Understanding & Conquering Depression | Huberman Lab Podcast #34

This episode, I explain what major depression is at the biological and psychological level and the various treatments that peer-reviewed studies have revealed can help prevent and treat depression. I explain the three major chemical systems that are altered in depression: norepinephrine, serotonin and dopamine. I discuss genetic predispositions to depression and how stress, thyroid hormone and cortisol play a role in many forms of depression. I also discuss inflammation as a common feature of many depression symptoms. I review 8 specific science-supported protocols for treating and avoiding depression, including EPA fatty acids (which have been shown to rival certain prescription treatments), how exercise protects against depression, studies of creatine, adjusting dopamine balance and more. I also discuss the results of ongoing clinical trials for ketamine and psilocybin for depression, how these compounds work and finally, I review how ketogenic diets can help in certain cases of depression, especially treatment-resistant major depression.

#Depression #HubermanLab #Dopamine

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Timestamps:

02:00:10 Support & Additional Resources

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- 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. This month, we're talking all about disorders of the mind, things like depression, attention deficit disorders, eating disorders, schizophrenia, and bipolar disorder. During the course of this month, we are going to discuss the psychological and biological underpinnings of mood disorders of all kinds. You'll learn a lot of science. You'll also learn a lot about the various treatments that exist and that are in development for these various mood disorders. We will talk about behavioral tools, things like exercise, meditation, breath work, but also prescription drugs, supplements and novel compounds that are now being tested in various clinical trials. Across the month, I think you'll start to realize that there are common pathways underlying many mood disorders. In fact, mood disorders that look quite different from one another often depend on the action of the same neurochemicals or neural circuits in the brain and body. That actually should be a point of great relief because what it means is that by understanding the biology of one mood disorder or understanding how one treatment or behavioral intervention can impact a mood disorder, we gain insight into other mood disorders as well. As always, we will discuss science and science related tools that people could implement should they choose. Before we dive into today's topic, I'd like to discuss a very particular set of scientific findings that relate to today's topic, and that are important for understanding all mood disorders and all states of motivation, happiness, and sadness, as well as depression. Basically, I'm going to paraphrase a brief segment of my discussion with Dr. Anna Lembke, who I sat down with to discuss addiction and the biological basis of addiction and addiction treatment. A very important aspect of that discussion was when Dr. Lembke described the pleasure pain balance,

literally the circuits in our brains that control our sense of pleasure and pain, and ultimately whether or not we remain happy in our pursuit of pleasure or not. This is an absolutely crucial aspect to the way that we function in everyday life, and especially under conditions of mood disorders. The pathway that she was describing is the so-called pleasure system. However, what most people don't realize is that the pleasure system is also directly associated with, and in fact is the very same system that modulates mental or psychological anguish and pain. Essentially what she described is that whenever we pursue something that we think will bring us pleasure, and that could be anything that we think will bring us pleasure from food, to video games, to sex, to a particular job or goal, short-term or long-term, that we experience release of the neuromodulator dopamine. Now, dopamine is associated with increased levels of motivation and drive. It is not the molecule of reward, it is the molecule of craving motivation and drive. However, as Dr. Lembke pointed out, when we are in pursuit of something, there is a release of dopamine in our brain that makes us feel motivated, and in general, it makes us feel good. But very shortly thereafter and beneath our conscious awareness, there is a tilt of the pleasure pain balance in the brain, literally a shift in the neural circuits that underlie pleasure and pain, such that every bit of pleasure or pleasure seeking that causes release of dopamine will be balanced out by a little bit of pain. And we don't experience this as physical pain, at least not at first, we experience it as craving for more of the thing that brought us pleasure. Now, that sounds pretty good. You get pleasure and then you get a little bit of pain to balance it out. It's subconscious and you experience it as the desire to seek out more pleasure. However, it's actually more diabolical than that. And we really need to keep an eye on this if we are to remain happy, if we are to remain in pursuit of our goals. The crucial thing to understand is that if we remain in constant pursuit of pleasure, the pain side of the balance tips so that each time we are in pursuit of that pleasureful thing, activity, or substance, we are going to experience, we literally achieve less dopamine release each subsequent time. So we get less pleasure and the amount of craving increases. Now, after a certain point or threshold, we call that addiction. And the way to reset the balance, and this is very important, the way to reset the balance is actually to enter into states in which we are not in pursuit of pleasure, to literally enter states in which we are bored, maybe even a little bored and anxious, and that resets the pleasure pain balance so that we can return to our pursuit of pleasure in a way that's healthy, and then in an ongoing way, won't lead to this over tipping or this increase in the amount of pain or addiction. So this is very

important. And if this seemed vague, what this means is we should always be cautious of any state of mind or body or any pursuit that leads to very large increases in dopamine. And if it does, we should be very careful to not pursue that repeatedly over time. During today's episode, I'm going to give an example, a real life example of a discussion that I've been in with a young man who's 21 years old who's dealing with a disruption in this pleasure pain balance. He is essentially depressed and he's depressed because of his ongoing pursuit of a particular activity that initially led to a lot of dopamine, but over time has led to less and less dopamine and more and more of this pain side of the balance. We could call him addicted to that particular activity. Whether or not he's addicted by clinical standards or not, really, isn't important. What is important is that he experiences this as depression, as low affect as it's called or anhedonia, an inability to experience pleasure from that thing or from anything else. And he's currently undergoing treatment through a rebalancing of his pleasure pain pathway. So while I can't reveal his identity to you, that wouldn't be appropriate. He did give me permission to reveal the general architecture of what he's coping with. And I spent some hours with him on the phone this week, talking to him as well as to the various people that he's working with to really understand what's going on here 'cause I think it can illustrate the relationship between dopamine, pleasure, and pain for sake of addiction, but also for understanding how to avoid depressive states, how to remove ourselves from depressive states. And as you'll see today, as we discussed depression, many of the molecules and neural pathways and biological mechanisms that we know can be used

00:07:10 Sponsors

to counter depression, feed back onto this pleasure pain balance. Before we begin, I'd like to say 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 InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from blood and DNA to help you better understand your body and help you reach your health goals. I've long been a believer in getting regular blood work done for the simple reason that many of the factors that impact our immediate and long-term health can only be detected from a quality blood test. The problem with most blood tests, however, is that

you get information back about hormone levels, metabolic factors, et cetera, but you don't really know what to do with that information. Some things might be flagged as too high or too low, but really interpreting those data and taking action to bring those numbers into the ranges that you want is what it's really about. An InsideTracker makes all that very easy. They have a platform, it's a dashboard that will tell you for instance, what sorts of dietary changes or supplementation changes or exercise changes will help you bring various hormones, metabolic factors, and other factors into the ranges that are right for you. If you'd like to try InsideTracker, you can go to insidetracker.com/huberman. And if you do that, you'll get 25% off any of InsideTracker's plans. Just use the code "huberman" at checkout. Today's episode is also brought to us by Athletic Greens. Athletic Greens is an all-in-one vitamin mineral probiotic drink. I've been using athletic greens since way back in 2012. And so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and that I still take Athletic Greens is that it really covers all of my foundational nutrient and micronutrient needs. It has vitamins, minerals, and the thing that's especially important to me these days is the probiotics, because there are so many data that show that having a healthy gut microbiome is vital to having a healthy immune system and for healthy gut brain axis, literally the functioning of your brain, your mood, various aspects of brain inflammation or limiting brain inflammation are facilitated by having a healthy gut microbiome. And that's facilitated by getting the proper probiotics. If you'd like to try Athletic Greens, you can go to athleticgreens.com/huberman. And if you do that, you can claim their special offer. The special offer is five free travel packs, which make it very easy to mix up Athletic Greens while you're on the road or in the car, and a year supply of vitamin D3K2. Vitamin D3K2 have been shown to have a number of different positive health effects on hormones, on cardiovascular health, and so on. Again, that's athleticgreens.com/huberman to claim their special offer. Today's episode is also brought to us by Belcampo. Belcampo is a regenerative farm in Northern California that raises organic, grass fed, and finished certified humane meats. I don't need a lot of meat. Typically my diet regime is one in which I fast until about noon, and then I have a lunch which is fairly low carbs. So I'll have some piece of meat or chicken or fish and some salad typically. And then in the evening is when I tend to emphasize carbohydrates. That helps me be really alert during the day and sleep well at night. When I do eat meat, I insist that the meat be of the very highest quality and that it is sourced in humane ways. Belcampo's animals graze on open pastures and seasonal

