Episode 57: SSRIs and Seizure Risk - Rethinking Serotonin in Epilepsy

Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. So this week we're going to be taking a look at the surprising link between serotonin and seizures.

This was an episode suggestion from one of our followers, so thank you. Before we dive into the science too hard, Rebecca, I want to explore your understanding of serotonin. Oh. And I don't mean this in a very scientific way.

What I mean is, is when you were younger, before you studied biochemistry, was your view of serotonin what it is now? No. Explain. Well, I don't think it was ever something I really covered in like great detail, even like going through uni and things, especially doing like a hardcore biochem degree.

It was all proteins and things. Okay, so you didn't actually cover it at university. That's interesting. So I think growing up, it was one of those words that gets thrown around, wasn't it?

Serotonin is the happy hormone. Serotonin is what makes you happy. And if you take things that increase your serotonin, that's the secret to happiness. And then one day I was in a lecture at university and I was being taught about carcinoid syndrome.

Oh yeah. So serotonin producing tumors. And suddenly I realised serotonin was way more complicated than, oh, it's just a hormone that makes you happy. We're going to be having a look this week at serotonin as a neurotransmitter.

Also how certain antidepressant drugs can influence serotonin, but also serotonin's potential surprising role in epilepsy. Before we jump 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 on there. And for those of you who don't use social media but still want to get in touch with episode suggestions or any comments about episodes, you can email us at thetoxlab@gmail.com.

So depression is a really, really complex illness. And understanding has really evolved quite a lot over the last 50, 60 years or so. But our original understanding of depression was what was called the monoamine hypothesis. And that said that depression was caused by alterations in monoamine neurotransmitters.

So noradrenaline, dopamine, serotonin. And we thought this really because drugs that influenced those seemed to show effects in improving depression. And the role of serotonin in depression actually has a really, really interesting history. Back in the 1950s, there were some studies going on for a tuberculosis drug called iproniazid.

And remarkably, the patients who were treated with this drug to try and treat their tuberculosis actually got quite cheerful and it was a very odd side effect. And it turns out that this drug not only treats tuberculosis, but it's also a monoamine oxidase inhibitor. So it increases the half-life essentially of monoamines, serotonin, noradrenaline, dopamine. And so this was really the start of the monoamine theory for depression.

And from there, lots of different drugs that auto monoamines have been trialed. And our focus this week really is on SSRIs. And these are selective serotonin reuptake inhibitors. So how do they work?

So if you imagine your synapse between two serotonin-powered neurons, serotonin is released into the synapse and activates downstream neurons. This protein called CERT then pulls serotonin back into the presynaptic neuron, which clears the signal and recycles the receptor. SSRIs, so drugs like sertraline, fluoxetine, citalopram, they bind to CERT and they stop it from drawing serotonin back into the presynaptic neuron. So essentially SSRIs increase the amount of serotonin within the synapse.

It's a little bit more complex than that though, because just increasing the amount of serotonin doesn't seem to really help depression all that much. In fact, when you start on SSRIs, it can actually take weeks before there's a noticeable effect in mood. And it's because a couple of other things then happen. As you've got more serotonin within that synapse, there is downregulation of the presynaptic serotonin receptors.

And these are what we call auto receptors, and they form part of the feedback loop. So in other words, there's more serotonin in the synapse. So the presynaptic neuron produces less serotonin. And over a longer period of time, these auto receptors actually desensitize.

And eventually you end up at a new baseline where these neurons actually end up firing a little bit more. And so you generally increase the serotoninergic tone. And probably most of the antidepressant effect actually comes from then downstream alterations in plasticity. There's an increase in BDNF, which stands for brain-derived neurotropic factor.

And this is a protein that is expressed when neurons undergo growth. And so the theory now is the SSRIs work by, yes, they increase serotonin within the synapse, but it's actually thought that it's the long-term adaptation to this increased serotonin that leads to an increase in brain plasticity. And that's what helps treat the depressive symptoms. But the question we were asked was about SSRIs and seizure risk.

