Episode 65: Monoamine Oxidase Inhibitors and Psychoactive Drug Interactions

Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're going to be taking a look at monoamine oxidase inhibitors. We've mentioned them a little bit on the podcast when we were looking at the effects of various antidepressants.

The monoamine oxidase inhibitors have got a really really rich history. They were the first real class of antidepressant drug and this story we have told whereby they were discovered accidentally because a tuberculosis drug was in fact also doubled up as an antidepressant. It worked as a monoamine oxidase inhibitor and whilst that bit was discovered somewhat by accident when the effect was actually figured out a series of pharmaceutical versions that were pure monoamine oxidase inhibitors were developed and these drugs were really transformative. There wasn't an established medical treatment for depression prior to these.

People were institutionalized, people were sedated with barbiturate drugs but there wasn't an antidepressant available and so these drugs actually saw quite a lot of use but they did come with a big problem. There were quite a few serious adverse effects noted. In particular patients would sometimes develop profound hypertension, high blood pressure and sometimes it was even fatal and one day somebody collated some of these cases and they realized there was a common link linking all of these adverse effects and that common link bizarrely was cheese and so we need to understand a little bit about what these drugs do.

They inhibit the enzyme monoamine oxidase. Monoamine oxidase has a few functions in the body.

The reason you get antidepressant effects is because monoamine oxidase breaks down monoamine neurotransmitters so serotonin noradrenaline dopamine are all broken down by monoamine oxidase and by inhibiting that enzyme you get increasing amounts of these neurotransmitters but monoamine oxidase is also really important in the gut and quite a lot of foods contain dietary biogenic amines and if they make it through the gut to the bloodstream they can have an effect including this hypertension and the culprit in cheese was this compound tyramine and tyramine has this effect on neurons where it can cause this dumping of noradrenaline into the synapse and so tyramine can induce this huge adrenaline surge effectively and it's not just cheese is it?

It's a few different foods which are quite high in tyramine cheese, pickles, olives, cured meats. So all my favorite components of the charcuterie board? Exactly charcuterie board big no-no on monoamine oxidase inhibitors. Very sad times.

And so this cheese effect really did limit the use of these drugs. People had to undergo strict diets to avoid all the best cheeses and a little while later SSRIs which we've talked a lot about were invented fluoxetine being the first big one that got marketed and so monoamine oxidase inhibitors really fell out of use. They didn't entirely go away they are still used very occasionally usually in the context of severe treatment resistant depression where other measures haven't worked but they're not considered to be a first line drug.

And this week we're going to be taking a look at some of those drug interactions and why monoamine oxidase inhibitors can sometimes be bad but actually may not be as bad as perhaps we've thought over these last 20 years or so. So this first thing we're talking about today is a massive review article looking at the potential interactions between monoamine oxidase inhibitors and commonly used psychoactive substances. This was quite an interesting review article whereby the premise here was to explore monoamine oxidase inhibitors and their interactions with various substances.

And the reason for this is that substance use disorder often presents alongside depression and the current conventional wisdom is that because of the monoamine oxidase inhibition and drug interactions these drugs are not really suited for people with substance use disorder and so therefore you've got individuals who have got substance use disorder a depression alongside it and you've got a limited toolbox with which to treat the depression. And this review really set out to explore whether that conventional wisdom that these drugs could never be used with substance use disorder in fact whether that's actually supported by the evidence.

So Rebecca why don't you take us through some of the drugs that were explored in this review article. So the first drug we're going to talk about is alcohol and tyramine which you talked about earlier is present in a variety of alcoholic beverages and this can interact with monoamine oxidase inhibitors. Substantial tyramine concentrations are present only in some types of beer and very few wines but the tyramine content of the alcohols don't correlate with the alcohol content and some non-alcoholic beverages have quite a high tyramine content.

So in terms of its interaction with alcohol it's more the tyramine that's in some of these brewed drinks and I'm guessing maybe raw beverages things like cloudy beers and sour beers and things like that might be the higher culprits. Hydrazine which the monoamine oxidase inhibitor can albeit very rarely induce an idiosyncratic and potentially fatal hepatotoxicity and in alcohol use disorder the risk of this is enhanced so mixing those isn't necessarily the best idea. Because they've got other liver stuff going on essentially. So the next class of drug I'm going to look at is classic hallucinogens.