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00:11:15 Major Depression

and using the code "Huberman" at checkout. That's belcampo.com/huberman for 20% off and use the code "Huberman" at checkout. Today we're discussing depression. In particular, we're going to talk about major depression. The phrase major depression is used to distinguish one form of depression from the other, the other one being bipolar depression. Bipolar depression, sometimes called bipolar disorder, is really characterized by manic highs. So where people aren't sleeping and they're talking very fast, and they're buying things and pursuing resources that they can't afford, they're starting relationships left and right, they're manic, followed by periods of crashes of feeling very low, lethargic, and so on. Bipolar depression is an absolutely crucial thing for us to discuss. And therefore we are going to have an entire separate episode related to bipolar depression. Today, we're going to talk about major depression, also sometimes called unipolar depression, just because it doesn't have the highs and lows. It's more characterized by the lows. We're going to talk about the biology, the psychology, and the various treatments, behavioral, drug, supplementation, diet, exercise, all of that. Before we go forward into the material, I just want to emphasize that any discussion about mood disorders carries with it a particular sensitivity, and that sensitivity is one related to self-diagnosis. Today's episode, and indeed in the future episodes for this month on mood disorders, you're going to hear various symptomologies that are used to diagnose and characterize these disorders. If you recognize some of these symptomologies in yourself or in others that you know, that's an important thing to take note of. However, accurate diagnosis really should be done by a qualified healthcare professional. So at once I'm saying, keep your eyes and your ears up for things that sound familiar to you that might be of concern. And at the same time, I'm saying don't necessarily leap to conclusions. Take those flags of concern if they're there and bring them to a qualified

healthcare professional, and they'll be able to properly diagnose you as having a particular mood disorder or diagnose somebody as having a particular mood disorder or not. And that's an essential step. I don't say this to protect us, I said this really to protect you. Okay, let's have a fact-based discussion about depression. And I promise you that where we don't know certain things about depression, I will be clear to tell you. In fact, we are going to talk about some treatments for depression that are looking very promising, and that right now are actually being used more and more. And from my read of the mechanistic literature, we're still a bit in the dark as to how these work. That's actually a common theme of medicine. Many times there are treatments that seem promising or that look really terrific. And there isn't a lot of understanding about mechanism. However, any good discussion about neuroscience and in particular about mood disorders, has to get into mechanisms. So we're going to do that. And in doing that, we're going to frame the discussion for the tools of how to keep depression at bay and how to deal with it if you happen to find yourself depressed, or if you know somebody else who's depressed. What is this thing we call depression? Was I mentioned before, it has two forms, bipolar depression, which we're not talking about today, and major depression, also called unipolar depression is the other. Major depression impacts 5% of the population. That is any enormous number. That means if you're in a class of 100 people, five of them are dealing with major depression or have at some point. Look around you in any environment and you can be sure that a good portion of the people that you're surrounded by is impacted by depression, or will be at some point. So this is something we really have to take seriously and that we want to understand. It is the number four cause of disability. A lot of people miss work, miss school, and before then likely perform poorly in work or school due to major depression. Now there's a very serious challenge in having a discussion about depression and it relates directly to the challenges in diagnosing depression. Earlier, I did an episode with Dr. Karl Deisseroth, who is indeed a medical doctor and a PhD. He's a psychiatrist. And he made a very important point, which is that the field of psychiatry and psychology are confronted with a challenge, which is they're trying to understand what's going on within the stuff that's in our brains that's deep to our skulls. We don't have access to that without brain imaging and electrodes and things like that. Someone just comes into the office and the dissection tool for depression so to speak is language. In order to determine if somebody has depression or not, we have to use language, how they talk about things, also how they carry their body. Also some general patterns of health. So

let's talk about depression the way that clinicians talk about depression, because one of the issues is that we use the word depression loosely. A lot of people say, "Oh, I'm so depressed. "I didn't get this job or I'm so depressed. "I just don't know, I had a really rough week "or I'm exhausted. "I'm so depressed or I'm so depressed "I thought I was going to go on vacation "and then they canceled the flight." Okay. That is not clinical depression. That's called being bummed out, being sad or disappointed. Now that person might be depressed, but clinical depression actually has some very specific criteria. And those criteria are mainly characterized by the presence of certain things and the absence of a few particular things. So let's talk about the things that are present in somebody that has major depression. First of all, there tends to be a lot of grief. There tends to be a lot of sadness. That's no surprise. The threshold to cry is often a signature of depression. Now that doesn't mean that if you cry easily, that you're depressed. Some people cry more easily than others, but if you're somebody who typically didn't cry easily and suddenly you find yourself crying very easily, that could be a sign of depression. And I want to emphasize, could. There's also this thing that we call anhedonia, a general lack of ability to enjoy things, things that typically or previously we enjoyed. Things like food, things like sex, things like exercise, things like social gatherings, a kind of lack of enjoyment from those things. Sometimes that lack of enjoyment is sad, and sometimes it's just flat, it's just kind of neutral. It doesn't feel good because nothing there. It's like bland food. It's like these experiences are analogous to biting into your favorite article of food and it just not tasting very good. It just doesn't taste like anything at all. And that's a common symptom of major depression. The other one is guilt. Oftentimes people with depression will feel very guilty about things they have done in the past, or they'll just generally feel badly about themselves. And we're going to talk about this because it relates to some of the more serious symptomology seen in depression sometimes, things like self harm, mutilation, or even suicide. But for the time being, we want to frame up anhedonia, this lack of ability to achieve or experience pleasure, or kind of a flat affect as it's called.

00:18:40 “Anti-Self” Confabulation

Sometimes even delusional thinking, negative delusional thinking, and in particular anti-self confabulation. What is anti-self confabulation? Well, first of all, confabulation is an incredible aspect of our mind and our nervous system. You sometimes see other forms

of confabulation in people who have memory deficits either because they have brain damage or they have age-related dementia. A good example of this would be someone with age related dementia sometimes will find themselves in a location in the house and not know how they got there. And if you ask them, "Oh, what are you doing here?" They will create these elaborate stories. "Oh, I was thinking about going to the shopping today, "and I was going to take the bus, "and then I was going to do this." They create these elaborate stories, they confabulate. And yet that person hasn't left the house in weeks and that person doesn't have a driver's license. And so they're really just creating this stuff. They're not lying to get out of anything, they're confabulating. It's as if a brain circuit that writes stories, just starts generating content. In major depression, there's often a state of delusional anti-self confabulation, where the confabulation are not directly or completely linked to reality, but they are ones that make the self, the person describing them, seem sick or in some way not well. A good example would be somebody who experiences a physical injury perhaps. Maybe they break their ankle, maybe it's an athlete, and they also happen to become depressed. And you'll talk to them and say, "How are things going? "How's your rehab though?" And they go, "Oh, it's okay. And I don't know. "I feel like I'm getting weaker and weaker by the day. "I'm just not performing well." And then you'll talk to the person that they're working with, their kinesiologist or whoever the physical therapist is. And they'll say, "No, they're actually really improving. "And I tell them they're improving, "but somehow they're not seeing that improvement, "they're not registering that improvement." You notice that sometimes it's subtle and sometimes it's severe, but they'll start confabulating. You'll say, "I actually heard you're doing much better. "You're getting better, you're taking multiple trips "around the building now "before you could barely get out of bed." And they'll say, "Yeah, well basically, they changed some things "about the parking lot that make it easier to move around. "So it's not really me." And these aren't people that are just explaining away their accomplishments 'cause they're trying to brush off praise. They are viewing themselves and they're confabulating according to a view that is very self-deprecating to the point where it doesn't match up with reality. It's not what other people see and it's actually not matched up with reality. And that's a symptom of depression that I think we don't often think about or conceptualize enough. So it's not just telling people, "oh yeah, it's not as good as it seems. Everything's bad." These people really believe that and it becomes disconnected from reality. So it's if they're sort of sinking into a pit and they're losing touch with the realities of the world, including data about themselves, their ability

to move and get around it,

00:21:42 Autonomic (Vegetative) Symptoms of Depression

for example, in that particular instance that I used as an example, but there are others as well. The other common symptomology of major depression is what they call vegetative symptoms, okay? So vegetative symptoms are symptoms that occur without any thinking, without any doing, or without any confabulation. These are things that are related to our core physiology. The word vegetative, you might know it sounds like vegetable. It actually relates to a system in the body that nowadays is more commonly called the autonomic nervous system. The vegetative nervous system and the autonomic nervous system, historically were considered sort of one in the same. And it relates to things like the stress response or to our ability to sleep. So vegetative symptoms be things like constantly being exhausted. The person just feels exhausted. It's not because they exercise too much, it's not necessarily because of a life event, it could be, but they're just worn out. They don't have the energy they once had. So it's not in their heads, it's probably, and now I think we have good data to support the fact that there's something off, something is disrupted in the autonomic or so-called vegetative nervous system. And one of the most common symptoms of people with major depression, one of the signs of major depression is early waking and not being able to fall back asleep despite being exhausted. So waking up at 3:00 AM or 4:00 AM or 5:00 AM just spontaneously and not being able to go back to sleep. I want to emphasize that that could happen for other reasons as well, but it is a common symptom or warning sign of major depression. So let's talk more about sleep and depression. It's well-known that the architecture of sleep is disrupted in depression. What's the architecture of sleep? I've done entire episodes about this, but very briefly in two sentences, although they're probably be run on sentences, early in the night, you tend to have slow wave sleep more than REM sleep or Rapid Eye Movement sleep. As the night goes on, you tend to have more Rapid Eye Movement sleep. That architecture of slow wave sleep preceding Rapid Eye Movement sleep is radically disrupted in major depression. In addition, the pattern of activity in the brain during particular phases of sleep is disrupted. Now this is during sleep. So this can't be that people are creating this situation for themselves. These are real physiological signs that something is off in this so-called autonomic or vegetative nervous system. And then there are some other things that relate to the autonomic

