regards to MDMA toxicity. No, that's not true. No, that's definitely not true.

And actually MDMA is interesting because it can actually cause water toxicity. Before we dive into today's episode, if you want to stay up to date with our content, you can find us on Instagram at @the_tox_lab. We also have a page on LinkedIn and we're fairly active over there. And for those of you who don't use social media but still want to get in touch with episode suggestions or comments about episodes, you can check out our new website at thetoxlab.co.uk.

So MDMA, I'd say probably one of the most famous recreational drugs. I'd say so, yeah. Certainly growing up in the 90s, it was something that I was aware was definitely a thing. Much more so back then than drugs like cocaine.

And it's never really gone away. It's always been a party drug on the scene. And it's got all sorts of street names. The Love Drug is what it's known as sometimes.

Oh, I've not heard of that one. Have you not? No. And that's interesting because it's due to its reputation of being probably the world's friendliest party chemical.

Yeah. And how it increases people's socialization. But what's interesting about MDMA is it's actually got some really, really interesting pharmacology. It doesn't just affect your brain, but it also affects the way that your body clears it.

And we're going to look at that phenomena a little bit later on. But also, MDMA can be quite toxic. And it is a drug that has, as I said earlier, relatively narrow window between recreational dose and dose that can lead to serious medical outcomes. And we're going to be exploring some of that this week.

And what does MDMA do? And how does it work? In your brain, you've got these serotoninergic brain cells. And they talk to one another by releasing serotonin.

And normally, serotonin gets released into the gap between the brain cells. We call that the synapse. And another transporter then essentially reabsorbs it. MDMA sort of makes it do the opposite and kind of dumps serotonin into that synapse.

And so you get this generalized increase in serotoninergic activity. And these brain cells that all fire on serotonin all suddenly get revved up relative to the rest of the brain cells in the brain. And it also releases dopamine. It's not entirely specific.

So you also then get this increase in reward and energy. And as a side effect, you also get this oxytocin release. And oxytocin, people think of as the bonding hormone. And obviously, as we may know, it's a big party drug.

MDMA causes heat production and can reduce heat loss. And you combo that with the environments. It's typically taken in, I don't know, loud raves in a packed warehouse. That can be a real problem.

It can actually lead to inappropriate anti-diuretic hormone release. So people retain water and people can drink too much. Don't forget, they're also hot. They're sweating.

So the natural response is to reach for the water bottle. And that can actually lead to dilutional hyponatremia, low sodium. You can get serotonin toxicity itself, this serotonin syndrome. And ultimately, it can cause cardiovascular failure.

And there's another dark side to MDMA that I think is often less well understood. And that is that you often have to pay back that energy and that serotonin. And so the come down can be particularly severe with MDMA. Not only have you had that big serotonin release and so your serotonin reserves may be a bit depleted.

But that big release has also led to the receptor downregulation. And sadly, there is this phenomena, the scene on the sort of Blue Monday, whereby people have been out partying on the Friday and by Monday, they're just so depressed from the after effect of the drug wearing off and the knock-on effect it's had on their brain chemistry. And sadly, that is a day where sometimes people do take their own lives. So why don't we look at a typical case first?

We found this case report in the literature and it describes a classic MDMA overdose. A 35-year-old male with no known past medical history presented to the emergency department of being brought to the medical tent at the Electric Daisy Carnival Ray Festival with altered mental status and hypothermia with a temperature of 42.7 degrees Celsius after taking MDMA with his partner. The patient received 200 milligrams of Dantraline, which binds to the ryanodine receptor type one, blocking calcium release within muscle cells leading to skeletal muscle relaxation. And this is used to help bring down temperatures.

And he was also placed in an ice bath for approximately 30 minutes. So one of the knock-on effects of that serotonin release is overstimulation of these muscles leading to this rigidity and hypothermia. At

the festival, he was made to have seizure-like activity and was given five milligrams of Midazolam and he was sedated and intubated using rock uranium and ketamine. On his way to the hospital, he was found to be hypotensive and was given Cal saline and IV venylephrine.

When he arrived at the emergency department, the patient was hypothermic with a temperature of 31.1 degrees Celsius and he was given warmed normal saline but continued to be hypotensive. The urine toxicology screen was completed and this showed that he was positive for THC and amphetamines. Other laboratory tests were also conducted which showed that the patient was in multi-organ failure. He'd had a stroke leading to seizure activity, he had an acute lung injury leading to respiratory failure and acute kidney injury leading him to require renal replacement therapy, rhabdomyolysis and a coagulopathy.

So really quite unwell, all as a result ultimately of MDMA toxicity. A lot of that I think is probably through the muscle issue, right, the release of muscle enzymes leading to the AKI. Yeah, so with MDMA, because you get that hypothermia, you also get oxidative stress and rhabdomyolysis and muscle breakdown. All of that assaults the other organs and leads to this multi-organ failure.

