What Alcohol Does to Your Body, Brain & Health | Huberman Lab Podcast #86

In this episode, I discuss the physiological effects that drinking alcohol has on the brain and body at different levels of consumption and over time. I also describe genetic differences that predispose certain individuals to alcoholism, binge and habit-drinking. I explain alcohol metabolism in simple terms and how it effectively acts as a poison, leading to cellular stress and damage. I then explain that it impacts neuronal function and changes our thinking and behavior – hallmarks of inebriation. I also discuss how alcohol consumption of different amounts impacts inflammation, stress, neurodegeneration, and cancer risk and negatively impacts the gut microbiome, brain thickness, hormone balance, mood and feelings of motivation. Additionally, I discuss the biology of hangovers and describe science-based strategies to mitigate the severity of a hangover. Since alcohol is one of the most widely consumed recreational substances, this episode ought to be of relevance to everyone. Indeed, even low-to-moderate alcohol consumption negatively impacts the brain and body in direct ways. The goal of this episode is to help people make informed decisions about their alcohol consumption that are in keeping with their mental and physical health goals.

Articles

Associations between alcohol consumption and gray and white matter volumes in the UK Biobank: https://go.nature.com/3PNFj7y

Gut Microbiota at the Intersection of Alcohol, Brain, and the Liver: https://bit.ly/3AaeF2F

Tolerance to alcohol: A critical yet understudied factor in alcohol addiction: https://bit.ly/3CmfCYo

Associations Between Drinking and Cortical Thickness in Younger Adult Drinkers: Findings From the Human Connectome Project: https://bit.ly/3AeUosJ

Moderate Alcohol Consumption and the Risk of Breast Cancer: https://bit.ly/3PHlJcK

Can alcohol promote aromatization of androgens to estrogens? A review: https://bit.ly/3dJjGHZ

Other Resources

Examine - Alcohol & Hangover: https://bit.ly/3QHYpx4

Timestamps

- Welcome to the Huberman Lab Podcast, where we discuss science and science-based tools for everyday life. I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today, we're discussing alcohol, one of the most commonly consumed substances on the planet Earth. I should mention that both humans and non-human animals consume alcohol either for recreational purposes because they like the feeling that it gives them or for medicinal purposes or for other purposes that we'll discuss. We are, of course, going to discuss the effects of alcohol on our biology, ranging from its effects on individual cells, on organs and organ systems in our brain and body. We are also going to discuss the effects of the effects of alcohol, that is, what being inebriated really does to our thinking and our behavior and how it

does it. And we are going to address what seems to be one of the more common questions out there, which is whether or not low to moderate amounts of drinking are better for our health than zero alcohol consumption at all. And of course we will talk about severe alcohol intake, binge drinking. We will also talk about hangover and what science says about ways to reduce the effects of hangover, either by doing things that are inoculatory, meaning before you drink or while you drink, as well as things to do if you happen to have a hangover. We will discuss some of the genetic differences for alcohol and alcoholism, and we will discuss alcohol consumption in young people and how that can be especially detrimental for reasons that I think are going to be quite surprising to most of you. My goal is that by the end of today's episode, you will have a thorough understanding of what alcohol does to your brain and body and that you will be able to make informed decisions as to whether or not you should be consuming zero, absolutely no alcohol, small to moderate amounts of alcohol, and, again, we'll define exactly what that means, small to moderate amounts, and if you or somebody else that you know is consuming excessive amounts of alcohol that are clearly detrimental to your health, some of the better routes and resources that you can use in order to remove that dependence and/or consumption. I'd like to preface all of that by saying that today's discussion is really geared toward giving you information. It is not about judging alcohol intake or lack of alcohol intake.

00:02:25 Momentous Supplements

I just want you to be able to make the most informed decision about alcohol possible. I'm pleased to announce that the Huberman Lab Podcast is now partnered with Momentous Supplements. We've partnered with Momentous for several important reasons. First of all, they ship internationally, because we know that many of you are located outside of the United States. Second of all, and perhaps most important, the quality of their supplements is second to none both in terms of purity and precision of the amounts of the ingredients. Third, we've really emphasized supplements that are single-ingredient supplements and that are supplied in dosages that allow you to build a supplementation protocol that's optimized for cost, that's optimized for effectiveness, and that you can add things and remove things from your protocol in a way that's really systematic and scientific. If you'd like to see the supplements that we partner with Momentous on, you can go to livemomentous.com/huberman. There, you'll see those supplements, and just

keep in mind that we are constantly expanding the library of supplements

00:03:19 Low to Moderate Alcohol Consumption & Neurodegeneration

available through Momentous on a regular basis. Again, that's livemomentous.com/huberman. Before we get into today's content in detail, I just want to answer a commonly asked question about alcohol consumption and the brain, and the question that so often comes up is whether or not low to moderate amounts of alcohol, so maybe one drink a day or one or two drinks a day kind of thing, whether or not that is bad for your brain, in particular, whether or not it causes degeneration of neurons or nerve cells. Now, the reason that question comes up so often is because, for many years, it's been known that high levels of alcohol consumption, so 12 to 24 drinks per week or more, is certainly causing neurodegeneration, in particular of the so-called neocortex, the outer layers of the brain that house associative memories, that house our ability to think and plan, that house our ability to regulate our more primitive drives according to context, et cetera. So to make very clear, drinking a lot, so having, you know, three or four drinks per night every night of the week, is clearly bad for the brain. A recent study, however, finally addressed the question of whether or not low to moderate amounts of alcohol consumption can cause brain degeneration. The title of the study is Associations between alcohol consumption and gray and white matter volumes in the UK Biobank, the United Kingdom Biobank. First of all, gray matter are the neurons, it's the so-called cell bodies that house the genome of the cells, et cetera, and white matter is the connections, the fibers, the so-called axons of neurons, and it's called white matter because that tissue is surrounded by a fatty tissue called myelin, which allows nerve cells to communicate with each other very quickly. So what this study did is it looked at the brains, both the gray matter and the white matter, of more than 30,000, and even more than 35,000 generally healthy middle-aged and older adults in the United Kingdom who were drinking various amounts of alcohol. What they found was that even for people that were drinking low to moderate amounts of alcohol, so one or two drinks per day, there was evidence of thinning of the neocortex, so loss of neurons in the neocortex, and other brain regions. And I don't say this in order to cause alarm. I tell you this because they are important data because they reveal and indeed answer the question that has been burning for so long as to whether or not chronic alcohol intake can disrupt the brain even if the chronic intake is very low. Now, we should talk about what the word chronic

means because many people, when they hear the word chronic, think high levels of whatever intake, okay? So they think 5 drinks a night or 10 drinks a night or people drinking every night. Now, in this study, they looked at people who, on average, were drinking one or two drinks per night. So that could be 14 drinks on the weekend, it could be one drink per night. it could be seven drinks on Friday, in other words, on average, one or two drinks per night. And I think many people out there are drinking somewhere between one and two drinks per night or day of the week on average, so that would be 7 to 14 drinks per week. So this is an important study because it says that if you're consuming even just seven glasses of wine across the week, it's likely that there is going to be some degeneration of your brain in response to that alcohol intake. Although, as mentioned earlier, we will talk about some of the things that can inoculate against some of that neuronal loss. For those of you that are interested

00:06:52 Levels, Eight Sleep, ROKA

in reading the study in more detail, we've put a link to it in the show note captions. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is, however, part of my desire and effort to bring zero-cost-to-consumer information about science and science-related tools to the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is Levels. Levels is a program that lets you see how different foods affect your health by giving you real-time feedback on your diet using a continuous glucose monitor. One of the most important features of our immediate feelings of well-being and our ability to focus and think and move and have energy, as well as our long-term health, are our blood glucose levels. That is, our blood sugar levels. And that's because all the cells and tissues of our body and especially neurons, nerve cells, rely on glucose for fuel. I realize some of you out there are ketogenic, and, yes, you can use ketones for fuel, but the vast majority of people are using glucose for fuel in their cells. If you want to maintain energy and focus throughout the day, you want to keep that blood glucose steady and you don't want it ever to spike or to drop too much, so you need to understand how different foods and indeed how different activities impact your blood glucose. I started using Levels about a year ago as a way to understand how different foods and exercise and supplements and combinations of food and exercise and even sequencing, like when I do what, how that affects my blood glucose levels. It's been

tremendously informative. It's completely reshaped when I exercise, how I exercise, when I eat relative to exercise, et cetera. So if you're interested in learning more about Levels and trying a continuous glucose monitor yourself, go to levels.link/huberman. Again, that's levels.link/huberman. Today's episode is also brought to us by Eight Sleep. Eight Sleep makes smart mattress covers with cooling, heating, and sleep tracking capacity. I've talked many times on the podcast about the fact that getting a great night's sleep is the foundation of mental health, physical health, and all forms of performance. And one of the key variables in getting a great night's sleep is making sure that your sleeping environment is the right temperature. Indeed, your brain and body have to drop by one to three degrees in order to get into sleep and to stay in deep sleep throughout the night. If your room is too hot or if you're running too warm, you will wake up. In fact, that is why you wake up in the morning. With Eight Sleep, you can adjust the temperature of your mattress and your overall sleeping environment and customize that to you. I started using Eight Sleep some time ago and it's just been a total game changer. I program mine so that there's a subtle drop in the temperature of my mattress at the beginning of the night and then it gets progressively cooler and then it heats up toward morning. It even has this nice little vibrate feature so it wakes me up by vibrating the mattress a little bit. And, of course, that mattress is warming and warming is the way that we wake up. If you'd like to try Eight Sleep, go to eightsleep.com/huberman. Check out their Pro Pod Cover and save up to $150 at checkout. Eight Sleep currently ships in the USA, Canada, and the United Kingdom. Again, that's eightsleep.com/huberman to save $150 at checkout. Today's episode is also brought to us by ROKA. ROKA makes eyeglasses and sunglasses that are of the absolute highest quality, and they also have some unique characteristics. The company was founded by two all-American swimmers from Stanford and everything about ROKA eyeglasses and sunglasses were designed with performance in mind. ROKA eyeglasses and sunglasses can be worn while running or cycling. If you get sweaty, they won't fall off your face, and they're extremely lightweight. In fact, most of the time, I can't even remember that I'm wearing them. I wear ROKA eyeglasses when I read at night, so I wear their readers, and I wear sunglasses at various times throughout the day. The great thing about ROKA eyeglasses and sunglasses is that even though they were designed for athletic performance, they have a terrific aesthetic. So unlike a lot of so-called performance glasses that make people look like cyborgs, in my opinion, ROKA eyeglasses and sunglasses are the sort that you could wear out to dinner or that you could wear to work. They have a terrific aesthetic. If

you'd like to try ROKA eyeglasses or sunglasses, you can go to ROKA, that's roka.com and enter the code Huberman

00:10:46 Historical Context & Uses of Alcohol

to save 20% off your first order. Again, that's ROKA, roka.com, and enter the code huberman at checkout. Let's talk about alcohol, and let's just acknowledge that human beings have been consuming alcohol for thousands of years. If you look at the archeological evidence from Mesopotamia, you'll find that 5,000 years ago, people had wine vessels. Or if you want to know when people first started distilling alcohol, much to people's surprise, that did not first take place in Ireland, and that's not a joke about the Irish. You'll see a lot of claims online that the Irish were the first to distill alcohol, but, in fact, they were not. It was the Chinese that were the first to distill alcohol, and that took place in China in the first century. Alcohol has been used for nutritional purposes, so there are cultures that believe, and indeed still believe, that the calories in alcohol are useful, although later we'll talk about how alcohol calories are indeed empty calories and what an empty calorie really is, why it's called empty. Alcohol has been used for medicinal purposes because indeed it does kill bacteria, and, as you'll soon find out, the fact that it kills bacteria, because that is absolutely true, it also kills the good bacteria in your gut, and the destruction of that good bacteria in your gut can lead to things like leaky gut syndrome and has all sorts of issues, and there are ways to deal with those issues and we'll talk about those. So alcohol has been used for medicinal purposes, it's been used to clean surfaces, it's used in my laboratory in order to make up so-called reagents to do our experiments, but most humans have been consuming alcohol in order to change their internal state, in order to feel differently than they would otherwise. That feeling of being drunk or inebriated or tipsy or lightheaded is something that many, not all, but many humans seem to enjoy and pursue even though, typically, it leads to a feeling of being less happy, less motivated, more stressed, et cetera, when the alcohol wears off. That's pretty incredible, right? I mean, we're talking about a substance that people have been highly motivated to pursue, that are still highly motivated to pursue, to create and to consume, that they'll spend money on, and that's despite the fact that it makes them feel good and then it makes them feel lousy. Now, some of you might be saying, "Well, I drink, but I don't drink to excess and, therefore, I don't feel lousy. I feel good when I drink and then it wears off and it allows me to get through my evening, and

then the next morning I'm ready to go." Okay, that very well may be true, I believe those people, and, as I mentioned in the beginning of the episode, I'm not here to demonize alcohol in any way. But I do want to point out what alcohol is and how it creates the effects that it does, and then I want to talk about what those effects are when you engage in consuming alcohol even as often as one or two nights per week, or let's say you're just somebody who has a drink or two on Friday, maybe a few more on Saturday, or maybe you're somebody who consumes all your alcohol