nervous system, but that we normally think of as more voluntary in nature. And these are things like decreased appetite. So you can imagine that one could have decreased appetite because of the anhedonia, the lack of pleasure from food, right? If you don't enjoy food, then you might be less motivated to eat it. That makes sense. As well because of these disruptions in the autonomic nervous system, these vegetative symptoms, as they're called, you can imagine that someone would have decreased appetite because some of the hormones associated with appetite, hypocretin orexin and things of that sort, ghrelin, that those will be disrupted. And if those names of hypocretin orexin and ghrelin don't make any sense to you, don't worry about it. What those are just hormones that impact when we eat, when we feel hungry, and when we crave food more, as well as when we feel full, we have enough so-called satiety. If you want to learn more about those, we did entire episodes on eating and metabolism. So you can see that the symptomology of major depression impacts us at multiple levels. There's the conscious level of how excited we are generally. Well, that's reduced. There's grief, there's guilt, there's crying, but then there's also these vegetative things. There's disruptions in sleep, which of course make everything more challenging when we're awake. We know that sleep is so vital for resetting. You're waking up early, you can't get back to sleep. That's going to adjust your affect, your emotions in negative ways. We know this. And appetite is off. And there are hormones that get disrupted. So cortisol levels are increased. In particular, there's a signature pattern of depression whereby cortisol, the stress hormone that normally is released in a healthy way only in the early part of the day is shifted to late in the day. In fact, a 9:00 PM peak in cortisol is one of the physiological signatures of depressive like states. It's not the only one, but it is an important one. So there are a lot of things going on in major depression. And by now you're probably thinking, goodness, this is dreadful. Like there's all this terrible stuff. And indeed it is terrible. It is a terrible thing to find oneself in a mode where things feel sad, you feel guilty, you're exhausted. And oftentimes there's also an association with the anxiety system. So just because people are exhausted and lethargic and they don't enjoy things, doesn't necessarily mean that there's an absence of anxiety. There can also be a lot of anxiety about what's going to happen to me. Am I going to be able to achieve my goals in life? Will I ever get out of this state? And so things really start to layer on. And if this sounds depressing to you, it is indeed depressing. This is really the place that many people find themselves. And it's a pit that they just don't know how to climb out of.

00:26:58 Norepinephrine, Dopamine & Serotonin

So let's just take a few minutes and talk about some of the underlying biology that creates this cloud or this constellation of symptomology. I think that's really important to do because if we want to understand the various treatments, how they work and why they work and how to implement them, we have to understand some of the underlying biology. So let's spend a few minutes talking about the biology of depression, what's known and what's not known. Because in doing that, I think you'll get a much clearer picture about why certain tools work to relieve depression and why others might not. So one of the most important early findings in the search for a biological basis of depression was this finding that there are drugs that relieve some of the symptoms of depression. Those drugs generally fall into three major categories, but the first set of ones that were discovered were the so-called tricyclic antidepressants, and the MAO inhibitors, the monoamine oxidase inhibitors. You don't need to understand that nomenclature, but I'm going to give you a little bit of detail so that if you want to understand it, you can. Most of this work took place in the late 1950s and in the 1960s, and continued well until the 1980s when new classes of drugs were discovered. And these tricyclic antidepressants and the MAO inhibitors largely worked by increasing levels of norepinephrine in the brain, as well as in the body, in some cases. And they were discovered through a kind of odd set of circumstances. We don't have time to go into all the history, but suffice to say that they were discovered because of the exploration for drugs that alter blood pressure. Norepinephrine impacts blood pressure, and drugs that lower blood pressure reduce levels of norepinephrine. And that in many cases, was shown to lead to depression or depressive like symptoms. And so these drugs, these tricyclic drugs, and the MAO inhibitors actually increase norepinephrine. And frankly, they do quite a good job of relieving some, if not all of the symptoms of major depression. However, they carry with the many side effects. Some of those side effects are side effects related to blood pressure itself, by increasing noradrenaline, norepinephrine as it's called, you raise blood pressure. That can be dangerous, that can be uncomfortable. But they also have a lot of other side effects. The reason they have other side effects is because they impact systems in the brain and in the body that impact things like libido, appetite, digestion, and others. And we'll talk about each of those in sequence. Okay, so the experience that clinicians had of observing some relief for depression with the tricyclic antidepressants

and with MAO inhibitors was terrific, but there were all these side effects, side effects that people really did not like, they didn't like these drugs at all. A lot of people get dry mouth, I mentioned the low libido, they'd have sleep issues, appetite issues, weight gain. They made some people so uncomfortable that they preferred not to take them, even though when they didn't take them, they had a worsening or a maintenance of their depressive symptoms. A decade or so later, there was the discovery of the so-called pleasure pathways in the brain. These are pathways, literally groups of neurons that reside in different locations in the brain but connect to one another. So it's a circuit. And when you stimulate these neurons with certain behaviors or with electrical stimulation in an experiment, believe it or not, that's been done in both animals and humans, animals and humans become very, very motivated to get more stimulation of these pathways. So this pleasure pathway or these circuits for pleasure are very what we call reinforcing. In fact, animals and humans will work hard to get stimulation of these brain areas even more than they will work to obtain sex, drugs, or even if they are addicted to a particular drug and they are in a state of withdrawal, the ultimate state of craving, if given a choice, a person or an animal will select to have stimulation of this pleasure pathway instead of the drug itself. And that is a major and significant finding. This pleasure pathway, as it's sometimes called, involves areas like the nucleus accumbens and the ventral tegmental area. These are areas of the brain that are rich with neurons that make dopamine. And if you think to the symptoms of depression, of anhedonia, lack of pleasure, a lack of ability to experience pleasure, well, that was a smoking gun that there's something wrong with the dopamine pathway in depression. And indeed that's the case. So it's not just norepinephrine, it's also the dopamine or pleasure pathway

00:31:50 SSRIs (Prozac, Zoloft, etc.): Selective Serotonin Reuptake Inhibitors

is somehow disrupted. And then in the 1980s, there was the discovery of the so-called SSRIs Most people are now familiar with the SSRIs, the Selective Serotonin Re-Uptake Inhibitors. The SSRIs worked by distinct mechanisms from the tricyclic antidepressants and the MAO inhibitors. As their name suggests, SSRI, Selective Serotonin Re-Uptake Inhibitors prevent serotonin from being wiped up from the synapse after two neurons talk to one another. What do I mean by that? Well, here's some very basic Neurobiology 101. If you don't know any neurobiology, you're going to know some in about 15 seconds. Neurons communicate with one another by spitting out chemicals into the little gap

between them. The little gap between them is called the synapse or by the Brits, the synapse. Those chemicals bind to the neuron on the opposite side and cause changes in the electrical activity of that neuron on the other side of the synapse. Serotonin is one such neurotransmitter or more specifically, it's a neuromodulator, can change the activity of large groups of neurons in very meaningful ways. Selective serotonin re-uptake inhibitor means when a person takes this drug, some of those drugs include things like Prozac or Zoloft, the more typical names or more generic names are things like fluoxetine, when people take those, more serotonin hangs out in the synapse and is able to be taken up by the neuron on the opposite side because of this selective re-uptake inhibition. It prevents the clearance of serotonin from the synapse and thereby more serotonin can have an effect. So SSRIs don't increase the total amount of serotonin in the brain. They change how effective the serotonin that's already in the brain is at changing the activity of neurons, okay? So they don't increase serotonin, they increase the efficacy or the function of serotonin in the way that I just described. So that was more than 15 seconds, but now you understand how SSRIs work. And I wouldn't be talking about SSRIs if they didn't in fact work. Yes, there are many problems with SSRIs. They do carry certain side effects in many individuals. Also, about a third of people that take SSRIs don't derive any benefit, it doesn't relieve their symptoms of depression. However, for the other two thirds, there's often a relief of some, if not all of the symptoms of major depression. The problem is the side effects that accompany those SSRIs. And so these days SSRIs are a complicated topic. It's sort of what I would call a barbed wire topic because we often hear about all the problems with them, but these drugs also have saved a lot of lives. They've also improved a lot of lives. The issue is that they tend to have varying effects on different individuals, and sometimes varying effects over time. So they'll work for awhile then they won't work for a while. There are also a lot of mysteries about the SSRIs, and those mysteries bother people. What mysteries am I referring to? Well, SSRIs increase the amount of serotonin or more specifically, they increase the efficacy of serotonin at the synapse, that happens immediately, or very soon after people start taking SSRIs. But people generally don't start experiencing any relief from their symptoms of depression if they're going to experience them at all, until about two weeks after they start taking these drugs. So there's something going on there that's not clear. One idea is that the SSRIs actually can improve symptoms of depression or even remove symptoms of depression through so-called neuro-plasticity by changing the way that neural circuits function. And there are many on this, but the

main categories of studies on SSRIs that relate to neuroplasticity fall into two camps. One is that the ways in which SSRIs might, and I want to emphasize, might be able to trigger the production of more neurons in the brain, in particular areas of the hippocampus called the dentate gyrus and others, that impact memory. This is important. We're going to come back to memory. The other is that the SSRIs have been shown in various scientific studies to reopen critical periods of plasticity. I'll just briefly describe one of those studies. There was a study done by Lamberto Maffei's group in Pisa, that explored brain plasticity that's known to be present in young animals and disappear in older animals. And this is also true in humans that younger humans have a far more plastic brain that can change in many more ways more easily than can the older brain. And what they showed was that fluoxetine, Prozac, given to adult animals can reopen this incredible period of plasticity, can allow more plasticity to occur. That was interesting. I mean, it's purely through increases in serotonin transmission. And there are other studies showing that fluoxetine can increase the number of new neurons that are born into the adult brain,