And it's recognized that quite a few antidepressant medications can increase the risk of seizures. And this week we thought we'd have a look specifically at SSRIs. So Rebecca, why don't you dive into our first paper? So as Rob mentioned, seizures are a debated adverse effect of antidepressant use.

And there have been several cohort studies that have demonstrated an increase in seizure risk among those who use antidepressants even after the adjustment of the demographic variables and medical history. Interestingly, anxiety and mood disorders are risk factors for developing epilepsy and one in three patients with epilepsy receive a psychiatric diagnosis in their lifetime. So this paper is looking at individual case safety reports from the WHO Global Pharmacological Vigilance Database mentioning seizures associated with antidepressant use between 1967 and 2023. And they grouped the antidepressants by class.

So you've got SSRIs, SNRIs, tricyclics, and then they've got other antidepressants. So a massive study trying to answer the question do antidepressants lead to increased seizures? Yes. So there were 131,255,418 reports in total in the database with just over 2 million reports relating to antidepressants.

And of these, 23,331 mentioned seizures as the adverse outcome. There was a significant increase in reports over time with the greatest number of reports submitted between 2010 and 2019 with 29% of reports being submitted between 2000 and 2009. SSRIs were the most frequently mentioned antidepressant and they appeared in 38% of cases. In terms of individual antidepressant drugs, Bupropion was the most frequently suspected medication in 23% of cases.

And this was followed by Venlavaxin in 12%, fluoxetine in 10%, and duloxetine in 10%. The largest age group in these reports were adults aged between 18 and 44 years with women being more affected. The median time to onset of a seizure from the start of medication was 22.95 days and there were fatal clinical outcomes reported in 6% of cases. The majority of these cases came out of America and this was about two thirds followed by Europe with 29% of the reports.

So tricyclic antidepressants were the most prominent antidepressants featured but their mentions decreased and SSRIs and SNRIs became more prevalent from about the 90s. New antidepressants such as 4-2-oxetine and anagomeletine showed a significant increase in the number of reports since 2010. An overall antidepressants were collectively associated with the seizures and those with the highest reporting odds ratio and information component were observed for tricyclic antidepressants and this was followed by SSRIs and then SNRIs. The SSRIs that were associated with seizures included talopram, acetalopram, fluoxetine, peroxetine, and sertraline.

Venlavaxin and duloxetine were associated with an increase in seizures from the SNRI category but Des Venlavaxin showed no association with seizures. Individual tricyclics all showed a disproportionate association with seizures with chlamypromine showing a notably higher estimate compared to imypromine and bupropion showed the highest reporting odds ratio and information component estimate among all the medications are examined. So this is a massive data set, isn't it? Huge numbers of data points here over a very long period of time.

What you've described in terms of reports related to different classes of antidepressant really pretty much mirrors prescribing practice over those years, doesn't it? Initially tricyclic use moving on towards SSRIs because they were considered to be less toxic and now some of the newer agents which are only just starting really to get more mainstream use starting to appear. It's interesting, isn't it? So we know there's an association between depression and epilepsy.

Is this just mirroring the fact that those two conditions overlap? You're more likely to have depression if you've got epilepsy. Depression and epilepsy seem to have this bi-directional relationship based on increased risk of occurrence and severity of one in the presence of the other and depression does seem to precede the first seizure at higher rates than in control groups and there does seem to be a lot of pathological mechanisms that overlap both epilepsy and depression including neuroinflammation, aberrant neurogenesis and hyperactivation of the hypothalamic pituitary adrenal axis which is observed in both epilepsy and depression.

Could that be responsible for some of the meta-analysis indicating an association between particularly the safer antidepressants like SSRIs and still there seeming to be an overlap with seizures? Yeah. So you pointed out there was quite a few differences between some of the different classes of antidepressant and I think that's where we need to start diving into the detail a little bit, don't we? Bupropion, particularly associated with seizure risk and that's a really interesting drug because it's a first-line antidepressant treatment in the US.