00:13:28 Alcohol Metabolism, “Empty Calories”

one night per week or one night per month. We'll talk about how that's affecting your biology. So let's address what alcohol is and how it affects the cells and tissues and organs of your body. Then we'll take a look at some of the epidemiology, that is, how many people are consuming alcohol and how much they're drinking. And then you will be able, I think, to get a good sense of how the alcohol that you're drinking, if you're drinking any at all, is impacting your brain and body and the choices you might want to make about how and when to drink alcohol, or even if you want to eliminate alcohol altogether. Okay, so some basic chemistry and biology of alcohol, and, again, I'll make this very clear even if you don't have a chemistry and biology background. Because of the structure of alcohol, it is what's called both water-soluble and fat-soluble. Translated into what's meaningful for you, what that means is when you drink alcohol, it can pass into all the cells and tissues of your body. It has no trouble just passing right into those cells. So unlike a lot of substances and drugs that actually attach to the surface of cells, to receptors, as they're called, little parking spots, and then trigger a bunch of downstreams, like, domino cascades of effects, alcohol actually has its own direct effects on cells because it can really just pass into those cells. So it's water- and fat-soluble, and the fact that it can pass into so many organs and cells so easily is really what explains its damaging effects. I should mention that there are three main types of alcohol. There's isopropyl, methyl, and ethyl alcohol, and only the last one, ethyl alcohol or ethanol, is fit for human consumption. However, it is still toxic, okay? It produces substantial stress and damage to cells. I'd love to be able to tell you otherwise, but that's just a fact. Ethanol produces substantial damage to cells, and it does that because when you ingest ethanol, it has to be converted into something else because it is toxic to the body. And there's a molecule inside of all of us called NAD, and you may have heard of

NAD because it's quite popular, there's a lot of discussion about NAD in the longevity literature right now. NAD is present in all our cells from birth until death. The levels of NAD tend to go down across the lifespan. There are ideas that increasing levels of NAD may extend lifespan. A lot of that is still controversial, or, at least we should say, is ongoing in terms of the research. But nonetheless, when you ingest ethanol, NAD and related biochemical pathways are involved in converting that ethanol into something called acetaldehyde, it's broken down into acetaldehyde. And if you thought ethanol was bad, acetaldehyde is particularly bad. Acetaldehyde is poison. It will kill cells. It damages and kills cells and it is indiscriminate as to which cells it damages and kills. Now, that's a problem, obviously, and the body deals with that problem by using another component of the NAD biochemical pathway to convert acetaldehyde into something called acetate. Acetate is actually something that your body can use as fuel. And that process of going from ethanol to acetaldehyde to acetate does involve the production of a toxic molecule, right? Again, acetaldehyde is really toxic. And NAD, and if we want to get technical, it's the NAD-to-NADH ratio, and that chemical step is the rate-limiting step to ethanol's metabolism. What does that mean for you? What that means is that if your body can't do this conversion of ethanol to acetaldehyde to acetate fast enough, well, acetaldehyde will build up in your body and cause more damage, so it's important that your body be able to do this conversion very quickly. And the place where it does that is within the liver, and cells within the liver are very good at this conversion process, but they are cells and they are exposed to the acetaldehyde in the conversion process, and so cells within the liver really take a beating in the alcohol metabolism events. So the key thing to understand here is that when you ingest alcohol, you are, yes, ingesting a poison, and that poison is converted into an even worse poison in your body, and some percentage of that worse poison is converted into a form of calories that you can use to generate energy, generate ATP. And the reason why alcohol is considered empty calories is because that entire process is very metabolically costly, but there's no real nutritive value of the calories that it creates. You can use it for immediate energy, but it can't be stored in any kind of meaningful or beneficial way. It doesn't provide any vitamins, it doesn't provide any amino acids, it doesn't provide any fatty acids, it's truly empty calories. I know some people talk about sugar is empty calories, but sugar actually is a far better fuel source than alcohol or acetate. But nonetheless, when you ingest alcohol,

00:18:23 Inebriation: Top-Down Inhibition, Impulsivity & Memory Formation

some percentage is being shuttled into a worse poison and some is being shuttled into a fuel source. Now, the important thing to understand is that it is the poison, the acetaldehyde itself, that leads to the effect of being inebriated or drunk. I think most people don't realize that, that being drunk is actually a poison-induced disruption in the way that your neural circuits work. And so we should ask ourselves, like, which neural circuits, what brain areas, what body areas are involved in feeling drunk or inebriated? Now, in thinking about this state of being tipsy or happy or really drunk or a little bit drunk, I want to mention something that I think most people aren't aware of, and that's the fact that for people that are regular drinkers or that have a genetic predisposition to alcoholism, when they drink, they tend to feel very energized and very good for longer periods of time. Again, people who have a genetic predisposition to alcohol or people who are chronic drinkers or even just, if you recall, chronic doesn't have to mean a ton of alcohol but they're drinking one or two per night or they're every other night type drinkers or Thursday through Sunday drinkers, those people typically experience an increase in alertness and mood when they drink, whereas occasional drinkers will have a briefer, meaning less long-lasting, period of feeling good when they drink and then more quickly transition into a state in which they're tired or they start losing motor skills, they start slurring their speech. I also want to emphasize this is distinct from tolerance. We'll talk about tolerance later and exactly what tolerance means. But I really want to highlight the fact that when people ingest this poison, 'cause indeed it is poison, the range of effects is very different, and you can reliably predict who are the people with a predisposition to alcoholism and who are the people who are more regular drinkers by the contour or the timing of the different effects. And, again, people who tend to feel more alert and excited every time they drink, they tend to get a real lift, they become kind of the life of the party and that lasts a long while, those people are the ones that really have to be careful about predisposition for alcoholism. And those people also need to be careful about their drinking and the amount of drinking that they're doing, even if they're not full-blown alcoholics. Now, of course, people who are ingesting alcohol who are not accustomed to drink alcohol have to be concerned about drinking alcohol for other reasons, because it can impair motor function and judgment, et cetera. But in thinking about the biochemical effects of alcohol and what it's doing to the body, what it's doing in all cases is it's consumed into the gut, right? Goes into the stomach, the liver immediately starts this conversion that we talked about before of ethanol to acetaldehyde to acetate, and some

amount of acetaldehyde and acetate are making it into the brain, it crosses the blood-brain barrier. Again, the brain has this fence around it that we call the blood-brain barrier or the BBB. Many things, most things, thankfully, can't pass across the blood-brain barrier, but alcohol, because it's water- and fat-soluble, just cruises right across this fence and into the milieu, the environment of the brain, which is made up of a couple different major cell types, neurons, nerve cells, and so-called glial cells, which are in between the nerve cells, and we'll talk about the effects on each of those soon. So what happens when alcohol gets into the brain that makes us feel tipsy or drunk and, in some people, makes people feel really especially energized and happy? Well, alcohol is indiscriminate in terms of which brain areas it goes to. Again, it doesn't bind to particular receptors, but it does seem to have a propensity or an affinity for particular brain areas that are involved in certain kinds of thinking and behavior. So one of the first things that happens is that there's a slight, at least after the first drink or second drink, there's a slight suppression in the activity of neurons in the prefrontal cortex. This is an area of your neocortex that's involved in thinking and planning and, perhaps above all, in suppression of impulsive behavior. So if you go to a party and they're serving alcohol and people are consuming drinks, what you'll notice is that a few minutes into that party, the volume of people's voices will increase, and that's because people are simply not paying attention to their voice modulation, and as other people start speaking more loudly, other people are speaking more loudly. We've all had this experience, right, of going to a party and then you step outside for a moment and you go, "Oh, my goodness, I was shouting." You come home, the next day, you've got a sore throat. It might be that you picked up some sort of bug, some virus or something, but oftentimes it's just the fact that you've been shouting all night just to be heard because as the prefrontal cortex shuts down, people stop modulating their level of speech quite as much. You also notice that people start gesticulating more, people will start standing up and sitting down more, they'll start walking around more, if there's music on, people might spontaneously start dancing. All of this is because these areas of the prefrontal cortex normally are providing what's called top-down inhibition. They are releasing a neurotransmitter called GABA onto various parts of the brain that are involved in impulsive motor behavior and thought patterns, and as you shut down the prefrontal cortex, that GABAergic suppression of impulses starts to be released, so people will say things that they want to say without so much forethought about what they're saying, or they might do things that they want to do without really thinking it through quite as much or they might not even remember thinking

it through at all, or experience, I should say, thinking it through at all. We haven't talked about blacking out yet and the effects of alcohol on memory, but as long as we're there, I'll just tell you that alcohol has a very strong effect in suppressing the neural networks that are involved in memory formation and storage. This is why oftentimes we forget the events of a night out if we've been drinking. One of the more important things to know about the effects of alcohol in the brain is this disruption in top-down inhibition, but, also, that areas of the brain that are involved in flexible behavior, sort of considering different options, like I could do A or I could do B, I could say this to them or I could say that, I could say it in that way or I could say it in this way, this might be a little more tactful,

00:24:23 Long-Lasting Effects & Impulsivity, Neuroplasticity & Reversibility

those brain areas basically shut down entirely and people just tend to say what they want to say. So the key thing to understand is that when people drink, the prefrontal cortex and top-down inhibition is diminished, that is, habitual behavior and impulsive behavior starts to increase. Now, what's interesting is this is true in the short term, so after people have one or two, maybe three or four drinks, but it's also true that the more often that people drink, there are changes in the very circuits that underlie habitual and impulsive behavior. This is really important to highlight, so much so that I want to drill into it a bit more deeply. For the person that drinks, say, every Thursday night or every Friday night or goes out only on Saturdays but every Saturday, there's evidence that there are changes in the neural circuits of the brain that control habitual behavior and impulsive behavior, and they are modified and strengthened in ways that make those people more habitual and more impulsive outside the times in which they are drinking, and when they drink, impulsive and habitual behavior tends to increase even further. This is something that's not often talked about when discussing the effects of alcohol. I mean, we all know the effects of being drunk can be bad, right? Can be bad in terms of judgment, motor coordination, certainly driving drunk is a terrible thing, get you or other people killed and so on. But rarely do we hear about the changes in neural circuits from just one or two nights of regular drinking. Again, chronic drinking doesn't necessarily mean every day and every night. It could be the person that simply drinks every Thursday or every Friday or just once a week has three or four drinks or maybe even a few more. That person is going to experience a decrease in this top-down inhibition, so an increase in impulsivity and habitual behavior, because the brake on those behaviors

has been removed while they're drinking, but also changes in the very neural circuits that allow habitual and impulsive behavior to occur more readily even when they're not drinking. And if you want to know the actual substrate for that, the cellular substrate, I can briefly describe it. It's really interesting. Again, you don't need to know any biology to understand this. What it does is it increases the number of synapses, the actual points of connection in the neural circuits that control habitual behavior. So there's literally a growth of the neural circuits in your brain that lead to existing habit execution, all right, the performance of things you already know how to do, and a reduction in the neural circuits, or I should say a reduction in the number of synapses, of the contacts, within the neural circuits that are controlling behavior. So this, again, is a not often discussed aspect of alcohol intake. Fortunately, it is reversible. So in animals or humans that undertake a period of abstinence of anywhere from two to six months, these neural circuits return to normal except in cases where people have been chronically drinking large volumes of alcohol for many, many years. And in those cases, while there is some recovery of brain circuitry after people get sober, meaning completely sober, they stop drinking entirely, there is evidence of long-lasting impact of heavy alcohol usage throughout the lifespan. But, of course, this doesn't mean that anyone that's suffering from alcoholism or that used to should not continue to focus on their health. You absolutely should. All is not lost. But for people that have been drinking for a lot of years, maybe you went to college and you drank a lot in those years and your neural circuits changed, if there's a period in which you don't drink alcohol, again, from two to six months and ideally longer,