00:37:00 Epinephrine/Motor Functions, Dopamine/Motivation & Craving, Serotonin/Emotions

so called neurogenesis, the production of new neurons. So it's very clear that there are at least three major chemical systems in the brain; norepinephrine, dopamine, and serotonin that relate to and can adjust the symptoms of depression. And those actually can be divided into separate categories. So for instance, epinephrin or norepinephrine is thought to relate to the so-called psychomotor defects, sometimes called psychomotor retardation. This is the lethargy, this is the exhaustion, this is the inability to get out of bed in the morning. Dopamine is thought to relate to the anhedonia, or I should say lack of dopamine in depressive patients is thought to lead to the anhedonia. The lack of ability to experience pleasure. And serotonin is thought to relate to the grief, the guilt, some of the more cognitive or more emotional aspects of depression. So we've got the norepinephrine system related to activity and alertness, the dopamine system relating to motivation, pleasure, and the ability to seek and experience pleasure, and then the serotonin system that's related to grief. And unfortunately, brains and organisms don't work in a simple mathematical way where you just say, oh, well, this person's experiencing a lot of grief, but they don't have any problems with lethargy. And so let's

just boost up their serotonin. On paper it works, but oftentimes it doesn't work clinically. And another patient, you might get somebody who can't experience pleasure, but they're kind of anxious. They don't have any trouble sleeping, but they're just much more anxious and frustrated than they normally are, and they meet the symptoms of depression. Well, you might think, oh, well, do you just give that person some drugs increase dopamine and everything will be better? And indeed, in some cases that's true. There are drugs like Wellbutrin, which function more specifically on the dopamine system to increase dopamine and they also increase norepinephrine. Many people get great relief from things like Wellbutrin. They don't really impact the serotonin system so much. And therefore you don't get a lot of the serotonergic or serotonin related side effects. However, some people feel far too anxious on those drugs, some people get addicted to those drugs in a way, because a lot of those drugs that increase dopamine make you want more of those drugs. So you start to realize that what makes sense on paper doesn't always make sense clinically. And this is why it's complicated. And a really good psychologist and a really good psychiatrist will work with someone to try and pull and push on these various systems to find the combination of drugs that may be or may not be correct for them.

00:39:33 Physical & Emotional Pain are Linked: Substance P

There's a fourth aspect of the chemistry of depression that's really important to understand. And that's pain. We've talked about pain on this podcast before, but even if you didn't hear the episode on pleasure and pain, just want to emphasize that pain is something that we experience in our body, no surprise there, an injury, a cut, et cetera, but that we also experience emotional pain. And those systems are linked in very intricate ways. There's actually some data showing that pain relievers, Tylenol, Aspirin, these sorts of things, can help certain people with emotional pain. Now I'm not recommending people run out and take those things for emotional pain. But actually, if you think about it, that shouldn't come as any surprise. given the enormous number of people that take painkillers, opioids and things like them to try and relieve their psychological pain. And as we know, those drugs are very, very problematic for many individuals. They can help certain individuals, but they are very prone to abuse and they can induce addiction very easily in a number of people. There's a substance that's literally called substance P, the letter P, that's manufactured by neurons in our brain and

body, which underlies our sensation of pain. And indeed substance P inhibitors have been used to treat depression, and in some cases works. A lot of people with depression are hypersensitive to pain, and of course they could have multiple things going on. They could have chronic pain or chronic injury and major depression. So you start to get the constellation of the many things that could happen. So that's all I want to say today about the chemistry underlying depression or major depression. There's a lot more there, but I think if you understand the norepinephrine system and that it relates to some of these things like lethargy, the psychomotor defects, as they're called, dopamine and how it relates to motivation and lack of motivation and lack of dopamine and depression, and serotonin and its relationship to grief, and that low serotonin can lead to extreme grief and shame and higher serotonin levels can sometimes restore a sense of wellbeing and safety and feeling good about oneself. If you understand that and you understand that physical pain is somehow involved in certain cases, I think you will know more about depression and its underlying chemistry than most all people out there. And if you'd like to learn more, I invite you to pursue searching those terms further on the internet.

00:41:50 Hormones & Depression: Thyroid & Cortisol

And we'll certainly go into them in more depth. But that really sets the stage for where we're headed next. So next I'd like to talk about hormones and how they relate to depression. And I'd also like to talk about stress and how it relates to depression, as well as talk about some of the genetics or the predispositions to depression. And for those of you that are thinking, hey, I want the tools. I want to know how to fix depression. I understand the desire for that. I will just ask if you hang in here with me a little bit longer, not only will you learn a lot more about how this complicated mood disorder works, some of the more interesting things about it, but it will also position you to get a lot more out of the tools that we will describe. You always have the option to skip forward of course, but I think it's important to understand some of the hormonal and stress-related aspects of depression. So let's talk about hormones. 20% of people that have major depression have low thyroid hormone. Thyroid hormone is related to metabolism. Oftentimes we think about thyroid is only related to having a fast metabolism, but thyroid is related to all forms of metabolism, including our ability to synthesize new tissues like protein and repair injuries. I did a whole episode on thyroid and growth hormone. If you want to check that out, all of that is archived at hubermanlab.com. It's all timestamped, et cetera.

You can find on YouTube, Apple, Spotify, all those places. So if you're curious about thyroid hormone and growth hormone, and you want to do the deep dive on those, and you want to learn how to alter their levels using various approaches, check that out. But 20% of people with major depression are hypo thyroidal. They don't make enough thyroid. And that leads to low energy, low metabolism in the brain and body. And there's a condition called Hashimoto's, which is essentially low thyroid output. And again, I don't want to get into all the tools related to thyroid. Sometimes a psychiatrists will prescribe thyroid medication to increase thyroid output in people that are depressed and that will work to relieve the symptoms. So there isn't necessarily a direct problem with serotonin, dopamine, and norepinephrine or substance abuse. Sometimes it's a thyroid problem. So there are certain situations or conditions that can impact the thyroid hormone system and make people more susceptible to depression or make a pre-existing depression worse. And those are things like childbirth. So it's well-known that women who give birth can often undergo what's called postpartum depression. It actually comes from the word post parturition depression. They give birth, what's happier, what's more joyful than the birth of a new healthy child, and they will lapse into a depression. And that's thought to be hormonally related, either directly to the thyroid system or perhaps to the cortisol system as well. We'll talk about cortisol in a moment. As well, certain women during certain phases of their menstrual cycle experience symptoms that are very much like clinical depression, and oftentimes are diagnosed with clinical depression appropriately. And of course the menstrual cycle is associated with shifts in hormone levels. As well, menopausal and post-menopausal women are more susceptible to major depression, regardless of whether or not they've had that major depression earlier in their life. So these are things to be on the lookout for and to definitely talk to a doctor and get a blood panel that hopefully includes measures of thyroid hormone and cortisol hormone. Why cortisol hormone? Well more stress is correlated with more bouts of major depression across the lifespan. How many bouts? Well, it turns out that as you go from having one to two to three, well, when you hit four to five bouts of really intense, stressful episodes in life, these tend to be long-term stressful episodes, your risk for major depression goes way up. So whether or not you have a genetic predisposition to depression or not, one of the best things you can do to try and avoid getting depressed is to learn to control your stress system, to not go from short-term stress, which everybody experiences, we all have short-term stressors, to medium term stress to long-term stress, and to not have too many bouts of long-term stress because that probability of getting depressed goes

way, way up. And this is something I've seen over and over again, not just in my scientific career, but just throughout life. People in all sorts of domains, young and old, I've seen that people will go through a very intense relationship, a breakup, sometimes it's the staying together that stressful, sometimes it's a graduate school that can be stressful, sometimes it's some other event. And then some months later they become depressed. And that's because the stress system is associated with the release of cortisol. The cortisol system can dramatically impact the way that these different neuromodulators, dopamine, norepinephrine and serotonin function. And so there's this kind of latent or longer lasting impact on the systems that impact mood and wellbeing. So learning how to control your stress is really key. If you're not depressed or you're somebody that has not lapsed into a depression recently, take control of your stress system. And we did an entire episode on how to conquer stress,

