THE TOX LAB

Podcast Transcript

Episode 13: Mice, Music, and Methamphetamine Toxicity

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TRANSCRIPT

Welcome back to The Tox Lab. I'm Rebecca.

I'm Rob. What happens if you mix methamphetamine, The Prodigy, and mice?

This week we're going to be looking at a study that tried to explore exactly that, as well as the sensational media response that followed.

So Rebecca, why don't you introduce us to the study?

This week we're going to be talking about a study from the University of Cambridge published in 2001. The paper is titled Methamphetamine toxicity in mice is potentiated by exposure to loud music.

In this study, the researchers wanted to assess whether loud music affected how toxic methamphetamine was. It was already known that increased ambient temperature can raise core body temperature and worsen methamphetamine toxicity in mice and rats, so they wanted to see whether loud music might have a similar effect.

For the study they used music-naive mice, which I do feel a bit sorry for. These mice had apparently not been exposed to music before the experiment.

It is a sad little life.

They were placed in an open field for 30 minutes to acclimatise, then given a subcutaneous methamphetamine injection at 7.5 milligrams per kilogram. That dose was chosen because it was the highest dose in pilot work that did not kill any mice.

The mice were then returned to the open field for three hours and exposed to four different sound conditions. The first was silence, which still had an ambient background noise of about 55 decibels. Then there was loud white noise at 95 decibels, loud rave music, for which they chose The Prodigy, and loud classical music, specifically the Allegro movement from Bach's Violin Concerto in A minor.

I don't know whether that was a personal favourite of the study designers.

Maybe. The music had been edited so that it maintained a consistent tempo and volume, and it was repeated continuously so there was no variation from tracks ending and starting.

So: methamphetamine, a powerful stimulant; The Prodigy, iconic rave music; and then a classical control.

If you've never listened to The Prodigy, I would recommend it. Have you got a favourite track?

I do quite like Firestarter, actually.

That is a solid choice.

But importantly, they did also have control conditions: silence, white noise, and classical music. So the aim was really to compare whether The Prodigy made methamphetamine toxicity worse than silence or non-musical loud noise, and whether there was something specific about music itself.

Exactly.

They looked at a lot of things in this study. They assessed seizure activity and locomotion in the open field. The open field was divided into squares, and they monitored how often and which squares each mouse entered over time.

They also looked at stereotypy, meaning repetitive movements such as circling, chewing, or jumping, which can be associated with impaired behavioural inhibition and altered affective state.

To make the analysis easier, they pooled the data into 30-minute bins.

For locomotor activity, the control mice that received saline were not affected by the sound condition. Whether it was silence, white noise, classical music, or The Prodigy, most of them were asleep within 30 minutes.

So even with The Prodigy blasting, they just had a nap.

Apparently so.

The mice given methamphetamine in the silence or white-noise groups showed what you would expect from methamphetamine intoxication: an initial period of hyperactivity followed by stereotypic behaviour and altered place preference, with reduced locomotion overall, before later returning to a more hyperactive state.

So they kind of peaked and then crashed?

Essentially, yes.

What about the music groups?

The mice exposed to loud music rapidly became stereotypic and remained so for more than two hours. They had significantly reduced locomotion compared with the white-noise group, so they really were moving around much less in the usual sense.

They also showed different repetitive movement patterns. Mice exposed to music were more likely to display backwards walking and circling, which was not seen in the same way in the white-noise or silent groups. When they were listening to The Prodigy, they also tended to move in tighter circles.

I don't know whether that depends on the track.

It might.

The researchers also looked at place preference within the open field. Mice listening to The Prodigy or the classical music spent proportionately more time in the inner squares. This was significant for the Prodigy group at 30 minutes.

The authors suggested that place preference might reflect changes in anxiety, although I am not completely convinced I would feel less anxious listening to The Prodigy on repeat.

That may depend on your taste in music.

True. And we should remember these mice were music-naive, which is probably relevant.

The researchers also looked at seizure activity as a marker of toxicity. Some mice in the methamphetamine groups had seizures, but there were more seizures in the mice exposed to loud music than in those kept in silence. There was also increased mortality in the music groups.

So in other words, the mice exposed to The Prodigy, but also the classical music, seemed to do worse than the silent group?

Yes. The effect was not simply "music equals no effect and white noise equals the same." There did seem to be something about the loud musical conditions that worsened outcomes.

Following the behavioural part of the experiment, the researchers then looked at markers of brain damage. Mice were killed on days 1, 3, 7, 14, or 35 after the experiment, and serial sections of the brain were examined for reactive astrogliosis using GFAP staining.

Reactive astrogliosis is basically a marker of injury response in the central nervous system. You can see it in things like stroke, epilepsy, and neurodegenerative disease, so it is a reasonable marker for neurological insult.