00:27:55 Food & Alcohol Absorption

those neural circuits can then be remodified back to their original state. So let's consider some of the other neurochemical effects of alcohol in the brain and body. And, again, for right now, we're confining the conversation to people that are drinking, on average, one or two drinks per night. Now, some people might think that two drinks per night is a lot, and a lot of that will depend on body weight. So for instance, people who weigh 110 pounds, for them to ingest two alcoholic drinks is going to be substantially different in terms of the biochemical effects than somebody who weighs 220 pounds. Of course tolerance will also factor into this, genetic background will also factor into this, and indeed whether or not people have eaten will factor into this, so there are a lot of factors

and we'll talk about that. For the time being, if you're curious about how food impacts the effects of alcohol and your feelings of being drunk, you may have heard, for instance, that if somebody's inebriated and they want to sober up, they should eat something. Turns out that does not work. Here's how it does work, however. If you eat something prior to drinking alcohol or while ingesting alcohol, it will slow the absorption of alcohol into the bloodstream. In other words, you won't feel as drunk as fast, for many of you, this probably comes as no surprise, in particular, if that meal includes carbohydrates, fats, and proteins, okay?. The inclusion of all three major macronutrients seems to slow the absorption of alcohol into the bloodstream far more than having any one of those or two of those macronutrients present. Now, if you are already inebriated or you've had a glass of wine or a beer and you eat something, chances are that alcohol has already made it into your bloodstream because it moves into the bloodstream so quickly. Again, it's fat-soluble and water-soluble, so within minutes, right? If you have an empty stomach, within five to 10 minutes, that alcohol is going to be within your bloodstream and distributed throughout your body, maybe even faster depending on the type of alcohol and your metabolism. But if you're already drunk and you eat something, it's not going to sober you up more quickly, but it certainly will blunt the effects of any additional alcohol that you might consume. And if you're somebody who is concerned about getting too drunk too quick,

00:30:07 Alcohol & Serotonin, SSRIs & Depression, Risk for Alcoholism, Blackouts

even from a small amount of alcohol, having some food in your gut can certainly be beneficial. Now, that's food and alcohol and the absorption of alcohol, but let's go back to talking about the biochemical and neurochemical effects of alcohol on the brain. We talked about top-down inhibition, and we talked about habitual and impulsive behavior circuitry. There are also dramatic changes in the activity of neurons that control the release of so-called serotonin. Serotonin is a neuromodulator. It changes the activity of neural circuits and many neural circuits, in particular, those involved in mood and feelings of well-being. Recently, there's been a lot of interest in serotonin because of a study that was released that showed pretty conclusively that serotonin levels can't really explain depression and depression-like symptoms. I want to make it very clear that although that study did show that serotonin levels are not necessarily associated with depression, the study was interpreted by many to mean that SSRIs, selective serotonin

reuptake inhibitors, which have the net effect of increasing serotonins, these are things like Prozac, et cetera, that those drugs are somehow not helpful because they increase serotonin and serotonin isn't involved in depression. That logic doesn't really hold together so I'm going to use this as an opportunity to just clarify what really occurred there, and then we'll talk about how serotonin relates to alcohol consumption in things like feeling good and in depression. The key thing is this, SSRIs can help alleviate depression. That's right. SSRIs can help alleviate depression. They are often, not always, associated with side effects, dosage is very important, et cetera. But they probably support relief from depression by changing neural circuits, not necessarily by increasing serotonin itself. That is, increasing serotonin with these drugs likely changed the neural circuits involved in mood, allowing people to feel better through so-called neuroplasticity, which is the brain's ability to change itself in response to experience. So there's a bit of confusion, and, again, I'm using this episode on alcohol to highlight some of the confusion because I think it's timely, because the study just came out and there's a lot of chatter about this out there that when people are depressed, it's not necessarily because serotonin levels are low. However, if serotonin levels are increased with things like Prozac, Zoloft, and other SSRIs, oftentimes there is, yes, a relief from depression, but that's probably not because of restoring serotonin levels, per se. It's probably because serotonin facilitates the changes in neural circuits that need to occur in order for people to feel elevated mood, okay? So, again, that's a bit of a tangent and aside, but I do think it's a vital one for people to know about. Again, if you're thinking about taking SSRIs or you're currently taking them and you've heard this news, definitely talk to your doctor. Again, there is great utility for some of these SSRIs, and, also, in conditions like OCD, they've been shown to be very beneficial, so we really don't want to throw SSRIs out as a potentially valuable treatment. Getting back to the effects of alcohol on serotonin, it's very clear, beyond any doubt, that many of the circuits in the brain that are involved in mood and feelings of well-being and also sort of self-image and how we see ourselves employ the neuromodulator serotonin, and alcohol, when we ingest it and it's converted into acetaldehyde, it goes and that acetaldehyde acts as a toxin at the very synapses, the connections between these serotonergic neurons and lots of other neurons. In other words, when we ingest alcohol, the toxic effects of alcohol disrupt those mood circuitries, at first making them hyperactive. That's right, making them hyperactive. This is why people become really talkative, people start to feel really good after a few sips of alcohol, at least most people do. And then as they ingest more alcohol

or as that alcohol wears off, serotonin levels and the activity of those circuits really starts to drop, and that's why people feel less good. And typically what they do, they go and get another drink and they attempt to kind of restore that feeling of well-being and mood. Now, typically what happens is that as people ingest the third and fourth, maybe even the fifth drink, there's an absolute zero chance of them recovering that energized mood, right? Most people, as they drink more and more, will now start to feel more and more suppressed. The forebrain is now shutting down quite a lot, a lot of the motor cortical areas that control coordinated movement and deliberate movement start to shut down, so people start to slur their speech, people start to shuffle their feet, people forget their posture, people start to lean on things, people start passing out on couches. There's a great depression, not depression of the psychiatric depression sort, but a depression of alertness and arousal, and eventually people will pass out. Now, I said most people because there's a subset of people that have gene variants or who are chronic drinkers or who are chronic drinkers and have gene variants that, as they ingest the third and fourth and fifth drink, what happens? They become more alert, they start talking more, they feel great, they have all sorts of ideas about the fun they could have that night. And they're the ones that, if you've ever fallen asleep at a party for whatever reason, or you're getting tired and you're yawning, you're looking around the room and, like, these people are still drinking and partying and they're having what seems to be this amazing time, often, not always, those are the future alcoholics in the room, or those are the people that have a genetic predisposition for alcoholism, or those are the chronic drinkers, the people who have built up enough of a tolerance or who have the chemical genetic makeup such that increasing amounts of alcohol make them feel better and better and better. And of course, they, too, have a threshold beyond which their nervous system will start to get diminished and they'll pass out, fall over, et cetera, but that threshold is way, way higher than it is for most people. Now, this is important to understand, and it's important to understand because I think everyone should know and recognize their own predisposition and kind of risk in terms of developing alcoholism. It's also important to understand because it relates to the phenomenon of blackout. Many people think that blacking out is passing out, but blackout drunk is when people drink and they're talking and doing things, sometimes, sadly or tragically, they'll often drive home or walk home or they'll hop on a bicycle and ride home or they'll go swimming in the ocean, all, of course, very dangerous activities to do when people are really drunk, or even a little bit drunk in some cases. So these people will do these sorts of things and

they do them because they have the energy to do them and they feel good while doing them, but they are doing them while the activity of neurons in the hippocampus, which is involved in memory formation, are completely shut off. And this is why the next day, you tell them, "Hey, maybe we should talk about what happened last night." Like, "What happened last night?" You said, "Well, do you remember going to the party?" "Yeah, I know, it was great. We did this, we did this." "And then what?" And it's very clear all of a sudden that they have no recollection of all the things they were doing despite being awake. Now, I wish I could tell you that there's some sort of blood test or other biomarker or even a fingerprint test that would allow you to determine whether or not you have a propensity to be one of these drinkers that has a predisposition for alcoholism. And if you've ever been blackout drunk, and certainly if you've been blackout drunk more than a few times, you should be quite concerned. And as we talk more about the more chronic effects and long-lasting effects of alcohol consumption a little bit later in the episode,

00:37:39 Predisposition for Alcoholism; Chronic Consumption, Cortisol & Stress

I think it'll become clear as to why you should be concerned. But in any case, there is something that can tell you whether or not you might be in that category versus likely not in that category, and I alluded to this a couple of times already, but I want to be really clear that when people drink, no matter who you are, initially, there's that shutting down of those prefrontal cortical circuits, there's a gradual shutting down of the circuits that control memory, but then people divide into these two bins. And these two bins are the people who, after more than a couple of drinks, start to feel sedated, and the people who, after more than a few drinks, do not start to feel sedated. Now, of course there's going to be differences created by how quickly people are drinking, whether or not they're combining different types of alcohol, the types of alcohol, et cetera, but in general, that can predict whether or not you're somebody who has a predisposition for alcoholism or not. One also very interesting finding is that alcohol changes the relationship between what's called the hypothalamus and the pituitary gland and the adrenals. Now, the hypothalamus is a small collection of neurons about the size of a large gumball that sits above the roof of your mouth, and it houses neurons that are responsible for some incredible aspects of our behavior and our mindset, things like rage, things like sex drive, things like temperature regulation, very primitive functions,

including appetite, thirst, et cetera. Alcohol, because it can go anywhere in the brain, remember it's water- and fat-soluble, has effects on the hypothalamus. The hypothalamus normally provides very specific signals to what's called the pituitary gland. This is a little gland that actually sticks out of the brain, but it receives instructions from the hypothalamus. And then the pituitary releases hormones into the bloodstream that go and talk to your adrenals, and your adrenal gland sit right above your kidneys in your lower back. And the adrenals release, as the name suggests, adrenaline, also called epinephrine, and also a molecule called cortisol, which is involved in the kind of longer-term stress response and it has some healthy effects, too, on the immune system. Okay, so the hypothalamic-pituitary-adrenal axis, I know that's a mouthful, you don't need to remember the names, but the hypothalamic-pituitary-adrenal axis maintains your physiological balance of what you perceive as stressful and what you don't perceive as stressful. People who drink regularly, so this, again, could be just one or two drinks per night or it could be somebody that drinks just on Fridays or just on Saturdays or maybe just on the weekend, two to four drinks, well, those people experience changes in their hypothalamic-pituitary-adrenal axis that result in more cortisol, more of this so-called stress hormone, being released at baseline, when they are not drinking. This is really important. People who drink a bit, and when I say a bit, I don't mean one or two sips or even a glass of wine every once in a while. I mean, again, people that are maybe having one drink a night with dinner and maybe on the weekend a few more. Again, I offer a bunch of different patterns to explain how it could also be two or three drinks on Friday or six drinks only on Saturday. Well, all of those groups experience increases in cortisol release from their adrenal glands when they are not drinking, and as a consequence, they feel more stressed and more anxiety when they aren't drinking. This is a seldom talked about effect of alcohol because so often we hear about the immediate effects of alcohol, right? And we've been talking about some of those effects, effects like reducing the amount of stress. I mean, how many times have we heard somebody say, "Ugh, I need a drink." And then they have a drink and they're, like, calmed down, now they can shake off the thoughts about the day's work they can start to think about things in a maybe more grounded or rational way, or at least they believe that, or they can somehow just relax themselves. Well, while that very well may be true, that it can relax them, when they are not drinking, that level of cortisol that's released at baseline has increased substantially. Again, this relates to a defined neural circuit between brain and body, and it has to do with the ratio of cortisol to some of the other hormones involved in

the stress response. We'll provide a reference to the study that describes how all of this works for those of you that really want to delve into it, but let's go back to this issue of those who are prone to alcoholism versus those who are not. Remember, there are people who have genetic variants, meaning genes that they inherited from their parents, that make it more likely that they will become alcoholics. But there are also people who drink often who start to experience this increase in alertness the longer they drink across the night. Part of that effect, we think, is because of changes in this hypothalamic-pituitary-adrenal axis. So alcohol is kind of a double hit in this sense. It's causing changes in our brain circuitry and neurochemistry that, at the time in which we're inebriated, are detrimental, and it's causing changes in neural circuitry that persist long past the time in which we're experiencing the feeling of being tipsy or drunk. Now, again, I don't want to demonize alcohol. I'm not saying, oh, you know, if you have a glass of wine now and again or you drink a beer now and again or even have, you know, a mixed drink now and again or a shot that that's necessarily terrible for you. I certainly do not want that to be the message. What I'm saying is that if people are ingesting alcohol chronically, even if it's not every night, there are well-recognized changes in neural circuits, there are well-recognized changes in neurochemistry within the brain, and there are well-recognized changes in the brain-to-body stress system that generally point in three directions, increased stress when people are not drinking, diminished mood and feelings of well-being when people are not drinking, and, as you'll soon learn, changes in the neural circuitry that cause people to want to drink even more in order to get just back to baseline or the place that they were in terms of their stress modulation and in terms of their feelings of mood before they ever started drinking in the first place. So again, I don't want to demonize alcohol, but I do want to emphasize that there are long-term plastic changes, meaning changes in neural circuitry and hormone circuitry, that, across a period of several months and certainly across a period of years of the sorts of drinking patterns I described, which I think, for most people, are going to sound, like, pretty typical, right? I mean, nothing that I described so far was about drinking a case a night or about binging on alcohol in the way that we often hear about it in the news. These are pretty common patterns of alcohol consumption. I mean, all you have to do is board a transatlantic flight or actually go to an airport on a Sunday afternoon in a sunny area of the US and, you know, people are having three, four, five, six beers, et cetera. Again, personal choice is personal choice. I'm not telling you what to do. But it's very clear that those sorts of drinking patterns are changing neural circuitry and they're changing

hormone circuitry, and I'd love to be able to tell you that they're changing them for the better, but they simply are not. They're actually changing them for the worse, and worse is defined as making people