00:46:50 Genetic Susceptibility to Depression: Impact of Stress

and that involves dealing with stress in the short term, the medium term, and in the long-term. And there are a lot of different ways to do that. One of the more important reasons for learning how to counter stress in order to offset depression is that there is a genetic predisposition that certain people carry to become depressed. There are these studies now of many, many thousands of individuals, these were mainly done in New Zealand, but these studies have now been done elsewhere, looking at many tens of thousands of individuals who carry particular copies of genes, what they call polymorphisms, in particular of a gene called 5HTTLPR, which is a serotonin transporter. So this is a gene that controls or regulates how much serotonin is available in the brain. If you have this gene, this polymorphism, it doesn't necessarily mean that you will be depressed, but it greatly shifts your susceptibility to depression under conditions of stress. So I realize some people are listening to this and some people are watching it on YouTube. So I'm going to describe this in a way that doesn't require looking at any graphs. What I want you to imagine is a very, shallow hill, like a very mellow hill. It's just a ramp set at about 10 or 15 degrees, okay. What we're plotting there in your mind is that with each about of serious stress, so that could be trying to finish a degree or a relationship breakup, or a family member that's sick, or the loss of a loved one or a pet, with each about of stress, the probability that you will experience a major depression goes up. However, if you carry this gene, this HTTLPR gene, the steepness of that curve goes way, way up where

it's actually more like a line such that you need far fewer bouts of stress in order to lapse into a major depression, okay? So if the typical person who doesn't carry this polymorphism has to experience two or three or four or five bouts of stress before they lapse into a depression, somebody with this gene is susceptible to getting depression after just one about or two bouts of intense stress, okay? So that's how these genes work. They don't preordain or determine you to be depressed. They raise a susceptibility. And many genes, many things related to heritability in general, work in that way. And we know there's a strong genetic component to depression. How do we know? Well, in what are called concordant monozygotic twins. So these will be identical twins. And they can either be in one biological sack or two biological sacks while in utero, what's called monochorionic or dichorionic. Well, typically it's monochorionic. And identical twins, for which one of those twins goes on to have major depression, there's a 50% probability that the other one will have major depression. So it's not 100%, it's not 100% inherited, it's not 100% generic, as you might say, but there's a much higher predisposition for depression. Whereas in fraternal twins, that number drops, and in siblings, that number drops to about 25%, and in half siblings, it's about 10%. The numbers vary from study to study, but basically the more closely related you are to somebody who has major depression, the more likely it is that you will also get major depression. And therefore, if you haven't gotten major depression, the more likely it is that you should take steps to learn to mitigate stress because stress is the major factor that can trigger one of these depressive episodes. So we've covered a lot related to the stress and the hormones and the neurochemistry of depression. In fact, I think this is probably the deepest I've ever gone into the biology of any topic on this podcast before getting to any specific tools. I mentioned that learning how to mitigate stress and deal with stress,

00:50:50 Understanding Biological Mechanism Is Key: Recipes versus Skills

learning how to measure and adjust your thyroid hormone, those might be useful. But next I'd like to turn to some very specific tools that people who both have depression or who are prone to depression, as well as people who don't have depression and simply want to maintain a good mood, who want to maintain a positive affect and pursuit of things in life, what are the things that you can do? It turns out there are things that you can do and all of the biology that underlies the utility of those things. Meaning the

reasons those things work will now make sense to you because they adjust things like serotonin and dopamine, and they adjust them through very specific pathways. I know for many people learning about mechanism is kind of grueling. I realized this podcast isn't necessarily one that you can listen to passively while doing other things. Although I would hope that you could do that and still enjoy it and extract the information. Why mechanism? Mechanism is so key because mechanism is a little bit like understanding some of the chemistry of cooking. If you read a recipe and you can follow a recipe, you often hear people say, oh, I can follow a recipe. That means that if you have every ingredient in that recipe, you're good. You likely can make that dish. You can make that meal. However, if you understand a little bit of the chemistry of why salt has to be added third and not first, or why the heat has to be adjusted at a particular time, well then not only can you follow a recipe, but that also gives you flexibility for when salt isn't available, or when you want to adjust the flavor of the dish, or when you want to try a new dish, or you want to get experimental. So when you understand mechanism, it puts you in a tremendous place of power to work with your system. So it's not just plug and chug, like take 12 milligrams of this, you either feel better or you don't. You can really start to understand how prescription drugs, supplements, nutrition, behavioral tools, how those things weave together to either work for you

00:52:50 Tools for Dealing with Depression: Logic & Implementation (Protocol 2)

or not work for you and get you to paths of healthy mind and body. So let's think about why any tool would work to relieve depression. We've talked about how some of the drugs that impact these different chemical systems might work and why they create some of the problems they create. Problems are mainly created by the fact that they impact lots of systems in the brain and body. So you take a drug to increase serotonin, but that serotonin is also related, not just to mood, but to things related to libido and appetite. And so you start disrupting multiple systems. The same could be said for behavioral tools, right? That any behavioral tool that adjusts the levels of a particular chemical ought to perhaps, provide some relief for some of the symptoms of major depression. Let's take an example that I've talked about before on the podcast, which is, if you get into a very cold shower, you take an ice bath, you will release norepinephrine and epinephrine in your brain and body. There's no question about that. I don't think anyone can really escape that. It's a kind of a universal response to being in cold water.

Well, if some aspects of depression are related to low levels of norepinephrine, will taking cold showers relieve your depression? Perhaps it might even relieve certain aspects of that depression. Is it a cure? Well, that's going to depend on the individual. Will exercise help? Well, if you go out for a run, you're going to increase the amount of norepinephrine in your body. If you enjoy that run, it's likely that you'll increase the levels of dopamine and probably serotonin in your brain and body as well. Will that cure your depression? Well, there are a lot of studies exploring how exercise can impact depression. And indeed, regular exercise is known to be a protective behavior against depression, but it also can help relieve some of the symptoms of depression. So you may ask yourself, why would you need drugs at all? Why would there be prescription drugs or the need for supplementation or other things to alleviate the symptoms of depression? Ah, well, that's the diabolical nature of depression, which is if people are far enough along in this thing, this sometimes called disease, sometimes called disorder, but major depression, oftentimes they can't get the energy to even get up and take a bath or a shower. They have no motivation to do it, they have no desire to go for a run. So you say, "Come on, let's go, you'll feel better. "I know you feel better, it generates all these chemicals "I heard on the whatever podcast, Huberman Lab podcast, "or another podcast that getting into action "does all these things." And they just don't want to do it. And to you, a person who's not experiencing depression, that perhaps could just seem like the most frustrating and confusing thing in the world. But it's very important to highlight the fact that these circuits that are accessible to some of us, the circuits for happiness, for pursuit of pleasure, for exercise, for getting in a cold shower, if that's your thing, that those circuits are present in all people, but for certain people that are experiencing major depression and are really in the depths of their depression, they can't really access those circuits in the same way that people who are not suffering from depression can. So I hope that makes it clear. It's not offering any excuses for them. And indeed, I think those behaviors would help jolt them out of some of the symptomology of depression, but they're just not accessible to everybody. So let's talk about the things that people can do to deal with depression. And again, anytime you add a behavior or a tool or a supplement, or subtract a behavior, tool, supplement, drug, et cetera, you absolutely should talk to your physician,

00:56:25 Brain Inflammation & Mental State: Cytokines, Prostaglandins, etc.

especially if you're somebody that's dealing with major depression. I want to focus on the stress system. And I'm not just going to tell you to get sunlight in your eyes and to get a good night's sleep, although I think everybody should do that on a regular basis, ideally every day, talked about those ad nauseum on this podcast. They will help your sleep, they will help you alleviate stress. I think you should have tools to deal with stress in real time, et cetera. But let's look at depression from the standpoint of a deeper biological phenomenon, which is inflammation and the immune system. There's growing evidence now that many forms of major depression, if not all of them, relate to excessive inflammation. Now inflammation plays an important role in wound healing. It is a positive aspect of our immune system. Our ability to combat wounds, combat illnesses, et cetera, but inflammation gone unchecked, inflammation that lasts too long, or is of too high amplitude, meaning too many anti-inflammatory or inflammatory cytokines and things of that sort in the body is bad. And there's decent evidence now that inflammation can lead to or exacerbate depression. And that if we want to control depression, or limit or eliminate depression, that focusing on reducing inflammation and its associated pathways is a really good thing to do. And I think this is a really good thing for everybody to do regardless of whether or not you suffer from depression or not. And today we're going to talk about exactly how depression comes about through the inflammation pathway. So, first of all, who are the major players in creating chronic inflammation in the brain and body? They are the inflammatory cytokines. Things like IL-6, interleukin-6, things like Tumor Necrosis Alpha, TNF alpha, things like C reactive protein, alright? Not all of these are cytokines. You have interferons and prostoglandins and a lot of these things. But when we are stressed, chronically stressed, we get inflamed, our brain and various locations of the brain become inflamed because certain classes of cells, in particular, those glial cells, the cells that are typically thought to just be support cells, those cells and their biochemistry and their dialogue with the neurons of the brain and body starts to become disrupted. I may have mentioned it earlier, I don't recall. But I certainly mentioned it in an earlier podcast that adrenaline epinephrin, when it's released in the body, it doesn't cross the blood brain barrier, but there are certain things that are able to cross the blood-brain barrier when we are stressed. Things like the E2 prostoglandins, those cross the blood brain barrier. And our blood and our brain, therefore our brain and our body can communicate because certain things can pass through this barrier we call the BBB or the Blood Brain Barrier. And also we have something called the glymphatic system, which is really a plumbing system