So these are partial agonists at 5Hg2a post-synaptic receptors and effects will vary due to the structural diversity of classic hallucinogens. And they mimic the effect of serotonin effectively don't they? Yeah simultaneously ingesting certain classic hallucinogens and pharmaceutical monoamine oxidase inhibitors could intensify or prolong hallucinogenic effects but chronic monoamine oxidase use before consuming a classic hallucinogen can attenuate its effects. So I'd really encourage you guys to go and check out this paper if you're interested they detail many different drugs within each class we're talking about.

So I've only picked one which is LSD and several studies have shown that treatment with monoamine oxidase inhibitors substantially diminishes the psychological and physical effects of LSD. Possible explanations of this include LSD competition with elevated endogenous serotonin and downregulation of the post-synaptic 5Hg2a receptors. Interestingly short term exposure to monoamine oxidase inhibitors did not have the same dampening effect of LSD.

Moving on to non-classical hallucinogens and I've selected MDMA as an example of this and this acts primarily by reversing the serotonin transporter leading to non-exocytotic release of serotonin with lesser effects on dopamine and noradrenaline via the dopamine transporter and the noradrenaline transporter. And this is potentiated by the inhibitor of vesicular monoamine transporter 2 which increases cytoplasmic monoamine availability for transporter mediated efflux. And in humans there have been several reports of serious side effects including serotonin toxicity and hypertensive urgency from combining MDMA and monoamine oxidase inhibitors.

And this makes sense doesn't it because MDMA actually increases the amount of serotonin in the synapse monoamine oxidase inhibitors would do the same thing. So one case in the literature involves a 50 year old male who experienced marked hypertension, diaphoresis, altered mental status and hypertonicity five to six hours after taking a relatively low dose of 50 to 100 milligrams of MDMA with a monoamine oxidase inhibitor. Also in a survey of MDMA users one in 25 reported intentionally combining MDMA with moclobamide which is a monoamine oxidase inhibitor to potentiate MDMA's effects or reduce the duration of the post-recovery period.

But this combination does come with higher risk of side effects such as muscle rigidity, involuntary eye movement, dizziness, headaches and excessive sweating. So moving on to opioids. Opioids can also cause serotonin toxicity when combined with monoamine oxidase inhibitors, but this risk varies depending on the class of opioid we're talking about. For example, tramadol, which has weak mu opioid receptor agonism, can also act as an inhibitor of noradrenaline and serotonin reuptake and is contraindicated with monoamine oxidase inhibitors.

There is also a case in the literature of delirium that was reported in a patient following monoamine oxidase inhibitor and tramadol use, and there is one reported case of associated serotonin toxicity in the literature which involved a fatality secondary to overdose of tramadol, clomipramine and moclobemide. Tramadol is quite unusual isn't it because it's an opioid but it has also got this serotonergic effect. Moving on to sedatives. Benzodiazepines can lower blood pressure and in combination with monoamine oxidase inhibitors could lead to monoamine oxidase inhibitor-induced postural hypotension.

There are also two case reports in the literature where individuals developed gross oedema within weeks of starting chlordiazepoxide in combination with phenelzine and isocarboxazid, and discontinuing the monoamine oxidase inhibitor and treating with furosemide did resolve the oedema.

So finally when looking at stimulants caffeine can cause antagonism of adenosine receptors and weakly inhibits monoamine oxidase A and monoamine oxidase B and there's one case report in the literature that was noted in this review of extreme jitteriness and irritability from combining Ipranizid which is a monoamine oxidase inhibitor with 10 to 12 cups of coffee daily which resolved after a reduction to two to three cups but I mean 10 to 12 cups of coffee daily would probably make anyone jittery. That is quite a lot of coffee isn't it and I drink quite a lot of coffee.

Another patient also experienced significant insomnia from a single cup of coffee whilst on isoniazid which did resolve after coffee cessation so. So the second half of the review looked at efficacy data of monoamine oxidase inhibitors in patients with substance use disorders as it's believed because monoamine oxidase inhibitors can enhance dopaminergic transmission this could help in treating substance use disorders. So when looking at alcohol use disorder they identified five case series and clinical trials which have investigated the efficacy of monoamine oxidase inhibitors for alcohol use disorder.