In the UK, it's not used for depression at all. In fact, it never made regulatory approval because of the seizure risk. It is used very occasionally in the UK as an aid to quit smoking but it's not been licensed for depression use. And you also pointed out some of the tricyclics, didn't you, and how they were also associated with a greater proportion of seizure risk.

So I think there probably is more nuance to the data than just depression and epilepsy overlap. So what about then SSRIs? They were a big chunk, weren't they? So do SSRIs specifically increase seizure risk?

Well, that is an interesting question. So let's delve a little bit more into this. We found a case study, didn't we? So this case study involves a 30-year-old female who was diagnosed with viral meningoencephalitis at two years old and experienced multiple generalized tonic-clonic seizures over the next three years of her life, which were treated with phenobarbital.

At the age of 15, her seizures recurred in the form of blank staring spells associated with epigastric rising, which is a feeling that starts in stomach and moves upwards through the chest and can be described as a rising feeling, nausea or indigestion. She also experienced speech arrest and occasionally generalized to full convulsions. She was diagnosed with complex partial seizures without secondary generalization, and that basically means that the seizure begins in one half of the brain and then spreads to both sides.

An EEG showed left frontotemporal epileptic discharges and continuous monitoring captured multiple seizures, all of left temporal origin. MRI showed left lateral inferior lobe encephalomalacia, which is the permanent softening and loss of brain tissue in the lower outer regions of the cerebral lobes. And it also showed left mesial temporal sclerosis, which is scarring and loss of neurons and is a cause of epilepsy and focal seizures. Phenytoin, carbamazepine, valproate, lamotrigine and levetiracetam were not effective treatments in her case.

A lot more response was obtained on clobazam at 40 mg twice a day and lacosamide at 200 mg twice a day. And this resulted in a reduction in the frequency of seizures to two seizures per week. So lots of first line anti-seizure medication did nothing. Yeah.

Had to resort to some of the more complex newer agents. And that had an effect, but still wasn't seizure free at this point. Yeah. From the age of 15 to 27, she was experiencing eight to 20 seizures in a month.

At the age of 27, she was undergoing an evaluation for seizure surgery and during this time, she became depressed. She was then started on sertraline, reaching a dose of 200 mg a day and within a week of being on this dose of sertraline, her seizures stopped and she didn't have one for another three years. Her sertraline dose was reduced to 150 mg a day for a week in which her seizures returned. But this stopped again when her dose was increased.

So this is just a single case study, but this is remarkable, isn't it? Yeah. The use of an SSRI sertraline actually pretty much completely stopped her seizures and with a clear withdrawal of that drug leading to a return of the seizures, it seems quite clear actually that sertraline seemed to be having an anti-seizure effect. So in mice, sertraline has been shown to have an anticonvulsant effect.

So in seizures, activation of the voltage-gated sodium tunnels is prolonged and some anti-epileptics inhibit the increased permeability of sodium channels, reducing the release of the excitatory neurotransmitter glutamate. Sertraline also inhibits sodium channel currents and has been shown to inhibit presynaptic sodium channel mediated responses in hippocampus-isolated nerve endings in rats, which might be a potential mechanism as to why sertraline has some sort of anticonvulsant effect.

Let's just very briefly touch on the physiology of epilepsy and I'm not going to do this in any great detail, but a seizure is essentially where there is an imbalance, isn't there, between excitatory neurons within the brain and inhibitory neurons in the brain. And we typically treat seizures by either dampening one or enhancing the inhibitory tone. And that's more often what we do, isn't it? We treat with GABAergic drugs, or we modify sodium channels and sodium channels are what allows the voltage to travel along a neuron.