All the mice given methamphetamine showed increased GFAP staining, regardless of whether they had seizures. In the silent group, the damage peaked around day 3, then decreased significantly by day 7 and was gone by about two weeks.

The white-noise group also returned more or less to baseline by around two weeks. But in the groups exposed to music, either classical or The Prodigy, GFAP staining was still elevated at day 7 and took longer to resolve.

It is worth noting that six of the mice exposed to music had died within 24 hours, and their brains were not examined. So in a sense, the measured neurotoxicity may actually be an underestimate, because the animals with the worst outcomes were not available for follow-up histology.

So in other words, mixing music and methamphetamine looked worse than methamphetamine alone, at least in this model.

Yes, at least in this model.

Did the authors go into why they thought this might be happening?

They did not give a very satisfying explanation for the brain injury side of it, but they did discuss how methamphetamine alters neurotransmitter release and how that might relate to some of the observed behaviours.

Methamphetamine causes release of dopamine, serotonin, and noradrenaline. Dopamine-driven effects can include forward locomotion and head-bobbing, which were seen more in the silent and white-noise groups.

Serotonergic effects in rodents can include things like forepaw treading, wet-dog shakes, and Straub tail, where the tail is carried upright. Those were only seen occasionally.

Interestingly, the backwards walking behaviour seen in the music groups may require both dopaminergic and serotonergic involvement, so the authors speculated that the music condition might somehow have altered the balance of those signalling systems.

This study was carried out some time ago now, and at the time it generated a lot of sensational media coverage. One headline I found was something along the lines of "Scientists kill mice with dance music."

Which is definitely a leap.

It is. Technically, some mice exposed to dance music did die, but that is not really a fair summary of the study.

There was also criticism from animal rights campaigners, and to be fair their argument was not unreasonable. They basically said we already know that drugs and loud music can be harmful, so why do we need to do a study like this in animals?

And that is a legitimate ethical question.

It is. The team also received criticism because the work appears to have gone beyond the kind of licensed scope people expected from that animal facility. So there were concerns not just about the idea of the experiment but about the governance around it as well.

I guess the big question is whether the study was scientifically justified, and I am not sure the answer is clear-cut.

On the one hand, the data are interesting. They suggest that loud, repetitive music may worsen stimulant toxicity in this animal model, whether that music is rave music or classical music.

On the other hand, there are obvious ethical concerns, and it is not clear how well any of this translates to humans.

Exactly. You cannot just assume the same thing applies to people at a nightclub, although that is obviously the scenario the paper makes you think about.

Could it apply to other stimulants as well? We are talking about methamphetamine here, but people more commonly think of ecstasy or other stimulants in loud music settings.

Potentially, yes. That is one of the reasons the paper drew so much attention. But again, we are extrapolating from a mouse model under quite specific conditions.

It is also worth noting that although the music was loud, about 95 decibels, it was still quieter than many real club environments.

So if the effect were real in humans, it is possible real-world settings could be even more extreme.

That is a fair point. On the other hand, the mice were given quite a large methamphetamine dose, so the relevance to typical human recreational exposure is not straightforward either.

Exactly. They were deliberately working near a dose that would produce marked toxicity.

Another interesting question is whether the result would have been different with different types of music. Jazz, for example.

We do not know. The classical music was edited to match tempo and continuity, so the study does suggest that it was not specifically about rave music as a cultural category. It may have been more about loud, repetitive auditory stimulation.

Which sounds quite stressful when you say it out loud.

It does.

And I suppose another question would be whether there is a dose-response relationship with the sound itself. If it were louder, would it be worse?

Possibly, but it is hard to imagine how you would ethically investigate that.

Exactly. You are not really going to put human volunteers on methamphetamine in a controlled sound exposure experiment.

That would be difficult to get through ethics.

Very difficult.

So what does the study actually reveal about the dangers of drug use in high-sensory environments? Does it tell us anything useful at all?

I think it suggests there may be some interaction between environment and toxicity, even if we do not fully understand it. Set, setting, and sensory environment can matter with drugs, but we do not often think about the mechanistic basis for that.

As toxicologists, it is certainly not something we normally factor into routine interpretation of stimulant toxicity.

No, not at all.

So I think the conclusion is: what happens if you mix methamphetamine, mice, and The Prodigy?

The answer is: possibly worse toxicity, possibly more brain injury, and certainly a very controversial experiment.

Even if the ethics are debatable, the results themselves are interesting.

Yes, but I do not think there is any obvious justification for doing a big follow-up animal series on different genres and different volumes. It does not really seem warranted.

I agree.

I think we are going to wrap it up there. I hope you have enjoyed listening this week.

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Thank you all so much for listening. Hope you have had a great week, and we will see you next time. Bye.