So after eight days in the ICU, the patient was downgraded to an intermediate care unit, neurological exam showed intact gross cranial nerve function without any focal deficits, but he needed physical therapy due to weakness in both his upper and lower extremities. He was discharged after 20 days and was continued on hemodialysis as an outpatient due to his renal failure. And did his renal function ever recover? They didn't say, I don't think they followed up long-term.

Given how unwell he was, I think he was probably lucky to survive. Yeah. This is a classic case of MDMA toxicity. Now, we should say actually that a lot of people probably take MDMA in party situations and most of them don't end up in hospital.

Yeah. But it is well-documented that it can happen. Hypothermia is one of those side effects that you see with MDMA use. It's probably multifactorial.

As we say, a lot of people are using this in dance environments where they're moving. Yeah. You get an increase in metabolism from the dopamine effect, similar to stimulants in general. You also get vasoconstriction and serotonin also seems to have a regulatory effect on the hypothalamus.

And unfortunately, once your body temperature gets above, I don't know what, 40 degrees, everything starts going wrong. Yeah. Enzymes are built to work at 37 and you can push them a little bit to 38, but once you start getting to 40, you start to see muscle breakdown, metabolism starts going sideways. That's where you see the kidney injury, clotting abnormalities.

Basically, the body really doesn't work very well. Above 40 degrees. And that's one of the risks with MDMA. So why don't we turn now to the metabolism of MDMA and how that can affect, how people can break this drug down and how that can have a role.

So in vitro studies have shown that most psychostimulants like MDMA are metabolized by the enzyme CYP2D6. And this is a polymorphic enzyme, which basically means that the enzyme can come in different forms. So some people have a version that works better and some have a version of the enzyme that functions poorly or doesn't function at all. And there are over 70 alleles of CYP2D6 and the combination of these leads to four different phenotypes.

So there's a poor phenotype where you lack two functional alleles, an intermediate where one exhibits reduced activity and the other one is non-functional, or where you can get two that exhibit reduced activity, and an extensive phenotype where one or two functional alleles are present, and an ultra-rapid metabolizer phenotype where you get gene duplications of functional alleles leading to an

increase in protein expression of the enzymes, you basically have more of it around. So in other words, people can break drugs down at various different rates. Yeah, and the prevalence of these different phenotypes can vary in different groups.

This varies with ethnicity, which is quite a common thing. So five to 10% of the Caucasian population are poor metabolizers with CYP2D6 and that makes them quite vulnerable to not being able to break down certain drugs and then leading to negative effects basically. So how does CYP2D6 relate to MDMA? So it's involved in the O-demethylenation of MDMA leading to the production of 3,4-dihydroxymethamphetamine, or HHMA.

Approximately 10% of MDMA undergoes N-demethylation via another CYP enzyme, so like CYP1A2, to produce MDA which can then undergo demethylenation via CYP2D6 to produce a different metabolite. And then these metabolites often undergo methylation or glucuronidation to be excreted. MDA is a drug in its own right. It's not something you see very often these days, but back in the 90s, it was reported to be in circulation in certain ecstasy tablets.

It's interesting actually, MDA. It seems to have possibly more neurological toxicity than MDMA. Oh, okay. So MDMA acts as a substrate and a potent mechanism-based inhibitor of CYP2D6.

So this mechanism-based inhibition occurs shortly after a single recreational dose and it activates most of the hepatic CYP2D6 enzyme within two hours, and it only returns to a basal level of activity after at least 10 days and requires de novo synthesis of the enzyme. So you need to basically reproduce the enzyme to regain your activity. So despite the original phenotype that an individual may have, for example, a poor metabolizer status or an ultra-rapid metabolizer status, individuals all appear to have a poor metabolizer status. And previous clinical trials have shown this phenomenon in 67% of male subjects and 100% of female subjects.

And this may mean that those taking repeat doses of MDMA or other drugs that rely on CYP2D6 metabolism may be an increased risk of overdose. And so this is a bit like a shredder, right? A paper shredder. Yeah, kind of.

It's good. You put a sheet in, it shreds it, everything's fine. Then MDMA comes along, which is a piece of paper with a staple in the corner. It gums up the shredder and suddenly all of these sheets of paper keep piling up.

Yep, that is a good analogy. I like that. And this is a problem, isn't it? If you're out on a night out and you take one MDMA tablet and you have a great time, and then a few hours later you take a second MDMA tablet, the two doses could be identical.

The exposure to you in the brain could be very different. Yeah, exactly. So those with the poor metabolizer status have been shown to display increased plasma concentrations and are at an increased risk of developing hypothermia. Side effects of MDMA use may also be linked to low activity of CYP2D6 with individuals that are poor metabolizers having an increased induction of plasma hypo osmolality, hyponatremia, and increased ADH after taking MDMA.