00:59:20 Protocol 3: Essential Fatty Acids (Omega-3, EPAs: Eicosapentaenoic Acid)*

that links the brain and body. It's the link between the immune system and the brain. Well, there is a set of actions that we can take in order to limit inflammation. And this has been shown in several quality peer reviewed studies now to reduce inflammation and to relieve some, and in some cases, all of the symptoms of major depression. One of those approaches is to increase our intake of so-called EPAs or Essential Fatty Acids. There's now a very long list of papers in quality peer review journals showing that when people ingest a certain level of EPA omega-3 fatty acids, the relief from depressive symptoms matches the SSRIs. That's incredible, right? That essential fatty acids could relieve symptoms of depression, as well as some of the prescription antidepressants. Now, this doesn't necessarily mean you run off and stop taking your antidepressants if you've been prescribed them, please don't do that. Please talk to your physician. And I should mention that some of the same studies have shown that increasing our intake of these essential fatty acids, in particular, the EPA variety of omega-3s, can lower the effective dose of things like SSRIs. Meaning if we required a 50 milligram or 40 milligram dose of fluoxetine, that one can get by on a lower dose and thereby perhaps not experience as many or as severe side effects by taking or supplementing with EPAs. Now, the threshold level seems to be about one gram, 1000 milligrams of EPA. So you will sometimes see on a bottle of krill oil or fish oil or any other source, even plant source or other source of EPA that it's 1000 milligrams or 1200 milligrams. But what's really important to look at is whether or not there's more than 1000 milligrams of EPA, because the EPA in particular is what's important here. And actually in exploring some of the literature on the effects of EPAs on cardiovascular health, excuse me, as well as their effects on depression, there's some interesting dose dependent responses, such that people who took anywhere from 400 milligrams to 5,000 milligrams of EPAs, achieved a variety of different benefits. And in some cases, some side effects, we'll talk about those. And it does seem that this 1000 milligrams is the critical threshold for benefiting or getting some relief from depressive symptoms. But people who took two grams seem to do better. And in the cardiovascular health realm, there it's a little more complicated. Some studies point to a very positive effect on cardiovascular health by taking increasing amounts of EPA, others, not so much. The current data point to the fact that for every gram of EPA that one ingest, there's about a 9% improvement in cardiovascular health,

the same dose dependent improvement on psychological health in combating depression can't really be stated. I wouldn't say that the more EPA you take, the better you're going to feel so to speak. I don't think the data point to that. However, it does seem that if you take a gram, 1000 milligrams or 2000 milligrams of EPA, there does seem to be some substantial relief for many people, should emphasize many, not all,

01:02:50 How EPAs Help Offset Depression: Serotonin Synthesis, Kynurenine, Quinolinic Acid

for many people in major depressive symptoms. So how would this work? Well, turns out that these inflammatory cytokines, they impact neurons and the circuits of the brain that relate to things like serotonin, dopamine, and norepinephrine. These inflammatory cytokines act in a variety of different ways, but they mainly act to inhibit the release of serotonin, norepinephrine, and dopamine, or the synthesis of serotonin, norepinephrine and dopamine. And I'll give you one example of how EPAs can positively impact this process. And then it points to a second tool, which is the proper utilization of exercise to offset the effects of depression. So now you should understand why having healthy levels of serotonin is important for maintaining healthy mood. It's not responsible for all the aspects of having a healthy mood, there's also dopamine and norepinephrine, but it is a very important one. Dopamine also called 5HT, essentially derives from a precursor called tryptophan. Tryptophan arrives into our system through our diet, okay, tryptophan is an amino acid. Tryptophan is found in Turkey, it's found in carbohydrates. And that should therefore raise the idea, hmm, I wonder if one of the reasons why people who are depressed have such an appetite for carbohydrate late in foods is because they're trying to get more tryptophan, and therefore more serotonin. And indeed that's the case. Tryptophan is eventually converted into serotonin. However, if there's excessive amounts of inflammation, these inflammatory cytokines cause tryptophan to not be converted so much into serotonin, but to be diverted down a different pathway. The pathway involves something called IDO, Indoleamine, which converts tryptophan into kynurenine. Kynurenine actually acts as a neurotoxin by way of converting into something called quinolinic acid. And quinolinic acid is pro depressive. So if that seems like a complicated biochemical pathway, what's basically happening here is that the tryptophan that normally would be made into serotonin, under conditions of inflammation is being diverted into a neurotoxic pathway. And ingestion of EPAs, because it limits

these inflammatory cytokines, things like IL-6, C-reactive protein, et cetera, can cause more of the tryptophan that one ingests

01:05:25 Protocol 4: How Exercise Offsets Depression

or has in their body to be diverted towards the serotoninergic pathway. Exercise, it turns out, also has a positive effect on the tryptophan to serotonin conversion pathway. And the way it does it is really interesting. You now know that tryptophan can either be converted into serotonin or it can be converted into this neurotoxin, which is a bad thing. Exercise, the activation of the muscles through rhythmic repeated use, in particular aerobic exercise, but also resistance training has been shown to do this to some extent, tends to sequester or shuttle the contouring into the muscle so that it isn't converted into this neurotoxin that is pro depression, okay? There are a lot of steps in the pathway leading to depression, but what this essentially means is that hitting a certain threshold level of EPA intake, whether by supplementation with fish oil or krill oil or through some plant source if you're not into ingesting fish or krill, or trying to get up above that 1000 milligram threshold for EPA by ingesting particular food sources, you certainly can do it through food, you don't have to supplement, but it's easier to do with supplements, that doing that will limit the inflammation that diverts tryptophan into this neurotoxic pathway. And exercise as well, augments this conversion of tryptophan into serotonin because it takes this thing that would potentially be a neurotoxin and it sequesters it, it pulls it away so that it can't actually go have its pro depressive effects. So you've got multiple steps here. We're describing two tools, increasing EPA and regular exercise as a way of increasing serotonin, somewhat indirectly, right? It's by limiting this bad pathway to promote the activity of a good pathway. But from the data that are published in Quality Peer Review journals, it really appears that this inflammation pathway does function to increase depression through these pathways. And so knowing that there are behavioral steps and supplementation based steps, or if you prefer getting your EPAs from typical food, from nutritional approaches, I find that very reassuring that the mechanisms all converge on a common pathway, serotonin. That gives me great peace of mind that when people say, hey, go out for a run, or you should get outdoors exercise, or you should take fish oil like the Scandinavians do, I have Scandinavian family members and they are known to, or I should say they are quite open about the fact that during the winter months in particular when depression is more likely, but throughout the year,

really, they make an effort to regularly ingest high levels of EPA, either through ingesting fatty fish and its skin, I'm not a particular fan of ingesting the skin of fatty fish, or by supplementing with Cod liver oil or other types of fish oil, sardines, and things of that sort, sardine oils. There are a number of different things out there that one could use. So I find it very reassuring that there's a common biochemical pathway that can explain why these things not just work, but why they should work. They should work because they operate in the very same biochemical pathways that antidepressants that are prescribed to people do. So what does this mean for you? Well, if you're somebody who suffers from major depression, again, don't stop taking your prescribed medication. Talk to your doctor, but talk to them perhaps about the EPAs and exercise and how these things can impinge on the same biochemical pathways. If you're somebody who is not suffering from major depression, I still think these pathways are really important to understand. And actually knowing these pathways is additional motivation to get regular exercise. I think we all know that we should be getting anywhere from 150 minutes to 180 minutes per week of so-called zone two cardio for cardiovascular effects. Zone two is the kind of melowish cardio where you can sort of hold a conversation if you needed to. But it's a little bit tough, you're kind of sucking for air a little bit. And that's going to limit these depressive like symptoms, I think in all of us. I don't think that we should think of depression as a strict threshold. I'm somebody who personally has made the choice to take 1000 milligrams of EPA per day. I do that by supplementing fish oil. There's debate out there as to whether or not it's better to take EPA NDHA in particular ratios, and whether or not DHA can impact the LDL, which is the so-called bad cholesterol. That's getting really down into the weeds. And we can talk about that in a future episode. But for myself, I notice a pretty substantial positive effect of taking anywhere from 1000 milligrams to 2000 milligrams of EPA per day. I do that through supplementation and I do strive to try and eat some fish, even though frankly, I've never liked the taste of fish. For those of you that would like a little more detail or perhaps a lot more detail into the effects of EPA on depression and in relieving depressive symptoms, and if you want to get into the nitty gritty of it, I invite you to go to examine.com, put in depression, EPA, they list off and have links to 28 studies on the effects of EPA on major depression. If you go to pub med, there are many, many studies on this now that date back several decades, really. If you're interested in the specific effects of EPA, as opposed to DHA, I want to point you towards a particular study entitled, not surprisingly EPA, but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty

acids supplementation and depression, evidence from a meta analysis of randomized control trials. This is a really wonderful paper. The author is Julian Martins, M-A-R-T-I-N-S. It was published in 2009. We will provide a link to this study in the caption. And that study is really the one that at least to me, points to why EPA in particular is what's effective, and that whether or not DHA is problematic or not as a separate issue, but it's really the EPA that one wants to hit a certain threshold level of if one's goal is to get relief from depression or to keep depression at bay by keeping mood elevated, which is why I take a high-dose EPA. So we've got EPA, we got exercise,