00:44:53 AG1 (Athletic Greens)

less resilient to stress, higher levels of baseline stress, and lower mood overall. Before we continue with today's discussion, I'd like to just briefly acknowledge our sponsor, Athletic Greens, now called AG1. Athletic Greens, AKA AG1, is an all-in-one vitamin, mineral, probiotic drink that also has adaptogens and digestive enzymes. I've been taking Athletic Greens since way back in 2012 so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and the reason I still drink Athletic Greens twice a day is that it supplies total foundational coverage of my vitamin and mineral needs, and it supplies important nutrients that I need to support my gut microbiome. The gut microbiome, as many of you know, supports the immune system. It also supports the so-called gut-brain axis, which is vital for mood, for energy levels, for regulating focus, and many other features of our mental health and physical health that impact our daily performance and high performance in any endeavors we might be involved in. If you'd like to try Athletic Greens, you can go to athleticgreens.com/huberman and claim a special offer. They're giving away five free travel packs, plus a year's supply of vitamin D3 K2 with every order. And, of course, vitamin D3 K2 are vital for all sorts of things like hormone health and metabolic health and K2 for cardiovascular health and calcium regulation.

00:46:07 Genetic Predisposition for Alcoholism, Consuming Alcohol Too Young

Again, you can go to athleticgreens.com/huberman to claim that special offer. Now, I've been talking a little bit about genetic predisposition, but there are a couple of important points I'd like to make about that. First of all, what sorts of genes are involved in setting someone down the path of alcoholism or not? Well, it should come as no surprise that the genes that chronic alcohol usage modifies, they tend to fall primarily in the pathways related to genetic control over serotonin receptors, GABA receptors, remember that top-down inhibition and the involvement of GABA, and, no surprise, the HPA, the hypothalamic-pituitary-adrenal axis. All of those, of course combined with environment,

they combine with patterns of abuse, right, we know that if you're in a social setting where a lot of people are drinking, the likelihood that you're going to drink is much higher, social pressures, trauma, right? Some people will use alcohol to self-medicate to try and turn off their thinking or to deal with trauma, et cetera. So they combine with the environment, but the genes that are in the serotonin synthesis and receptor synthesis pathway, GABA and HPA axis, combine with environmental pressures to give rise to alcohol use disorders. So there's a fairly coherent picture that we have here, right? This is not a case where, for instance, people that have a lot of the enzyme for metabolizing alcohol, which we'll talk about in a minute, alcohol dehydrogenase, it's not like they are necessarily the people that become alcoholics, whereas certainly in certain cultures, certain Asian cultures in particular, there are gene differences that lead them to have low levels of alcohol dehydrogenase. There are actually people who have so little alcohol dehydrogenase that when they ingest alcohol, they get very red and they just feel sick. So if you're somebody that has a sip of alcohol and you just feel horrible, it makes you feel nauseous, chances are you have gene variants that create a situation where you're not making very much alcohol dehydrogenase. You just simply can't metabolize alcohol so you just get a rapid buildup of the toxic effects of alcohol, the acetaldehyde, you're not converting it into those empty calories. But in cultures where you have a lot of genetic variants and genes expressed in people where they have a lot of alcohol dehydrogenase, sure, they can drink more, and they're converting more of that alcohol from its toxic form to a non-toxic form, and, yes, of course, you will observe more alcoholism in those communities because they're drinking more, but I do want to emphasize that the environmental factors are playing a strong role there, too, because if you can drink more, you're likely to drink more. If you're somebody that feels sick immediately from drinking, it's likely that you're not going to engage in alcohol consumption, especially if these things are genetically related, and, of course, genes and culture and location in the world tend to run together. So do you have the gene for alcoholism? Well, there isn't one single gene. Chances are if you have an immediate relative who's a chronic abuser of alcohol or several relatives who are chronic abusers of alcohol, well, that's going to predispose you to be an alcoholic. But since you don't know which genes you express unless you do genetic testing, and those things are available but most people aren't doing that, this assay, if you will, and it's not an assay, as we say, an assay is a test that you run in the lab to determine something, and it's not one that I recommend that you go drink in order to do, but if you've noticed that you or somebody

else is somebody who can drink a lot throughout the night and have increased energy and can just drink and drink and drink, and especially if there's blackout episodes, not remembering things the next day despite being alert throughout the entire night and so on, well, then I would be very concerned that you might actually have a genetic variant predisposing you to alcoholism. The other thing that predisposes people to abuse of alcohol is age. People who start drinking at younger ages are greatly predisposed to developing alcohol dependence regardless of your family history of alcoholism. Okay, so I'm going to repeat that. People who start drinking younger are at great risk for developing alcoholism even if they don't have alcoholism in their family. Now, of course, you don't have to be an epidemiologist to understand that if you grow up in a family of drinkers and alcohol is everywhere, and especially if there's peer pressure or lack of oversight, then there's going to be a higher tendency, or a higher probability, I should say, that you will start drinking at a younger age. However, even people that grow up nowhere near their relatives, if they start drinking at a young age, so for instance, at 13 or younger or 14 or 15, there's a much higher probability that they're going to develop a long-lasting dependence on alcohol. People who take their first sip of alcohol later, 15, 16, or one would hope even later, I can say one would hope 'cause I'm now of that, you know, age and generation where, you know, you think about all the things that young people do, and you go, "Oh, gosh, if they only would wait or if they only would abstain." You know? It's just what happens. I don't know, there's some neural circuit for that that I can't explain yet. But people who, for instance, drink only once they reach legal age of drinking, which in the US, I believe in every state is 21 years old, if they take their first drink at 21, the probability that they'll go on to develop full-blown alcohol dependence or alcohol use disorder, as it's called, AUD, is very low. Now, a subset of them will because they have such a strong genetic predisposition or maybe life circumstances create a pattern in which they become a chronic drinker. But I found this very interesting. Genes matter, but also the age in which somebody starts drinking really matters. Now, whether or not that's because there are changes in neural circuitry as a consequence of that drinking that make people want to seek out more and more alcohol, or whether or not there's some other effect, maybe it's a change in hormones, et cetera, that predisposes those young drinkers to become chronic drinkers or even full-blown alcoholics, certainly developing alcohol use disorder. There's a definition for that. We can talk about it. It involves the amount of drinking over a certain period of time, et cetera. So it's very clear that drinking early in life creates a propensity for the development of alcohol use disorder

later in life. And while there is a genetic component to developing alcohol use disorder, I find it very interesting that if people who have those gene variants delay their onset of drinking, well, then the probability that they'll develop full-blown alcohol use disorder drops as well. So again, it's genes and environments.

00:52:27 Gut-Liver-Brain Axis: Alcohol, Gut Microbiome, Inflammation & Leaky Gut

It's not an either/or and there's no single gene for alcoholism. Well, I promise you I will also talk about some of the documented positive effects of alcohol. Although they are very few and far between, they do exist. But before I do that, I would be remiss if I didn't emphasize some more of the terrible things that alcohol does and the way that it does it. And for those of you that enjoy alcohol, again, I'd like to say I feel guilty about telling you this because I know how much some people enjoy a good drink every once in a while, and I say a good drink because some people do like the taste of alcohol. I suppose I lucked out in that I don't really like the taste of alcohol and that it just puts me to sleep, but I know that people do enjoy it. And I do want to point out that there is zero evidence that, you know, provided somebody is of drinking age, certainly not in the stage of brain development, that having one drink or two drinks every now and again, meaning every three or four weeks or once a month, that is not going to cause major health concerns or major health issues for most people. I suppose if you have zero or very little alcohol dehydrogenase, it might make you feel sick, but then you're probably not the kind of person that's going to be drinking at all. So, again, if you enjoy alcoholic drinks, I'm not trying to take them away from you by any means, but you should know what drinking does if you're consuming it in this kind of typical chronic pattern, as we can now refer to it, which is that one or two a night or a few stacked up on Friday and maybe three or four on Saturday, this kind of pattern of drinking, which is quite common. And one of the more serious effects that we should think about is the impact on the so-called gut-brain axis, or for sake of today's discussion, the gut-liver-brain axis. I don't think the gut-liver-brain axis has ever been discussed on this podcast, maybe any podcast. Although at the moment I say that, you know, the gut-liver-brain axis, people are going to come after me with, I suppose, gut, liver, and brains. In any event, you have a brain. You have a gut. That gut runs from your throat down to the end of your intestine. Your gut and your brain communicate by way of nerve cells, neurons and nerve connections, the vagus nerve in particular, and by way of chemical signaling. Your gut also communicates by way of

chemical signaling and, believe it or not, by way of neural signaling, too, to your liver. And, as we talked about earlier, the liver is the first site in which alcohol is broken down or metabolized into its component parts. The liver is also communicating with the brain through chemical signaling and neural signaling, so we have the gut-liver-brain axis. And what you find is that people who ingest alcohol at any amount are inducing a disruption in the so-called gut microbiome, the trillions of little microbacteria that take resident in your gut and that live inside you all the time and that help support your immune system and that literally signal by way of electrical signals and chemical signals to your brain to increase the release of things like serotonin and dopamine and regulate your mood generally in positive ways. Well, alcohol really disrupts those bacteria, and this should come as no surprise. I mean, earlier, we talked about this and it's well known, if you want to, you know, sterilize something, you want to kill the bacteria, you pour alcohol on it. And I can remember scraping myself or cutting myself or I was always injuring myself when I was a kid, and, you know, the moment they take out the peroxide, you're like, "Oh, boy, here it comes." But if there's no peroxide around and you've got a wound there and you need to clean it out, yeah, they'll use alcohol, which I do not recommend, by the way. That's one of the harshest ways to clean a wound. But for centuries, thousands of years really, alcohol has been used in order to clean things and kill bacteria. So alcohol kills bacteria and it is indiscriminate with respect to which bacteria it kills, so when we ingest alcohol and it goes into our gut, it kills a lot of the healthy gut microbiota. At the same time, the metabolism of alcohol in the liver, which you now understand, that pathway involving NAD, acetaldehyde, and acetate, that pathway is proinflammatory, so it's increasing the release of inflammatory cytokines, things like IL-6, et cetera, tumor necrosis factor alpha. If you'd like to learn more about the immune system, we did an episode all about the immune system. You can find it at hubermanlab.com. It'll teach you all the basics of what are cytokines, what are mast cells, et cetera. In any event, all these proinflammatory molecules, those are being released. You've now got disruption of the gut microbiota. As a consequence, the lining of the gut is disrupted, and you develop, at least transiently, leaky gut. That is, bacteria that exists in the gut which are bad bacteria can now pass out of the gut into the bloodstream, so you've got a two-hit kind of model here. In biology, we talk about two-hit models, that is, it's kind of a one plus one equals four, and it's generally when you hear two-hit, it's not a good thing. So you've got bad bacteria from partially broken down food moving out of the gut, the good bacteria in the gut have been killed. You might say, why doesn't the alcohol kill the bad