And this is the water toxicity effect that we've mentioned already. What is interesting though is that only 30% of MDMA metabolism is mediated by CYP2D6 and other CYP enzymes are able to catalyze the OD methylation of MDMA. So it isn't all reliant on this one enzyme. So there is a bit of a debate as to how much this plays a role in toxicity.

That's fair, yeah. So how relevant is this on the ground scale of metabolism? And there are different phenotypes of other CYP enzymes. They're known to be highly polymorphic enzymes.

So I imagine the impact it has also depends on the phenotype that you express for the different CYP enzymes that can kind of take over this metabolism. If you're a poor metabolizer for all of them, then that obviously plays a bigger role than if you've got one that makes you an ultra rapid metabolizer and kind of compensate for this loss. Yeah, okay. So in other words, it's pretty unpredictable.

Yeah. At least between people. Two people could take the same dose and have two very different half lives and clearance rates. Now we need to look also at some of the other variables.

Ecstasy tablets are notoriously variable in terms of their MDMA content. And that in itself throws a spanner in the works, doesn't it? Two people could take two tablets that look identical and they've got two different doses within them. Similarly, two different people could have different metabolism.

One of them could have taken MDMA a week earlier and may have reduced metabolism as a result of their last dose. All in all, it just makes the whole situation really, really hard to predict, right? Yeah, for sure. And on top of that, the way these tablets are dosed, they are tablets, people swallow a whole tablet.

Yeah. And then it takes a little while for that tablet to take an effect. Yeah, and if you're not aware that there might be a delay between ingestion and effect, that does open up the risk of redosing prematurely and then being hit with double the amount that you were expecting. That has definitely happened.

And actually a paper that we haven't prepped to talk about but came out a few years ago looked at the dissolution rates of MDMA tablets. Oh, okay. And showed not only does the MDMA content change, but also the rates of dissolving of different tablets can be variable. Yeah, that's really true.

I hadn't thought about that being a factor. Yeah, it was a really interesting study. I'll drop a link below the episode. I think this all in combination is potentially what leads to that situation where you've got two people, they all take the same tablet.

One of them has a great night, one ends up in ITU. And there seems to be no prediction as to why. Yeah. I think this unpredictability does really highlight the need for good harm reduction practices.

I think that if people do choose to take MDMA despite all the risks, and we know people will, there are things that people can do to help reduce those risks. And I think that's really, really important that that information gets to users and that people kind of engage with that because it does have the real potential to save lives. Clearly not doing MDMA is the safest thing, but if people are going to do it, then there are ways of reducing that risk. Don't mix it with alcohol.

Don't mix it with other drugs. Don't repeat dose. Wait until that tablet's taken effect. That sort of thing.

It's tricky, isn't it? Is it MDMA that causes the toxic symptoms and gets people in ITU? Or is it the fact that people are taking this drug at a rave with loud music and lots of bodies and lots of dancing? Well, in terms of leading to like the hypothermia and then it probably doesn't help.

It's really unfortunate, isn't it? You've got the effects of this drug and the environment that it's in really doesn't help at all. Yeah, it just compounds the effects, isn't it? Certainly compounds the sort of the physiological toxic effects of potential leading to rhabdo and hypothermia.

So controversial question. What is more dangerous, MDMA or horse riding? That is a controversial question. I feel like my answer is quite controversial.

I think horse riding probably puts more people in probably to you than MDMA does. So this was actually a quote from Professor David Nutt. He highlighted this point. Not to encourage MDMA use.

Don't misinterpret what we're saying here. This isn't to encourage MDMA use. But when you look at risk stats, people's perception of risk stats are often skewed. And you're right, at the time, risk of serious injury from horse riding, one per 350 riding sessions, risk of serious injury from MDMA.

We think, we don't know, we don't have good data on this. We think about one adverse event per 10,000 uses. So relatively, quite a bit less risky. Now, obviously, various safety precautions happen with horse riding, such as helmets and training and so on.

And you don't have that regulation with MDMA. So this isn't to encourage MDMA use. But it raises the point that risk perception, I think is often poorly communicated. Yeah, it's so hard when you're looking at statistics and someone just gives you a number of like, oh, there's this many incidents per this many thousand people or whatever, and trying to put that in perspective, against other things.

It's quite hard for lots of people to do. I really struggle with it. And I have had training in statistics and come from a science-y background, but it's still, it's a challenging concept to get your head around. Yeah, I think that's fair.

And, you know, for balance, as I say, MDMA is definitely not without risk. And there are definitely ways in which people can reduce that risk if they choose to take MDMA. But ultimately, the only truly safe way to take MDMA is not to take MDMA. And that applies for every drug.

Absolutely. Well, I hope you've enjoyed listening to us this week. As we explore some of the sides of MDMA, do, as always, give us a like, give us a follow. And as we said, jump on, give us a rating on Spotify.

We would love that. Hope you all have an amazing week and we'll see you next time. Bye.