01:11:44 Protocol 5: Creatine Monohydrate, Forebrain Function & NMDA receptors*

now you understand how they work to adjust mood. Now, I want to talk about something that at least for me, was quite surprising when I first learned about it for sake of treatment of mood disorders, and that's creatine. Creatine has a number of very important functions throughout the body. For those of you that are into resistance training, and actually for those of you that are into endurance training as well, creatine has achieved a lot of popularity in recent years because supplementation with creatine can draw more water into muscles and can increase power output from muscles. So it's something that does indeed work. There have been debates about whether or not it's unhealthy for the kidneys to take long-term creatine, supplementation at high doses. And I invite you to go down that rabbit hole. I think most people now accept the idea that for most people, not all, but for most people, low dose creatine supplementation of anywhere from one gram to five grams per day can have a number of positive effects on physical performance. People with kidney issues, et cetera, need to be especially cautious, but creatine is interesting for that purpose. However, there's also a so-called phosphocreatine system in the brain, and that phosphocreatine system has everything to do with the dialogue between neurons and these other cell types called, glial, and glial comprise several cell types, microglia, astrocytes, et cetera, but the foster creatine system in the forebrain in particular, in the front of our brain, has been shown to be involved in regulation of mood and some of the reward pathways as well as in depression. And there are now several studies, at least three, although they're probably more by the time this comes out because they're coming out very quickly now, at least three quality studies pointing to the fact that creatine supplementation doesn't just have these positive effects on physical performance, but can also be used as a way to

increase mood and to improve the symptoms of major depression. This has been now done in several double blind placebo controlled studies. The studies have looked at women, have it looked at men, have looked at adolescents, some of whom were taking SSRIs, some of whom were not, they've done magnetic resonance spectroscopy. So spectroscopy is a way that you can look at the concentrations of particular in the brain in real time in humans, it can be used for other things as well, of course. And basically what's been observed is that increasing the activity of the phosphocreatine system in the forebrain can be beneficial or at least is correlated with improvements in mood. So let's just talk for a moment about what's involved with using or supplementing creatine in order to improve mood and perhaps even treat depression. First of all, when I talk about creatine, I'm talking about creatine monohydrate, there are a number of different forms of creatine. Here I'm talking about creatine monohydrate. The American Journal of Psychiatry in 2012, published a study, which was a randomized, double blind placebo controlled trial of oral creatine monohydrate. And what it found is that it could augment or enhance the response to a selective serotonin re-uptake inhibitor, in particular, in women with major depressive disorder. So like EPA, creatine supplementation seems to either lower the required dose of SSRI that's required to treat depression, or can improve the effectiveness of a given dose of SSRI. However, there are other studies that have looked directly at creating supplementation in the absence of SSRIs. And those are interesting as well. There's a wonderful and very comprehensive review on creatine for the treatment of major depression that includes beautiful tables of all the subjects and the dosages, et cetera. I'm not going to read off every line and every column in that review, but we will provide a link to that review as well. One of the things that's really striking about the lists of studies that they include is that most of them used dosages that are pretty reasonable for most people, anywhere from three grams to five grams, sometimes up to as many 10 grams per day of creatine. Many of these also were shown to increase activity of this phosphocreatine system in the forebrain, and some show a relationship between that phosphocreatine system and a particular category of receptors in the brain called the NMDA receptor, N-methyl D-aspartate receptor. The NMDA receptor is one of the first things that every budding neuroscientists learns about because it is the receptor that has particular electrical and chemical properties that make it a critical gate for so-called neuroplasticity. So it's not a receptor that's activated in the brain, typically for just the functioning of the brain on a day-to-day basis. It's a receptor that's activated when circuits are going to change, when they are inspired to change by

some very strong stimulus, meaning some experience, or in some cases a drug, or in some cases something else. But the NMDA receptor is a kind of a key node for shifting brain circuitry. And so while the details aren't entirely clear, it seems that creatine supplementation leads to increases in the phosphocreatine system in the forebrain. And that increases in the activity of the forebrain phosphocreatine system relate to changes in the way the NMDA receptors function and may lead to some of the plasticity, the changes in neural circuits that underlie the shift from negative mood and affect to positive mood. Now, there are a lot of gaps. There are a lot of little boxes or bins in the diagram I just laid out for you. And some of them are still truly black boxes, as we say, meaning, we don't really know what's in them yet. And more mechanistic data are coming. However, when you look over the data in this review, or when I look over the data in this review, what you find is that they're pretty striking positive effects of creatine. And one of the more interesting effects is that creatine has actually been shown to increase mania in people that are already manic. And that's interesting, we're not talking about bipolar depression today, but it seems that creatine elevates levels of activation and kind of mood overall. And you could see why that would be a problem for somebody that's already in a manic phase, but it actually might be beneficial for somebody who is very low affect and has major depression. So should you supplement with creatine? Well, as always, talk to your healthcare provider, but if you're somebody who is thinking about things that you can do and things that you can take in order to improve your mood, keep depression at bay, maybe even support other treatments for major depression. the creatine system seems like a logical one. There's at least strong studies and a good number of them to look to, to determine whether or not that's right for you. I personally take five grams of creatine for other reasons. I take it for the physical performance, enhancing effects, but it's kind of nice to think that perhaps it's also helping me improve my mood. That's a choice that I've made for me is in within the margins of safety for me in my life. I don't know that it's right for everybody, but I find it very interesting. And again, I find it particularly interesting because there's a logical biochemical pathway to support the finding that it improves mood and can offset the effects of major depression in some cases, or can improve the effects of antidepressant medication in many cases. When I see mechanism and I see effectiveness, and the mechanism and the effectiveness map to a lot of the same mechanisms that are involved in prescription drugs, that gives me great reassurance that this isn't just some sort of mysterious pathway or mysterious compound by which a creatine might be working. So now we've

kind of clustered together EPAs, exercise, and their relationship to inflammation, creatine and its relationship to forebrain function, and the phosphocreatine system, and this NMDA receptor. And as you'll see in a few minutes, that NMDA receptor turns out to be vitally important and is actually one of the main nodes of action

01:20:30 Protocol 6*: Ketamine, PCP (*Prescription-Only), & NMDA-Receptor Function

for some of the more novel and exciting therapeutics that are being explored now in psychiatric clinics. So let's talk a little bit more about this NMDA receptor and how it relates to some of the more experimental or novel therapeutic compounds for the treatment of major depression. And the compounds that we're going to be talking about, you may have heard of before, one is ketamine, which is getting increasing interest in psychiatric clinics and in various experimental and clinical studies, and the other is PCP. Both ketamine and PCP are known drugs of abuse. For many years, people have abused these drugs, go by the street name, special K, et cetera. And they create dissociative anesthetic states. So dissociative states where people don't feel as closely meshed with their emotions and their perceptions. It's an odd state, I hear. And it's an odd state that clinicians are now leveraging for the treatment of depression. And we'll talk about why that is, but let's talk a little bit about this NMDA receptor and why ketamine and PCP might work for the treatment of depression or how they even could work. I want to be very direct that this is an area that still needs a lot of data. There are however, some excellent papers from really terrific groups. One of them is a paper that was published in nature last year, 2020. First author is Vesuna, Sam Vesuna, V-E-S-U-N-A, and the last author and the lead on the study, who was Dr. Karl Deisseroth, who was a guest on the Huberman Lab podcast a few months ago. He's world expert in neuroscience, he's a psychiatrist. And this paper from Sam Vesuna and Karl and colleagues explored how these dissociative states come about. And they looked at this both in animals and in humans and found that there was a, essentially a common mechanism whereby a particular layer of cortex, so your brain has this outer shell of tissue that is called the neocortex. It's where our perceptions lie, it's where our associations lie, it's a very important area for processing decision-making and planning, et cetera. It's literally stacks of cells, and one of those layers in the stack of cells is layer five. And the layer five neurons in particular, went into a particular rhythm of electrical activity, this one to three Hertz rhythm after mice or humans were administered ketamine

or PCP. There was activation of a particular area of the brain, this retro splenium cortex as it's called. And the dissociative state that emerged was an interesting one. And clinically what's described in the trials for ketamine and things like it, that people who are depressed will take ketamine, will experience a kind of separateness from their grief and from their emotions. And that possibly there's plasticity, there actually shifts in the neural circuitry, such that their emotions don't weigh on them so heavily, I'm using very loose language here, but that they don't feel as over written or as burdened by their own emotions as they did previously to the ketamine therapy. Now, absolutely in no way, shape or form am I suggesting that people run out and take ketamine in order to treat their own depression. These drugs are still very much experimental, although they are approved in certain contexts, at least in the U S, by prescription for the treatment of depression. What's interesting to me is that these dissociative states sound at least at the outset to be more of a separateness from everything. It sounds a little bit like depression itself. That's sort of like anhedonia and an inability to experience pleasure. And then one takes a dissociative anesthetic and somehow is able to get relief by getting even further away from an experience. To me, that doesn't make sense, but that just speaks to the fact that these drugs and these receptors and these pathways operate through very cryptic means. And we really don't understand all the pathways in the brain that relate to motivation and mood and so forth. And the results with these ketamine trials are looking very promising. In fact, there are a number of trials that show that a fair number of people that take ketamine in a therapeutic setting legally with a psychiatrist guiding the experience are able to get relief from their symptoms without the need for many, many treatments with the drug. Just how many treatments varies from individual to individual, but it's not like people have to take this stuff ongoing. This is really an attempt to tap into this NMDA receptor that is related to neuroplasticity. Both ketamine and PCP essentially act as antagonists, which means they block the NMDA receptor. They do it through different methods, non-competitive and competitive for you chemists and pharmacologists out there. You can look it up if you like. But what's therefore even more surprising is that every neuroscientist learns that activation of the NMDA receptor, not antagonism or blocking of the NMDA receptor leads to changes in neural circuitry in very profound ways. In fact experimentally, and I've done these experiments myself, if you want to prevent plasticity, you want to prevent an experience from reshaping neural circuitry, you give an MDA receptor blocker. I've done that many times in the course of my experimental neuroscience career, not to myself, obviously, but in the course of