bacteria in the gut? Well, the bad bacteria that are from partially digested food oftentimes escape the gut before the alcohol can disrupt them, and so now you've got leaks in the gut wall, you've got the release of this bad bacteria, you've got inflammatory cytokines and other things being released from the liver, and they are able to get into the brain through what's called a neuroimmune signaling. And what's really bizarre, in terms of the way that this manifests in the brain, I mean, it's not the way I would've done it, but then again, as I always say, I wasn't consulted at the design phase, and anyone who says they did, you should be very skeptical of them. The net effect of this is actually to disrupt the neural circuits that control regulation of alcohol intake, and the net effect of that is increased alcohol consumption. So this is just terrible, right? I mean, so you take in something that disrupts two systems, the gut microbiota, and it disrupts in two ways, it's killing the good gut microbiota and it's allowing the bad bacteria to move from the gut into the bloodstream, you've also got proinflammatory cytokines coming from the liver, and those converge or arrive in the brain and create a system in which the neural circuits cause more drinking. That's a bad situation. And this is why people who drink regularly, even if it's not a ton of alcohol, again, of the sorts of patterns of drinking I talked about before, and certainly for those that are chronic heavy drinkers, what you end up with is a situation in which you have inflammation in multiple places in the brain and body and the desire to drink even more and to further exacerbate that inflammation and the gut leakiness. So this is basically a terrible scenario for the gut-liver-brain axis, and it's especially prevalent in so-called alcohol use disorder, again, people that are ingesting somewhere between 12 and 24 drinks per week. For those of you that are interested in learning more about the gut-liver-brain axis and, in particular, alcohol use disorder,

00:59:46 Tool: Improving/Replenishing Gut Microbiome

I'll provide a link in the show note captions. There's a wonderful review on this that details that. But on the positive side, it points to the possibility that at least some, again, at least some, of the negative effects of alcohol consumption, whether or not you're somebody who's currently ingesting alcohol or who used to ingest alcohol and is trying to so-called repair these systems of the brain and body, whether or not replenishing the gut microbiota is going to be beneficial. And we know that there are ways to do that, and we know that there's at least some promise for the ability for this system to repair itself. How does one do that? Well, I've talked before about this on the podcast, but studies done by

colleagues of mine at Stanford, Justin Sonnenburg, who's been on this podcast as a guest, an amazing episode all about the gut microbiome, and his collaborator, Chris Gardner, also at Stanford School of Medicine, have explored not alcoholism, but what are ways to improve the gut microbiota, in particular, to reduce the production of inflammatory cytokines and to adjust what's called the inflammatome. You've heard of the genome and the proteome, et cetera. Well, the inflammatome is the total array or at least the near-total array of genes and proteins that control inflammation. How can you reduce inflammation and make that inflammatome healthier? Well, they've shown that two to four servings of fermented foods per day, and here, I'm not referring to fermented alcohol. I'm talking about low-sugar fermented foods, so things like kimchi, sauerkraut, natto, for those of you that like Japanese food. There are others, I know, things like kefir or things like yogurts that have a lot of active bacteria, again, low-sugar varieties of all these things. Those are terrific at reducing inflammatory markers and at improving the gut microbiome. One could imagine that either inoculating oneself from some of the effects of alcohol, although I'd prefer that people just not drink alcohol chronically, frankly, or if somebody's trying to repair their gut microbiome because they ingested a lot of alcohol or because they had a lot of these inflammatory cytokines for many years or even a short period of time, regular ingestion of two to four servings of these fermented foods can be quite beneficial. I want to make it clear, that has not been examined specifically in the context of alcohol use disorder, but because a huge component of the negative effects of alcohol use disorder are based in this gut-liver-brain axis and disruption of the gut microbiome and the inflammatory cytokines, it stands to reason that things that are well-established to improve inflammation status, in other words, reduce inflammation, such as ingesting two to four servings of low-sugar fermented foods per day, makes sense in terms of trying to repair or replenish the system. One could also imagine taking probiotics or prebiotics. Certainly that would work as well, although I've sort of favored the discussion around fermented foods and replenishment of the gut microbiome mostly because there are more studies that have examined that in humans and because of the direct relationship

01:02:44 Reducing Alcohol Consumption & Stress

that's been established between doing that and reducing negative markers within the inflammatome. And I should mention, along the lines of repair and recovery, I put out a

question on Twitter the other day. I said, "What do you want to know about alcohol?" I got more than 1,000 questions and I'll take some more of those questions a little later in the episode. But one of the things I noticed is that many of the questions, hundreds, in fact, related to the question of, well, if I drank a lot previously, am I doomed? Can I reverse the negative effects? Or, you know, I'm trying to drink less and I'm trying to improve my health as I do that. What should I do? Well, certainly focusing a bit on the gut microbiome ought to be useful. The other thing I should mention is as people wean themselves off alcohol, even if they're not full-blown alcoholics or have alcohol use disorder, they should understand that that increase in cortisol that we talked about earlier that leads to lower stress threshold and greater feelings of anxiety and stress, that's going to be present and it's going to take some time to dissipate. So for some people, it might even just be helpful to realize that as you try and wean yourself off alcohol or maybe you even go cold turkey, that increased anxiety and feelings of stress should be expected. And in that case, I would point you to an episode that we did on master stress. You can find that, again, at hubermanlab.com. It's got a ton of behavioral, nutritional, supplementation-based, exercise-based, I suppose, exercise is behavioral, but a lot of tools. You can navigate to those easily 'cause we have timestamps so you can go right to the topic of interest. Those tools are going to be very useful in trying to clamp or control your stress. And the point here is just that some increase in stress should be expected, and it should be expected because of that increase in cortisol

01:04:25 Hangover: Alcohol & Sleep, Anxiety, Headache

that occurs with even low-level consumption yet chronic alcohol consumption. Now I'd like to talk about a fairly common phenomenon, which is post-alcohol consumption malaise, also referred to as hangover. Hangover is a constellation of effects ranging from headache to nausea to what's sometimes called hangxiety, which is anxiety that follows a day of drinking. Hangxiety, I think we can understand physiologically if we think about that process of alcohol intake increasing the amount of cortisol and the ratio of cortisol to some other stress hormones. That well explains why some people wake up the day after or even the day the day after a night drinking and feel anxious and not well and stressed for reasons they don't understand. So if you're somebody who experiences hangxiety, then, again, I refer you to the master stress episode that we put out some time ago, and you can find that at hubermanlab.com, tools to deal with anxiety, tools to

deal with stress, ranging, again, from behavioral to nutritional and supplement-based, et cetera. That, of course, is not justification for going out and drinking so much that you get hangxiety-induced hangover, but for those of you that are experiencing post-alcohol consumption hangxiety, as it were, that could be a useful resource because I certainly don't want anyone experiencing uncomfortable amounts of anxiety, and there are great tools and resources for that. Now, the other aspects of hangover, such as the stomachache or headache or feelings of malaise or fogginess, those could be related to a number of different things and probably are related to a number of different things. First of all, the sleep that one gets after even just one, yes, even just one glass of wine or a beer is not the same sleep that you get when you don't have alcohol circulating in your system. And not trying to be a downer here, but this was discussed in the Huberman Lab Podcast episode where I had Dr. Matthew Walker from UC Berkeley on. And, of course, Dr. Walker is a world expert in sleep, runs one of the preeminent laboratories studying sleep and its effects, wrote the incredible book, "Why We Sleep," and so on. Dr. Walker told me, and it certainly is supported by lots and lots of quality peer-reviewed studies in animals and in humans, that when alcohol is present in the brain and bloodstream that the architecture of sleep is disrupted. Slow-wave sleep, deep sleep, and rapid eye movement sleep, all of which are essential for getting a restorative night's sleep, are all disrupted. So for those of you that are drinking a glass or two of wine or having a hard liquor drink or a beer in order to fall asleep, the sleep you're getting is simply not high-quality sleep, or certainly not as high-quality as the sleep you'd be getting if you did not have alcohol in your system, Of course, when we're talking about hangover, we're talking generally about the consumption of more than just one or two drinks. Of course, for some people, one or two drinks is probably sufficient to induce hangover, but for most people it's going to be having three or four, exceeding their typical limit, as it's called. Again, not the legal limit, that's a whole other business. But when one ingests too much alcohol for them, one of the reasons they feel terrible the next day is because their sleep isn't really good sleep. In fact, it's not even sleep. It's often considered pseudosleep, or at least that's what it's called in the sleep science field, because people are in kind of a low-level, hypnotic kind of trance, it's not real sleep, there are multiple bouts of waking up, they may not even realize they're waking up multiple times. Okay, so there's the sleep-induced effects. Then there are the disrupted gut microbiome effects, some of which we talked about earlier so now you understand the mechanism of alcohol destroying good, healthy gut microbiota, which then leads to

leaky gut and things of that sort. But one could imagine, again, could imagine, and there is some evidence starting to support this, that, again, ingesting low-sugar fermented foods or maybe even prebiotic or probiotics to support the gut microbiome might assist in some of the gut-related malaise associated with hangover. In other words, get those gut microbiota healthy again as quickly as possible, or maybe even before you drink, have those gut microbiota healthy. I would hope that you'd do that. I think everybody should be doing something to support their gut microbiome, whether or not it's the ingestion of low-sugar fermented foods daily or at least on a regular basis or ingestion of probiotic or prebiotic. The gut microbiome is so important for so many different things. In terms of hangover and headache, we know that that's caused by vasoconstriction, the constriction of blood vessels that tends to occur as a rebound after a night of drinking. Alcohol can act as a vasodilator, it can dilate the blood vessels. Part of that is associated with the increase in so-called parasympathetic tone. We have an autonomic nervous system and it's got a sympathetic component. These are neurons that make us more alert, and if they're very active, they make us very stressed. There's also the parasympathetic aspect of the autonomic nervous system. This is all just fancy geek speak for the parts of your brain and body, the nerve cells that make you very relaxed. When you're very relaxed, there tends to be vasodilation. It allows for more movement of blood and other things through the bloodstream, and alcohol tends to induce some vasodilation, at least in some of the capillary beds. And then when the alcohol wears off, there's vasoconstriction and people get brutal headaches. That's why some people will take aspirin or Tylenol or Advil or things like that, the sort of non-steroid anti-inflammatories. I should mention, there is a lot of literature coming out that some of these non-steroid anti-inflammatory drugs are not good for us for a number of different reasons, the way they impact the liver, the way they impact the immune system, and, no surprise, the way they impact the gut microbiome. So I'm not one to tell you what medications to take or not take, but you certainly would want to do a quick web search of effects of non-steroid anti-inflammatories and aspirin before you start taking those, or stop taking those, for that matter. Generally, they will alleviate headache, but they can often have other issues, including liver issues. And keep in mind, the night after drinking, your liver has already taken a beating because of the need of the liver to convert alcohol from acetaldehyde into acetate, which is now a pathway that you well understand. So I'm not certain and, in fact, I believe it's not the greatest idea to burden your liver further through the use of things that are going to cause it to have to work harder and

metabolize things if the goal is simply to alleviate a headache. There's a lot of kind of lore, old school lore about how to relieve a hangover. We already talked about how eating food won't do that but eating food will prevent the rapid absorption of even more alcohol into the bloodstream. There's the lore that one should simply ingest more alcohol. What terrible advice that is. That's just going to delay an even worse hangover. However, I'd be remiss if I didn't say that the reason that that myth came to be, or that, I should say, that truth came to be, because indeed ingesting more alcohol will alleviate a hangover but then a worse hangover will show up, the reason that came to be is because ingestion of more alcohol will cause those constricted vessels that are giving the headache to dilate again. But, of course, ingesting more alcohol to relieve a hangover is simply a bad idea. Just don't do it. I think this is called the hair of the dog approach. Maybe someone can put in the show note captions on YouTube why it's called the hair of the dog. I can come up with a few ideas but they're not going to be very good ones, and some of them would probably even be outright ridiculous. So do not ingest more alcohol simply to try and recover from a hangover.