One study from 1967 compared isocarboxazid, chlordiazepoxide and a placebo which found no statistically significant differences in the global measures of improvement including reduction in alcohol use or abstinence for six months.

A small 1960 case series described a favorable result for Ipranizid to treat depression in patients with alcohol use disorder after heavy drinking episodes although alcohol use disorder outcomes were not directly measured and as we talked about earlier Ipranizid was discontinued in that study for two patients who relapse in alcohol due to the concerns about the risk of Ipranizid induced hepatitis which we kind of touched on earlier which ultimately led to the drug being removed from the market.

When looking at opioid use disorder there didn't appear to be any clinical trial data but there is a case report in the literature describing successful treatment for IV heroin use dependence and ADHD with Moclobamide post-opioid detoxification abstinence and this was confirmed at a two-year follow-up with toxicology. There's also a rodent study where they used high dose selegalene which reduced morphine self-administration that did not significantly alter morphine withdrawal symptoms.

When looking at amphetamine use disorder there was a 1977 observational study examining phenylzine as a treatment for stimulant disorder for those who've become recently abstinent from misusing dextra, amphetamine, methamphetamines and methylphenidate and this kind of works like an aversion-based pharmacotherapy like disulfram for alcohol use disorder with participants warned of potentially serious side effects if they relapsed and among the patients who tolerated it 83% were essentially abstinent after six months of treatment. That does feel a bit bad doesn't it? So disulfram works by making alcohol make you feel awful essentially.

It blocks the enzyme that clears acetaldehyde so you build up the acetaldehyde intermediate when you detoxify the alcohol and it makes you feel rough. The idea of giving somebody a drug that if they relapse and take amphetamine whilst on it could have a hypertensive crisis feels pretty bad. Feels bad doesn't it? And finally when looking at tobacco use disorder there have been many randomized controlled trials throughout the years with monoiminoxidase inhibitors and these have demonstrated mixed and generally limited efficacy in treating tobacco use disorder.

So there's lots of potential drug interactions with various different classes of drugs. In general it sounds like the treatment outcomes were not that good at treating the various use disorders. Did it improve the depression that these patients have? Because really that's the key thing here isn't it?

It's an antidepressant drug so we probably wouldn't expect it to have tangible effects on people's drug administration. It may do but in general maybe we wouldn't I suppose perhaps through dopamine pathways we might expect some changes. But the big question is is were they alongside taking these drugs suffering from less depression I guess? It's an interesting question.

I feel like in a lot of the studies it's quite hard to characterize those sorts of outcomes and not a lot of those details were available in this review. Yeah a lot of those studies were like abstinent outcomes weren't they rather than okay but did the people feel better? Yeah. So they're really interesting class of drug monoiminoxidase inhibitors and our next paper we're going to shift gears a little bit because we're going to be looking at a novel stimulant drug but with a little bit of a sting in the tail in terms of its pharmacology.

So this next paper focuses on APBT and this was first synthesized in the 1960s and investigated for its effects on the central nervous system and was reported to act as a monoimin oxidase A inhibitor in rat brain mitochondrial preparations but there's no effect on monoimin oxidase B.

There are many isomers so you've got three APBT, five APBT and six APBT and these have previously been assessed in vivo and in vitro and it's confirmed that they inhibit monoimin reuptake in the synapse and induce transport to mediated substrate release so more of the neurotransmitter leaves the neuron and enters the synapse and this is a similar mechanism to MDMA.

In mice, APBT compounds did not produce locomotor stimulation which would have been a sign of hyperactivity and occurs with the classical stimulants like amphetamine and cocaine but they were shown to be agonists of serotonin receptor two subtypes and induced the head twitch response in mice. So this basically suggests that these drugs adds five HTTA receptors which is associated with hallucinogenic effects so these drugs are closer to hallucinogens rather than stimulants.

So this paper aimed to characterize metabolism of three APBT, five APBT and six APBT in vitro and in vivo using LC or higher as MS to identify the monooxygenases involved in its metabolism and to determine their monoimin oxidase A and monoimin oxidase B inhibition profiles. And they did a lot of this looking at rat urine and looking at microstone models as well and it's a really interesting paper if you really like nerding out about metabolites. Like you do. Like I do.