And also by modifying sodium channels, you can increase or decrease a nerve's depolarization threshold. So this proposed mechanism you've described is through the sodium channel mechanism,

isn't it? So by sertraline actually affecting sodium channels and reducing that glutamate transmission. This is sertraline specifically potentially having a role, but actually the role of serotonin in general in seizures is really an emerging area, isn't it?

So we came across an interesting review article that was talking about different aspects of serotonergic therapy in epilepsy. So early mouse experiments have showed that intracranial injection of serotonin can protect against audiogenic seizures and other models of epilepsy showed that serotonergic drugs reduce seizure frequency in chronic epilepsy. They also looked at funfluramine, which is a drug that increases serotonin release and inhibits transporter re-uptake, and in a randomized blinded placebo-controlled trial for seizures in Dravette syndrome.

This demonstrated a reduction of motor seizures, and this was significant when compared to placebo. So funfluramine we've actually talked about on this podcast before. I'm not sure if you remember, Rebecca. You're pulling a blank face at me.

It's not ringing a bell. We actually talked about it when we were talking about Ozempic. It was originally used as an appetite suppressant. It's actually a fluorinated amphetamine, and it's a fascinating compound.

As you say, it works as a serotonin releaser. So it actually increases the amount of serotonin released from presynaptic neurons. But it itself is also a serotonin agonist. It binds to specific serotonin receptor subtypes and seems to preferentially activate them.

And it's got this really unique activation profile that seems to be very anti-epileptogenic. And as you say, Dravette syndrome is a genetic form of epilepsy, often very treatment resistant. And yet, femfluramine actually seems to be showing quite a bit of promise. So in SUDEP, Sudden Unexpected Death in Epilepsy Patients, there are many risk factors which include three or more generalized tonic-clonic seizures per year and a lack of caregiver assistance during a seizure.

Respiratory dysfunction during seizures has been associated with serotonin abnormalities that may be prevented by sero-surgeon medications. And respiration has been demonstrated to be altered in clinical and animal models of epilepsy and is thought to contribute towards SUDEP. Depletion of serotonin or antagonism of serotonin prolongs and worsens seizures in animal models of epilepsy and serotonin may also regulate arousal and respiratory drive. So it looks like serotonin may be more involved in seizures than we first thought or rather preventing seizures.

It seems to have an anti-seizure effect most of the time. And this is independent of the sodium channel modulation that was proposed in the sertraline model. So the general consensus view then is that antidepressants, in general, broad term, antidepressants being lots of different compounds, can increase seizure risk. But SSRIs specifically, actually generally considered safe and there's emerging evidence that they may possibly help.

One drug I do want to touch on briefly, actually, is tramadol. So tramadol is an opioid often used in moderate to severe pain. But it also has some antidepressant-like effects and it acts as what we call an SNRI, so similar to venlofaxin, where it's a serotonin noradrenaline reuptake inhibitor. So it acts on both.

Like an SSRI acts in the same way but also on noradrenaline neurons. And tramadol is famous for actually lowering seizure threshold. And actually other antidepressant drugs like venlofaxin act through the same mechanism, actually have very similar effects. They can also lower seizure threshold.

So it seems that the noradrenaline pathways actually can promote seizure risk. And another class of compounds I do want to touch on, albeit very briefly, actually is psychedelics. Psychedelic compounds

interact directly with subtypes of serotonin receptor. And their risk of seizures is subject of quite significant controversy.

And I think brief teaser to the future. We might have to do an episode on that at some point soon. Sounds good. So really in summary then, there's massive overlap between epilepsy and depression.

Antidepressant use in epilepsy can be tricky, particularly with some antidepressants. SSRIs in particular, actually relatively safe in epilepsy and possibly even beneficial. And there's emerging evidence that serotonin itself is involved in, if not directly anti-seizure pathways but maybe having some modulation effect on seizures. So I hope you've enjoyed listening this week.

Once again, thank you for suggesting this episode. And if you've got any more thoughts on future episodes, do drop us a comment. We'd really like to hear from you. Hope you all have an amazing week and we'll see you next time.

Bye.