01:12:11 Hangover Recovery, Adrenaline & Deliberate Cold Exposure

I know many people have tried that one before but that's a terrible idea. Now, one thing that you'll also hear out there is that deliberate cold exposure, for instance, taking a cold shower, might relieve hangover. I find this one particularly interesting because we've done episodes on the benefits of deliberate cold exposure. We have an entire episode about that. You can find it, again, hubermanlab.com. There are direct links to some of the tools related to deliberate cold exposure and we have an entire newsletter on deliberate cold exposure protocols that you can find on hubermanlab.com, go to our Neural Network newsletter. So those of you that are interested in ice baths and cold showers and ways to leverage those, you can find that there. What you won't find there is a description of how to use deliberate cold exposure for sake of treating hangover. But here, I went into the literature and I found something kind of interesting. There is some evidence that increasing levels of epinephrine in the bloodstream can actually help with alcohol clearance. That was very surprising to me, and I want to point out this is not a large and robust literature, but there's some evidence pointing to the fact that when levels of epinephrine, adrenaline, are raised in the brain and bloodstream, that some of the components of alcohol metabolism can be accelerated and some of the inebriating

effects of alcohol can be reduced, so maybe this old school lore of taking a cold shower actually has something to it. So in thinking about the use of deliberate cold exposure in order to reduce the effects of hangover or to more rapidly clear alcohol from the brain and bloodstream, I want to be very clear and I want to emphasize your safety. The way to do that is to understand that alcohol lowers core body temperature, okay? It can make people slightly hypothermic. It's going to drop core body temperature. So if you were inebriated and you went and got into a body of water, right, a pool or a lake or something, first of all, that's extremely dangerous to do while you're inebriated, right? People drown all the time. People drown, they die as a consequence of doing that, so please don't do that. But also, if it's very cold water, your core body temperature is going to drop even further. Now, if you've heard the episodes that I've done on deliberate cold exposure previously, I've talked about how normally, when people are not ingesting alcohol, they get into an ice bath or a cold shower and their body temperature initially dips but then it rebounds and increases. That's a process that's going to occur when people do not have alcohol in their system. When you have alcohol in your system, one of the reasons that you become hypothermic is because there's a disruption in those hypothalamic brain areas, in particular, the brain area called the medial preoptic area that regulates core body temperature. So it's not so much that alcohol makes you cold, it's that alcohol disrupts the central command centers of the brain that control temperature regulation, and that leads you to be slightly hypothermic. So if you then go get into a very cold lake or you get into even a cold shower or an ice bath, there's the possibility of you going very, very far down the ladder into very hypothermic territory and that can be very dangerous. Now, in terms of dealing with hangover when the alcohol has been largely cleared from your system, well, that's where some of this old lore combines with some of the modern science and says, well, if you can spike adrenaline, and certainly getting into an ice bath or getting into a cold shower or any kind of cold body of water, provided you can do that safely, that will sharply increase your adrenaline and, I should say, your dopamine. That's been shown and we've talked about this on the podcast before. You get these long, extended increases, several hours of increases in dopamine from deliberate cold exposure. It's well-documented in humans, by the way. So one could imagine using deliberate cold exposure as a way to accelerate the recovery from hangover. Provided that's done safely, I think there's no reason to not explore that, and if you wonder what safely is and what temperatures to use, please check out the episode on deliberate cold exposure. Cold showers, therefore, might

actually be one way to at least partially relieve hangover. Certainly the science from various places in the literature converged to say that. But, again, be careful, please, please, please be careful not to get into cold water when you are inebriated. It's absolutely dangerous for all the obvious reasons, and it's dangerous also for the nonobvious reasons, not the least of which is the dramatic decreases in core body temperature that can make you dangerously hypothermic. Now, how would you go about using deliberate cold exposure to accelerate recovery from hangover? Well, there, I would look to the kind of standard protocols of, you know, one to three minutes or maybe even six minutes if you can tolerate it, or if you're really cold-adapted, maybe you do seven or ten minutes in a cold shower, although that could be a lot. Most people are going to experience a sharp increase in epinephrine, in adrenaline, and a long-lasting increase in dopamine from one to three minutes of deliberate cold exposure, ideally done immersion up to the neck, again, do this safely, please, please, please, or a cold shower where you're getting under the shower as much as possible. How cold? Well, that's going to vary person to person. I suggest making it as cold as is uncomfortable such that you really want to get out but that you know you can stay in safely without, for instance, giving yourself a heart attack, because if the water is really, really cold, of course you can give yourself a heart attack. Most showers won't go that cold, although probably some will. Again, please use caution.

01:17:16 Hangover Recovery, Dehydration & Electrolytes

Spike your adrenaline, spike your dopamine with deliberate cold exposure safely. Other components of hangover that could be good targets for trying to alleviate hangover, and, here, I hope you are getting the picture because it is accurate to say that hangover is a multifaceted phenomenon. It's not like one molecule and one receptor. It's a bunch of things happening in the brain and body. But is the dehydration associated with alcohol? Alcohol is a diuretic. For multiple reasons, it causes people to excrete not only water but also sodium. Sodium is an electrolyte critical for the function of neurons, so making sure that you have enough sodium, potassium, and magnesium, so-called electrolytes, is going to be important for proper brain function, bodily organ function. Even for people that have just had one or two drinks the night before, it's likely that your electrolyte balance and your fluid balance is going to be disrupted, and that's because alcohol also disrupts the so-called vasopressin pathway. I talked a lot about vasopressin and the way

that it interacts with and controls different aspects of water retention and water release from the body in the form of urine in the episode on salt. So, again, I'm referring to hubermanlab.com as the site where you can find that episode on salt balance and ways to restore electrolyte balance. Having your electrolytes at the proper levels before you drink is ideal. Some people will say for every glass of alcohol that you drink, you should drink one glass of water. I would say better would be two glasses of water given the dehydrating effects of alcohol, and even better would be water with electrolytes. That certainly would set you up for a better day the next day. And if you don't manage to do that, 'cause I suppose it's kind of geeky walking around with electrolyte packets out at the bar or whatnot, although, you know, geeky, in my book, is a good thing, the next day, you could take some electrolytes upon waking, maybe even some before you go to sleep the night of drinking. So hangover's made worse by disturbed sleep, made worse by disrupted gut microbiome, made worse by disrupted electrolytes, made worse by the depletion of epinephrine and dopamine. That's why replenishing the microbiome with fermented foods, low-sugar fermented foods, that is, that's why using safe deliberate cold exposure for spiking adrenaline and for increasing dopamine, and that's why consuming electrolytes are all going to be beneficial. The folks over at examine.com, a website that I really like because it just has so much useful information, have assembled a list of things that have been proposed, purported to improve, or, I should say, to remove the effects of hangover, and, as they point out and I would like to point out over there, there isn't a lot of quality science to support the idea that any one compound can eliminate hangover. And that's probably because hangover, again, arises from multiple organs and tissues and systems in both the brain and body. Nonetheless, they have a terrific list over there of things, everything from Japanese pear fruit juice has been proposed to do this, to some other really esoteric things, even things like yohimbine. Frankly, when I look at the literature there and elsewhere, one simply cannot find the magic substance, the one herb, the one potion that can wipe away hangover. Getting rid of hangover is going to be best solved by doing a collection

01:20:45 Types of Alcohol & Hangover Severity, Congeners

of a small number of very powerful things, of which I've already listed off a few. However, there are some additional things that one can do for relieving hangover, and one of them is to be very thoughtful about what sorts of alcohol one consumes. So I find this

interesting. There have actually been studies of which types of alcohol lead to the greatest hangovers. There's actually a lot of legend and lore about this as well. Some people have said, for instance, that drinks that have a high sugar content lead to greater hangovers. Turns out that's not the case, or at least that's not what the science points to. If you look at the expected hangover severity, what you find is that at the bottom end of the scale, there's a drink that I'm not going to tell you, for the moment, but what you find is that near it is, for instance, beer. The consumption of beer, provided it is not overconsumption, right, it's not far beyond the tolerance of the individual, so it's one or two beers, is less likely to cause a hangover than, say, whiskey. And a glass of whiskey, or, you know, not as much whiskey as beer, of course, but a glass of whiskey, for instance, is more likely to cause hangover than gin, as it turns out. Again, this is what's fallen out of the data. And yet a glass of rum or red wine is more likely to cause a hangover than any of the other things I've mentioned so far. At the top, top, top of the list of drinks that induce hangover is brandy. And one could then say, "Well, doesn't brandy have a lot of sugar? Maybe it's the sugar that's causing hangovers." And this is something that's been, again, discussed over and over, that people say, "Oh, it's the high-sugar drinks that cause hangover." It turns out, however, that when one looks at alcoholic drinks and sugar content and hangover, at the very bottom of the list is, gosh, this makes me cringe just to think about, is ethanol diluted in orange juice. Ugh, I can't believe people actually drink this, but ethanol diluted in orange juice. So this is not vodka and orange juice, okay? Vodka was third on the list from the bottom of drinks that induce hangover. Again, this is within amounts that are comfortable for the person to drink, that they have enough experience with or that they have the body weight to tolerate without getting very, very drunk. So the point is that if it were sugar that's causing hangover, well, then the ethanol diluted in orange juice would probably be at the top of the list in terms of inducing hangover. But it's not, it's at the bottom of the list, and brandy is at the top of the list. So what you find is that what scales from ethanol diluted in orange juice to beer to vodka to gin, here, I'm ascending the hierarchy of things that cause hangover, gin, white wine, whiskey, rum, red wine, and then brandy at the peak, it's sort of the world heavyweight champion of hangover-inducing drinks, well, what's increasing are congeners within those drinks. Congeners are things like nitrites and other substances that give alcohol it's distinctive flavor and that also lead to some of the inebriating effects of alcohol. Now, then you ask, "Okay, well, what is it that these congeners are doing? And what are these nitrites doing?" And guess what? While they do have effects on the

brain and on other tissues, their main effects are to disrupt the gut microbiome. So what this points to again is that having a healthy gut microbiome and perhaps ensuring that you bolster your gut microbiome the day after drinking is going to be especially important for warding off hangover or at least reducing the effects of hangover or the symptoms of hangover or both. I would love to see a study on this. I could imagine designing the study myself, although this isn't really the sorts of things my laboratory does, but can imagine some people getting probiotic and prebiotic, some regularly, some just after drinking, or low-sugar fermented foods, and see what the effects are in terms of subjective effects of hangover but also some physiological measures. I think the way to think about hangover overall is that, again, it represents a multifaceted, multi-organ, multi-tissue phenomenon, and the best way to deal with it is as a multi-cell, multi-tissue, multi-chemical phenomenon. And before I listed off some of the things that one could do in order to adjust hangover, again, the one that comes out at the top of that list, I believe, at least based on my read of the data, is to support the gut microbiome and certainly not to ingest more alcohol. And I suppose if we were to get really honest with one another