I'd really encourage you guys to go check out there will be a link in the description and episode notes below but essentially to very crudely summarize it there were only minor differences in metabolic pathways between the different isomers and these were similar to related compounds such as five APB, six APB and alpha-methyltryptamine and multiple isoenzymes were involved in its phase one metabolism. So then looked at the monoamine oxidase inhibition profiles of five APBT, six APBT and three APBT and they compared the monoamine oxidase activities to the model inhibitors.

So for monoamine oxidase A, this is five IT and for monoamine oxidase B, this is selegaline. We didn't talk about the different forms of monoamine oxidase, did we? There's two classes and they both break down the different neurotransmitters. So monoamine oxidase A breaks down serotonin and noradrenaline whereas B breaks down dopamine.

So five APBT and six APBT inhibited monoamine oxidase A activities to 5% and 7% respectively which was similar to the model inhibitor five IT. Three APBT showed a weaker inhibition with residual monoamine oxidase A activity of around 28%. Monoamine oxidase B was also significantly inhibited but the residual activities were higher compared to the model inhibitor, selegaline with residual activity with three APBT being 54%, five APBT being 63% and six APBT being 73% and they also looked at and calculated IC50s and for monoamine oxidase A inhibition the IC50 was well within the range of other well-known monoamine oxidase A inhibitors.

And this was a really, really impressive paper, wasn't it? There was an awful lot of data, modelling, metabolism, generation, there was some nice mass spectra. The thing that got me was that you've got this class of drugs so they're related to things like alpha-mefol-tryptamine and the benzofurans which are relatively novel stimulant drugs. A lot of them emerged as MPS before a lot of bands kind of went in place.

They act a bit like MDMA but as we've heard, MDMA and monoamine oxidase inhibitors in general is a bad combo but they're also monoamine oxidase inhibitors. I'm surprised they haven't really emerged as causing too much harm. There must be cases out there. They sound like they should be quite toxic, right?

Yeah. It does just show the complexities, doesn't it, of some of these compounds whereby we think they've got a main mode of action but actually when you look at the details sometimes they're acting in two or three different ways all at once and that can really complicate understanding of the pharmacology but also understanding how these drugs would interact with other drugs. Yeah definitely and when you're trying to look at a case and understand what has caused certain effects it just makes the whole thing even more messy. Particularly in sort of accidental overdose cases.

Yeah. It's rare that one drug's taken on its own. So often there's multiple there and if you've got a drug there that's new and it's doing three different things by these three different pathways it's really hard to sort of predict what's going to happen. Yeah for sure.

What's quite interesting is they contain sulfur, don't they, which is not that unusual but not common either. Most novel drugs we encounter typically are standard carbon, hydrogen, oxygen, nitrogen based. So to stick a sulfur in there, I mean is that what's causing this weird monoamine oxidase inhibition effect? My chemistry's not good enough.

I've got an idea. I think staying on the sulfur subject it does make you wonder how many other sulfur variations of compounds are going to emerge. And I guess one aspect that probably hasn't been touched on but should be considered, and I don't know if this is a real life risk or not, but actually a combination of these novel compounds with charcuterie boards presumably would be a bad idea. Yeah probably.

There was an article I read years ago about people putting MDMA in cheese at parties. I'll have to dig it out and find it. I mean I definitely need to see that. Seems unlikely that this might happen in this case but Brieing, they called it, apparently, had clever marketing.

We'll put a link in the description. So I guess really to wrap it all up then, monoamine oxidase inhibitors are an interesting class of drug but do still see some pharmaceutical use. They may have some limited role in treating people who also use drugs but in general the perception is is that they are a bad combination with many drugs. APBTs, on the other hand, are a fairly obscure research chemical that hasn't really seen much existence outside of these research chemical markets.

But really does carry with it both the monoamine oxidase inhibition but also the drug effect that you wouldn't want to combine with monoamine oxidase inhibition. And whilst they haven't really emerged as drugs there's not many clinical cases or post-mortem cases as yet. It does at least seem like, looking at this characterization, that they may well be a compound that carries with it quite a lot of risk. So I think perhaps one to keep an eye on if they ever do emerge.

Well I hope you've enjoyed listening to us this week. Do give us a like, give us a follow, share us with your friends. Hope you all have an amazing week and we'll see you next time. Bye!