01:25:25 Alcohol Tolerance, Dopamine & Serotonin, Pleasure-Pain Balance

and ask what's the best way to avoid a hangover, it would be to not drink in the first place. So we've covered the major effects of alcohol that lead to this state that we call drunkenness or inebriation. Again, there's a range there. You can be tipsy, people can be blackout drunk, people can be passed out drunk. We've also talked about hangover and the fact that it's a multifaceted phenomenon and recovery from hangover involves a multifaceted approach. Next I want to talk about tolerance. Tolerance to alcohol is a very interesting phenomenon. It has roots mainly in the brain and in brain systems. There's not time in the world, let alone within this podcast, to get into all the aspects of tolerance. There are more than 10 different types of tolerance. There's functional tolerance, chronic tolerance, rapid tolerance, there's metabolic tolerance, there's psychological tolerance. Let's keep it simple for sake of today's discussion. And for those of you that are interested in learning about all the different types of tolerance and aspects of tolerance, there's an excellent review, we will provide a link to this. This was published in 2021, so it's pretty recent, in the journal "Pharmacology Biochemistry and Behavior." Incidentally, or not so incidentally, that was the first journal I ever published in so I have a particular affection for that journal. Nonetheless, it is called Tolerance to alcohol: A critical yet

understudied factor in alcohol addiction. And while this paper does include alcohol addiction in the title, it's not just about alcohol addiction. Here's the basic summary of what tolerance is. First of all, tolerance refers to the reduced effects of alcohol with repeated exposure, and it is caused mainly by changes in neurotransmitter systems in the brain that are the direct consequence of the toxicity of alcohol, that aldehyde molecule that we talked about before. There's an enormous number of chemicals that change with repeated exposure to acetaldehyde, everything from GABA to dopamine to serotonin, second messenger systems, adenosine, and on and on. Rather than go into each of those in detail, I just want to talk about the contour of the reinforcing and the tolerance-inducing effects of alcohol. What do I mean by that? Well, here we are back to our old friend, meaning the molecule that comes up over and over again in these podcast episodes, which is dopamine. Whether or not somebody has a predisposition to alcoholism or not, whether or not they're experienced drinker or not, when people initially start drinking, there are increases in dopamine, or what we call dopaminergic transmission. Dopamine is involved in motivation, in craving, it creates a sense of well-being, it increases energy, again, typically only at the beginning of alcohol exposure. That occurs in most people as a sharp spike, as a increase. Again, if somebody does not have alcohol dehydrogenase or has very low levels of the enzyme that convert that acetaldehyde into acetate and that metabolize alcohol, in other words, they will feel sick and lousy in a way that will override any recognition of the dopamine release. They're going to be the people that are listening to this and just thinking, "Alcohol just makes me feel sick. I don't like it." Okay, that's a specific subcategory of people, but most people experience some sort of mild euphoria. That's why so many people drink, right? The current estimates are that in most countries, and certainly in the US, as many as 80% of the adult, legal drinking age population drinks alcohol, and that number could be even higher now because in the last couple of years, there's been a trend towards increased alcohol consumption, especially in the wake of the pandemic and during the pandemic. Topic for another time. So there's an increase in dopamine and an increase in serotonin, so it's kind of an increase in well-being, an increase in mood, but it's a very short-lived increase. Very soon after, and actually triggered by that increase, is a long and slow reduction in dopamine and serotonin and related molecules in circuits. So basically what you're getting is a blip of feel good followed by a long, slow arc of feeling not so great, which is why, typically, people will drink again and again across the night. The key thing to understand about tolerance is that with tolerance, the duration of that long, slow

reduction in dopamine and serotonin gets even longer. In other words, the negative effects of alcohol that happen after the initial feeling good, extend longer and, in fact, get more robust. However, there's also a reduction in the reinforcing properties of alcohol. There's a shrinking of the feel good blip that happens when one first ingests alcohol, and this has been measured in animals and humans. So the first drink that somebody has, provided they have enough alcohol dehydrogenase so that doesn't make them feel nauseous and sick right away, they feel really good. And then as it wears off, they feel kind of lousy and they want to drink more so they might drink more. With each subsequent drink, and even drinks on different nights or even different weeks, the amount of dopamine that's released is reduced, the amount of serotonin that's released is reduced. So what you're getting is less and less of the reinforcing properties of alcohol, the feel good stuff, and more and more of the punishment pain signal aspects of alcohol. This is the contour of chemical release in the brain that was referred to by my colleague, the incredible Dr. Anna Lembke, who's a medical doctor. She wrote the incredible book "Dopamine Nation." She was a guest on this podcast, on Joe Rogan's podcast, on Rich Roll's podcast and several other podcasts. World expert in addiction, and she talked about this pleasure-pain balance that extends beyond alcohol to things like sex and gambling and to other behaviors that can potentially become addictive but certainly includes alcohol. So tolerance, it seems, is a process in which people are ingesting more and more alcohol as an attempt to get that feeling of well-being back, but what they're really getting is an extended period of punishment, of pain, and of malaise from the alcohol. Now, you might say, "Well, how does that relate to tolerance?" Well, it turns out what they do behaviorally, and when I say they, I mean animals do this and humans do this, is they start drinking more and more in an attempt to activate those dopamine and serotonin neurons and receptors, and as they do that, there is an increase in alcohol dehydrogenase, so the enzyme that metabolizes alcohol is increased because the body and liver have to contend with all that alcohol, so now you've got, again, the two-hit model. You're getting less of the feel good chemicals, more of the negative chemical release, or pattern of subjective feeling, I should say, and you're metabolizing alcohol more quickly and more readily, but it's not taking you to a better place in terms of how you feel. That's one of the major underlying reasons for what we call tolerance. So if you're somebody who drinks and you notice that the feeling that you are seeking with alcohol is now requiring an additional drink, or drinks plural, chances are you are disrupting the dopamine and serotonergic systems of your brain, and you

are doing that in a way that is increasing the pain and punishment signals that follow alcohol ingestion. And again, that's not just on the night that you're drinking but afterwards as well. Is that all bad news? Well, pretty much. But the good news is that if you abstain from drinking for some period of time, then, of course, these systems reset. How long you need to abstain will depend on how much you were drinking and how long you were drinking for. Certainly people who have alcohol use disorder or who are alcoholics, their main goal should be to quit alcohol completely. I know there's some debate about this, and I don't want to get into that debate because I'm certainly not going to try and direct anyone's recovery. There are expert counselors and MDs and people that can work with people. In fact, for some very heavy drinkers and people with serious alcohol use disorder, going cold turkey, that is, stopping drinking completely, can actually be medically dangerous. So the path to sobriety for certain people looks different than the path to sobriety for other people. What I'm referring to here are people that are ingesting, again, somewhere between, on average,

01:33:36 Are There Any Positive Effects of Alcohol?, Resveratrol

one to two drinks per night, whether or not that's done night to night or whether or not that's condensed to weekend use. I know a number of people are going to ask, perhaps are screaming, "Is drinking good for me in any way?" For instance, many people have probably heard that resveratrol is good for people and that red wine is rich in resveratrol. I hate to break it to you but the reality is that if indeed resveratrol is good for us, and there's some debate about this, some people say strongly yes, some people say no, other people say maybe, the amount of red wine that one would have to drink in order to get enough resveratrol in order for it to be health promoting is so outrageously high that it would surely induce other negative effects that would offset the positive effects of resveratrol. So I wish I could tell you different. Again, I'm not here to be the bearer of bad news, but the statement I just made was confirmed by Dr. David Sinclair when he was a guest on this podcast. It's confirmed by other researchers who work on resveratrol and related pathways. I wish I could tell you that red wine is good for your health, and indeed it might be through some other mechanisms. So, for instance, there have been studies of low to moderate red wine consumption. This would be anywhere from one to four glasses per week. And I don't mean enormous glasses, I mean six-ounce glasses of red wine. And in those cases, some of the stress reduction that can be induced by

consumption of red wine, maybe some of the other micronutrients and components within red wines, in particular red wines that come from particular grapes, and this gets really nuanced and, frankly, is not well worked out in the peer-reviewed literature or certainly not clinical trials, at least not that I'm aware of. Tell me if you're aware of a great clinical trial on this. Well, there may be some positive effects of that very low level of consumption. I'm not trying to take away anybody's red wine. I'm not trying to take away anybody's anything. I would be remiss, however, if I didn't tell you that resveratrol as the argument for drinking, and drinking red wine in particular,

01:35:42 Alcohol & Brain Thickness

is just not a good one. It's just not supported by the peer-reviewed research. A few other things about alcohol and health. At the beginning of the episode, I referenced a study showing that indeed not just heavy alcohol consumption of 12 to 24 or more drinks per week, but also light to moderate alcohol consumption of any type, wine, beer, spirits, et cetera, does reduce the thickness of the brain. It really does reduce cortical thickness. In fact, it actually scales with the amount of alcohol that people drink, and this has been well-documented in a number of different studies. I can provide a link to several of these. One of the more striking ones actually shows that there's almost a dose-dependent increase in shrinkage of gray matter volume and in these white matter tracts, these axons, these wires, as it were, that connect different neurons as a function of how much alcohol people drink. And that's also what's been seen in this recent study that I referenced at the beginning and that's in the show note captions. So, again, probably the best amount of alcohol to drink would be zero glasses per week or ounces per week. For those of you drinking low amounts of alcohol, make sure you're doing other things to promote your health. And for those of you that are drinking moderate and certainly for those of you that are heavy drinkers, please do everything you can to move away from that and to quit entirely. But even for the moderate consumers of alcohol, you are going to want to be aware of some of the negative health effects and do things to offset those

01:37:11 Alcohol & Cancer Risk: DNA Methylation, Breast Cancer Risk

if indeed you're not going to stop drinking or reduce your intake. One of the really bad effects of alcohol, but that's extremely well-documented, is the fact that alcohol, because

of this toxicity of acetaldehyde and the related pathways, can alter DNA methylation, it can alter gene expression. That can mean many things in different tissues, but it is associated with a significant increase in cancer risk, in particular, breast cancer, and in particular, because breast tissue is present in both males and females, but in women, it's especially vulnerable to some of the DNA methylation changes, well, breast cancer in women has a relationship to alcohol intake, and alcohol intake has a relationship to breast cancer in women. In fact, there has been proposed to be a anywhere from 4 to 13% increase in risk of breast cancer for every 10 grams of alcohol consumed. How much is 10 grams? Well, there, we need to think a little bit about the variation in the amount of alcohol and different drinks across the world. Different countries serve different sized drinks and have different concentrations of alcohol in those drinks. So without going down too much of a rabbit hole and just giving you some good rules of thumb to work with, there have been studies of the percentage of alcohol included in different drinks and the sizes of different drinks that are served in different countries, and here's kind of a patchwork of those findings. In Japan, one beer, one glass of wine, or one shot of liquor, as it's served there, tends to include anywhere from seven to eight grams of alcohol. In the US, one beer, which generally is 12 ounces if it's in a bottle, one glass of wine or a shot of liquor tends to include about 10 to 12 grams of alcohol. And in Russia, one drink of the various sorts that I just described typically will have as much as 24 grams of alcohol because of the differences in the concentration of alcohols and the sizes of drinks that are poured in these different countries, okay? Of course, there are other countries in the world, those countries are also vitally important, but those are the ones that I extracted from the studies that I could find. What does this mean? Well, what we're talking about is that for every 10 grams of alcohol consumed, so that's one beer in the US, maybe a little bit more than one beer in Japan, or basically a third of a drink in Russia, there's a 4 to 13% increase in risk of cancer. That's pretty outrageous, right? And you might think, "Wait, how could it be that, you know, this stuff is even legal?" Well, look, as I described before, it's a toxin. It's also a toxin that people enjoy the effects of. I mean, in the US at least, they tried prohibition. It certainly did lead, yes, did lead to a reduction in alcohol-induced health disorders, in particular, cirrhosis of the liver. It also led to a lot of crime because it became a substance that a lot of people still wanted and that people were willing to break the law in order to provide, or, I should say, to sell and provide. But the point is that the more alcohol people drink, the greater their increase of cancer, in particular, breast cancer. And that's because of the fact that alcohol has these

effects on cells that include changes in gene expression, and cancer, that is, the growth of tumors, is a dysregulation in cell cycles, right? A tumor is a aggregation or the proliferation, aggregation is stuff sticking together, by the way, proliferation is stuff duplicating, a proliferation or aggregation of cells that could be a glioma, glial cells, glioma brain tumor, right? It could be lymphoma, so within the lymph tissue, et cetera. The mutations that alcohol induces to cause this are wide ranging, some of those are starting to be understood. For those of you that are interested in cell biology, I'll just mention that the PD-1 pathway, again, this is super specialized and for the aficionados only, you don't need to know this, the PD-1 pathway seems to be upregulated and, and we knew this from the discussion earlier, there's a downregulation in some of the anti-inflammatory molecules that help suppress this proliferation of cancers. Nowadays, there's a lot of interest in the fact that the immune system is constantly combating cancers that exist in us all the time. You know, little tumors start growing and our immune system goes and gobbles them up. Little tumors start growing, the immune system senses inflammation, sends out these incredible cells, these killer B-cells and T-cells, and beats them up. Cancers proliferate and take hold and cause serious problems when the proliferation of cells exceeds the immune system's ability to gobble up and remove those cells. There are other mechanisms of regulating cancers, but that's one of the primary one. And alcohol hits it. Again, it's a two hit model. It increases tumor growth and it decreases the sorts of molecules that suppress and combat tumor growth. So, again, even low to moderate amounts of alcohol can be problematic for sake of cancers, in particular, breast cancers. Epidemiologists and health specialists love to try and compare different substances in terms of how bad they are. Rarely do they compare substances in terms of how good they are, but sometimes they do. And what they'll sometimes tell you and what you can find in the literature is that ingesting 10 to 15 grams of alcohol a day, so that would be like one beer in the US or one glass of wine, is the same as smoking 10 cigarettes a day. Frankly, it's hard to make that direct relationship really stick because, you know, it's a question of, you know, how long people inhale, do they have a predisposition to a lung cancer, et cetera. But even if that number is off by plus or minus two cigarettes, or even if that number was the equivalent of one glass of wine equals one cigarette per day... I think there's general consensus now that nicotine consumed by vaping or by cigarette, it's bad for us in terms of lung cancer and other forms of cancer. And for some reason, I don't know why, because this knowledge about alcohol and cancer and these established relationships have been known since

the late 1980s. The first, you know, landmark paper on this was published in 1987. I can provide a link to that paper. It's actually quite interesting to read. Well, the relationship is there and yet we don't often hear about it, right? In fact, before researching this episode, I had heard before that alcohol can increase cancer risk but I wasn't aware of just how strong that relationship is. Because of the serious nature of what we're talking about and because I would hate to be confusing or misleading to anybody, I want to just emphasize that this statistic, that there is a 4 to 13%, depending on which study you look at, a 4 to 13% increase in the risk of cancer, in particular, breast cancer, for every 10 grams of alcohol consumed, that's 10 grams per day, so that's one drink per day. But I do want to emphasize that if that equates to seven drinks per week

01:44:31 Mitigating Cancer Risk, Folate, B Vitamins

and all those seven drinks are being consumed on Friday and Saturday, it still averages to 10 grams per day. And I also want to emphasize that there are things that people can do to at least partially offset some of the negative effects of alcohol as it relates to predisposition to the formation of certain kinds of tumors and cancers. I also want to be clear before I say it that doing the things I'm about to tell you is not a guarantee that you're not going to get cancer, nor is it a guarantee that alcohol is not going to lead to an increased predisposition for certain kinds of cancers, and the two things are consumption of folate and other B vitamins, especially B12. You know, the consumption of folate and B12 has been shown to decrease cancer risk in people that ingest alcohol, but not completely offset it. Why that is isn't exactly clear. It probably has something to do with the relationship between folate and B12 and other B vitamins in gene regulation pathways that can lead to tumor growth. At some point soon, we will get an expert in cancer biology, and, in particular, in breast cancer biology, on the program and we can ask them about this. But I realize this is going to raise a number of questions and maybe even cause some of you to go out there and start taking folate and other B vitamins and B12. Not incidentally, a lot of the reported hangover supplements and treatments include folate and B12. I don't know if they had the cancer literature in mind when they created those supplements and products. I doubt they did. Alcohol really does disrupt B vitamin pathways, both synthesis pathways and utilization pathways, so sometimes you'll hear, "Oh, you know, if you get your B vitamins, it helps you recover from hangover more quickly." Again, the literature doesn't support that, but also again, there aren't a lot of

studies. But more to the point as it relates to alcohol and the formation of tumors and cancers, it does appear that decreased folate and other B vitamins like B12 are partially responsible for the effect of alcohol in increasing cancer risk. And it does appear that consuming adequate amounts of folate in B12 might, again, might partially, really want to bold face

01:46:54 Alcohol & Pregnancy, Fetal Alcohol Syndrome

and underline and highlight partially, offset some of that increased risk. There's an additional category that I want to highlight, of course, and this is vitally important to state even though it's obvious, which is that people who are pregnant should absolutely not consume alcohol. Fetal alcohol syndrome is well known and established, it's terrible. Fetuses experience diminished brain development that's often permanent, diminished limb development, diminished organ development in the periphery, meaning, you know, the heart, the lungs, liver, et cetera. Ingesting alcohol while pregnant is simply a bad idea. And the reason I say this at all is, first of all, it's important to include in an episode like this, but also because we can look at two things. First of all, we can look at mechanism and then we can also look at some of the lore that still sadly exists out there. Let's take care of the lore that sadly exists first. If you look online, you will sometimes be able to find, sadly, that some people believe that certain kinds of alcohol are not detrimental to fetuses. They'll say, "Well, champagne is safe for a pregnant mother to drink but beer is not." That is absolutely categorically false. Alcohol is alcohol. There is no evidence whatsoever that consuming certain types of alcohol is safer for fetuses than others. Alcohol is a toxin, and the reason fetal alcohol syndrome exists is because the ability of that toxin to disrupt cellular processes. Remember tumor growth and the way that alcohol can accelerate tumor growth by proliferation of cells, the wrong cells, the ones you don't want to proliferate? Well, all of embryonic development, all of fetal development, it's not the growth of a tumor, it's obviously the growth of an embryo, and it's done in a very orchestrated way. I started off studying brain development. That's where I got my beginnings in neurobiology, and I still teach embryology to medical students and graduate students. The set of coordinated processes that has to take place from conception to birth in order to give rise to a healthy embryo is so, so dynamically controlled and so exquisitely precise, with checkpoints and recovery mechanisms and redundancy in the genes that are expressed to make sure that if anything goes wrong,

it's repaired, et cetera. Alcohol as a mutagen, I haven't used that word yet, but a substance that can mutate DNA through alterations in DNA methylation in these checkpoints in the cell cycle, alcohol as a mutagen is one of the worst things that a developing embryo can be exposed to. And, again, because it's water-soluble and fat-soluble, ingestion of alcohol when people are pregnant passes right to the fetus. Now, I realize that a number of people out there might be thinking, "Oh goodness, you know, I didn't realize I was pregnant until a certain stage of pregnancy, and before I realized, I was ingesting alcohol." Obviously, one can't undo what's been done, but I want to also emphasize that fetal alcohol syndrome, while, yes, there's a full-blown syndrome that manifests as changes in the cranial facial development that are very obvious, and you can look these up, you've probably seen these before, or the pictures before, rather, it has to do with eye spacing, forehead size, a number of other features of the cranial facial development, and of course stuff's going on in the brain too, it's along a continuum. So it is possible that some of the changes that occur are more minor, and, thankfully, the young brain, in particular, the early postnatal brain, is incredibly plastic. There are things that can be done in order to help recover neural circuits that didn't develop well, et cetera. But even though it's somewhat obvious, or should be obvious, I really want to make clear that there's zero evidence whatsoever that certain forms of alcohol are safer for pregnant women to ingest than others. Absolutely wrong, no one who's pregnant should be ingesting alcohol whatsoever. And certainly, if people feel like they can't avoid alcohol while pregnant, they really need to work with somebody

01:50:58 Hormones: Testosterone & Estrogen Balance

to make sure that it just absolutely doesn't happen because it is so detrimental to the developing fetus. Lastly, I want to talk about the effects of alcohol on hormones, and I want to distinguish between low amounts of alcohol intake, higher amounts of alcohol intake, and, again, this chronic alcohol intake versus occasional use versus really chronic use, meaning alcoholic or alcoholic use disorder, where people are drinking an immense amount on an ongoing basis. The literature on alcohol and hormones is quite extensive, and there are, of course, many, many different types of hormones. The hormones that most often get mentioned and talked about on this podcast are the hormones testosterone and estrogen, which are present in both men and women and that, in both men and women, are important for things like libido, they're also responsible

for sexual development, actual development of the genitalia before birth and after birth, they're responsible, for instance, estrogen is important for memory and cognition. You never want to drop estrogen too low in men or women 'cause it can disrupt cognition and joint health, et cetera. To keep this discussion relatively constrained, it's fair to say that alcohol, and, in particular, the toxic metabolites of alcohol, increase the conversion of testosterone to estrogen. Now, this occurs in a number of different tissues. This is not just occurring in the testes of males, this is occurring in lots of different tissues. And I'll refer you to a excellent review. We'll provide a link in the show note captions. This is a paper that was published in the year 2000 but the data are still quite strong. The journal is called, of all things, "Alcohol," yes, literally a journal called "Alcohol" for the publication of data and reviews on alcohol and its effects, and the title of the paper is Can alcohol promote aromatization of androgens to estrogens? Aromatization is this process of the conversion of testosterone and other androgens to estrogens through things like aromatase enzyme. And this is a beautiful review that describes every tissue, or near every tissue, from the ovary in females to the placenta to the liver to the testes, in which alcohol can increase the aromatization of testosterone to estrogen. Now, in females, this may be part of the reason why there's an increase in estrogen-related cancers. Breast cancer can be either estrogen-related or non-estrogen-related, there are other types of estrogen-related cancers outside of breast cancer, but it appears that one reason why alcohol increases the risk of breast cancer is because of this aromatization from, of testosterone, excuse me, to estrogen. In males, accelerated or abnormal conversion of testosterone to estrogen can actually lead to growth of the breast tissue in males, so-called gynecomastia, or other effects of high estrogen, or I should say of altered testosterone-estrogen ratios, 'cause that's really what's important. And these can include things like diminished sex drive, increased fat storage, and a number of other things that I think most people would find to be negative effects. I once talked about the fact that drinking alcohol can increase the aromatization of testosterone to estrogen. I posted that online, and I didn't get attacked but I did get criticized for the fact that it has been shown, yes, has been shown, that small amounts of alcohol ingestion, so five grams or so of alcohol ingestion, this would be half a glass of wine or half a glass of beer, at least in some studies showed increases in testosterone, which was kind of surprising. But I should point out, other studies have shown that alcohol ingestion causes decreases in testosterone over time. So there's always this issue of whether or not you're looking at a study of acute exposure versus chronic exposure, you know, one dose versus multiple

doses and exposure. I think it's fair to say, based on my read of the literature, this review and other reviews that focus more particularly on humans, that regular ingestion of alcohol is going to increase estrogen levels whether or not you're male or female, and it's largely doing that through the aromatization process, by increasing the aromatase enzyme. Yes, there's some dose dependence, but I think if you're somebody who's trying to optimize your testosterone-to-estrogen ratio, regardless of whether or not you're male or female,

01:55:09 Negative Effects of Alcohol Consumption

well then most certainly you're going to want to avoid drinking too much alcohol. So we've covered a lot of topics and data related to the mechanisms of alcohol, hangover, tolerance, cancer risk, et cetera. I acknowledge that I've mainly talked to you about the negative effects of alcohol. I want to acknowledge that many people enjoy alcohol in moderation or even light drinking, the occasional drink or the occasional two drinks or maybe even, on average, one drink per night, so seven drinks per week. I'm certainly not here to tell you what to do and what not to do. I do find it immensely interesting, however, that, first of all, alcohol is a known toxin to the cells of the body. Some of you might immediately say, "Well, wait, what about hormesis? What about this phenomenon where if we regularly ingest a toxin, it makes us stronger?" In other words, what doesn't kill us makes us stronger. Yeah, there's, you know, some reason to believe that might be beneficial in terms of some forms of cellular resilience maybe, maybe. No, sorry. It doesn't work that way. There are processes of hormesis in which, for instance, exposing yourself safely through increases in adrenaline through, you know, ice baths or other things that increase adrenaline can raise your so-called stress threshold, but here, we're talking about cellular stress and damage to cells. So my read of the literature, and, again, this is my read and I invite others to, you know, provide studies or I would prefer actually collections of studies that point in the direction, if they exist, that alcohol can be beneficial, but my read of the literature, or I should say my understanding of what I would call the center of mass of the literature on alcohol is that no consumption, zero consumption, consumption of zero ounces of alcohol is going to be better for your health than low to moderate consumption of alcohol, and that low to moderate consumption of alcohol is going to be better for you, of course, than moderately high to high alcohol consumption on the order of 12 to 24 or more drinks per week. I realize that for most

people listening to this, it's probably low to moderate alcohol consumption that is part of their standard repertoire, and I'm not here to give you justification for doing that nor am I going to tell you not to do that. I would like you to consider perhaps, however, the negative effects that we understand and that are documented. For instance, the negative effects of alcohol on the gut microbiome and the things that you can do to better support your gut microbiome, the negative effects on the stress system, that HPA axis that we talked about earlier, and the fact that even low to moderate levels of alcohol consumption can increase our levels of stress when we're not drinking, and to think about acquiring some tools and, you know, getting some proficiency with tools, behavioral or otherwise, that can help you with stress modulation that don't involve alcohol consumption. Again, the point here is to illustrate where the problems lie with alcohol consumption, but, also, what I've tried to do is to point you to some resources that can help offset some of those negative effects. Will they offset all the effects? I can't say that for sure, but certainly taking measures to offset some of the negative effects of any alcohol consumption that you might be having or doing is going to be beneficial to you.

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