doing experiments. So it's still a bit mysterious to me how this could work. A couple things. One is this layer five activation is pretty interesting. We're going to come back to layer five when we talk about yet another emerging treatment for depression, which has psilocybin, so-called magic mushrooms, and the effects of psilocybin on layer five neurons in the cortex. So there's a common theme emerging here, which is that layer five activity in the cortex may be important for rewiring the brain in certain ways that can lead to recovery or to an alleviation of some of the symptoms of major depression. So if this is sounding a little bit vague to you, it's because this is still truly experimental and new, and still very much on the cutting edge of what's happening now. We don't have all the answers. So if it sounds like I'm moving slowly through this, and I'm being extra careful about what I say, you are correct. Your antenna are correct in this case. I never want to misstep and say something that's not true, but that's especially the case when we're talking about experimental therapies and drugs, which formerly were taken as drugs of abuse, which are now being used as drugs for therapeutic treatment in the clinic. There is a very interesting study. This was published in science in 2019. So these are very recent studies. The last author on this is Liston, L-I-S-T-O-N. The title of the paper is "Sustained Rescue of Prefrontal Circuit Dysfunction "by Antidepressant Induced Spine Formation." And here, when we hear spine, we're not referring to spine as in your vertebrae, running down your spinal column, we're talking about the spines, which are these little protrusions on neurons. Neurons are not smooth by any stretch. If you zoom in on a neuron, if you were to come to my lab and look down the microscope at a neuron and zoom in on it, you'd find that some neurons are smooth, but most neurons have these little protrusions. And those little protrusions are called spines. And those little spiny protrusions are little sites where neurons can reach out and form and receive new synapses from neighboring neurons. So they increase the surface area of a neuron and allow new connections to be formed. And so spine formation is synonymous with neuroplasticity, which is synonymous with changes in circuit function, which is synonymous with changes in the ways that we think, we feel, and we behave. And what was shown in the study is really interesting. What they showed is that ketamine can relieve depressive symptoms rapidly by changing or increasing in this case, the spines on these neurons in the prefrontal cortex. And if that word prefrontal rings a bell, well, now you remember the phosphocreatine system, the ingestion of creatine monohydrate, and the forebrain, activation of the forebrain were related to, in some way or another, to relief or improvement of major depressive symptoms. So we're starting to converge on a

picture here whereby these drugs, ketamine, PCP, used in a therapeutic context, may be increasing neuroplasticity. Literally the changing of neurocircuits in the forebrain somehow through dissociative states. And I don't want to speculate too much about how that might come about, but one of the things that's such a resounding or repeating theme of major depression is that when you talk to somebody who has major depression, it is a real downer. And I'm not being disparaging of those people. But if you've ever had a conversation with someone who's depressed, they're always talking about how exhausted they are, or in really severe cases, they are not even responsive at all. They just kind of stare at you blankly, or they fall asleep. I mean, they're truly depressed. Their system is lowered in terms of its activation state. So I think that it's interesting that the application of drugs that allow people to separate from that state of not caring or being uninterested or unwilling to do anything is actually one of the paths to treatment. It's not always about just getting people peppy and excited and happy. There also seems to be requirement for getting them distanced from their own grief. And this brings us back to something that we talked about way back at the beginning of this episode, which was this particular feature of the anti self confabulation, that everything that happens is a reflection that I should say for the depressed person, that everything that happens is a reflection of how life is bad and their experiences just point to the fact that nothing is going to get better. This is the common language of depression. If this is very depressing to hear me talk about it, it is heavy. And that's what it's like to hear these things, it's even heavier, of course, for somebody to experience them. And those beliefs, those patterns of guilt and grief and anhedonia and delusional anti self confabulation, those are the things that eventually, if they get severe enough, start to convert into things like self harm mutilation, and in the most tragic of cases, of course, suicide. And so I think we can look to these treatments such as ketamine and PCP, but in particular ketamine and its use in the clinic, as ways for people to get distanced from the negative affect that they feel isn't just inside them or overwhelms them, but that for the very severely depressed person, they feel is them. And we hear this sometimes, you are not your emotions. That's a statement that I've always been a little bit challenged by. I mean, yes, indeed emotions are not who we are. They are states that we go into and out of, including happiness and sadness, but they are very much a part of us when we experience them. We don't experience them as next to us or behind us or across the room from us. We experienced them as our emotions. They are so much part and parcel with our experience of ourself that a statement like we aren't our emotions is a very hard

statement to digest, especially for the depressed person. And so I think that the NMDA receptor and its capacity to induce neuroplasticity, circuit changes, the fact that PCP and ketamine are both showing activation of neural circuits by way of suppressing activity of the NMDA receptor, and some of the positive or exciting therapeutic outcomes that are coming from this really point to the fact that ketamine and PCP and removal of negative experiences or the experience of a negative experience, sort of getting meta there. But the experience of a negative experience may be an important path by which people treat their depression, especially in its most severe forms

01:33:08 Protocol 7*: Psychedelics (*In Clinical Trials) for Major Depression: Psilocybin*

where people are veering towards self-harm, mutilation, and suicide. So you may have noticed a theme, which is that certain categories of approaches that we've been discussing for offsetting the symptoms of depression, such as exercise, ingesting EPAs, reducing inflammation, or even the SSRIs for increasing serotonin, focus on changing some core biological function, like raising the amount of a chemical, serotonin, or reducing the amount of inflammatory cytokines in the brain and body. And yet things like ketamine focus more on rewiring circuitry, changing neural circuitry so that it functions better in the immediate and hopefully in the long-term as well, and keep people with major depression in what they call, remission, away from major depression. Another category of treatments that's being actively explored now in laboratories and in the psychiatry realm are the psychedelics. And that's a huge category of compounds. However, one in particular, psilocybin is one that's being most intensely and actively pursued for its capacity to treat major depressive disorder. I want to be very clear that the work that I'm going to describe as work that's being done in university settings, university hospitals, by scientists and psychiatrists, and these are clinical studies, clinical trials, leading to peer reviewed data. And those are the data that we'll be discussing. Some of the major luminaries in this area include, of course aren't limited to, but include people like Matthew Johnson who's at Johns Hopkins. We'll discuss some of his work now, and fortunate to say that he will be coming on the podcast as a guest to just scribe the studies in a variety of laboratories, working on a variety of different psychedelic compounds, but let's focus on psilocybin for its capacity to rewire neural circuits and alleviate depression. There have been anecdotal data or evidence over the years that psilocybin has this capacity, how does psilocybin work? Well, psilocybin, magic

mushrooms, as it's sometimes called, mainly works on what's called the serotonin 5H2A receptor with some affinity for the 5HT1 receptor. What does that mean? Well, basically, you've got a lot of different kinds of serotonin receptors just as you have a lot of different kinds of dopamine receptors or other types of receptors. The advantage of having different receptors expressed in different parts of the brain and body, even on different parts of individual cells in the brain and body is that the same compound, serotonin, can have a diverse set of effects on different cells and tissues. This is also the basis of some of the side effect profiles of SSRIs, because maybe for instance, we know that taking Prozac fluoxetine will increase serotonin in one area, but also in another area. And then they will go have diverse effects on different brain circuits because of the variety of receptors. Receptors are just like parking slots where the molecule serotonin parks and has different effects. Well psilocybin engages or increases serotonin transmission, meaning it increases the amount of serotonin, mainly by acting at these 5H2A receptors, but where in the brain does it happen and what are the major effects? First, let's talk about the major effects 'cause I think that's what people are interested in. The study that I'd like to highlight is a fairly recent one. It was published in may of 2021 in Journal of the American Medical Association Psychiatry, so JAMA Psychiatry, and it's entitled, "Effects of Psilocybin Assisted Therapy "on Major Depressive Disorder, a Randomized Clinical Trial." It's an absolutely beautiful study, a very important study. It includes some of the luminaries in this area like Matthew Johnson, Patrick Finan, Roland Griffiths, and others. We will provide a link to this study. It is available in its full form at zero cost if you want to read it. It's got a lot of detail. So I'm just going to summarize a few things, but basically what they did was they screened for patients to come into the clinic. These were people that suffered from major depressive disorder, and administered either one or two rounds of psilocybin. They used particular dosages that are listed in the study. So you can look it up if you're really interested in that level of detail. Typically it was 20 milligrams per kilogram of body weight. So it depends on body weight. Or 30 milligrams of psilocybin per 70 kilograms of body weight. They were given in capsule form. So people weren't eating the mushrooms. This is obviously a very controlled study and they wanted to control the dosages appropriately. They were randomized to begin the treatment immediately or after an eight week delay. They had all the appropriate control groups that one would like to see. What's really striking this study is that there was a very significant improvement in mood and affect and relief from depressive symptoms in anywhere from 50 to 70% of the people that were subjects in the study who received the

psilocybin treatment. And whether or not it was 50 or whether or not it was 71%, varied according to how long after the study they maintain these antidepressive effects, whether or not they stayed in remission from the depression, but these are really enormous insignificant effects, and very exciting and are pointing in the direction of psilocybin very soon, becoming a treatment for various forms of depression, including major depression. Now, of course, this is limited to the laboratory at present. There are a number of elements of these studies that are important to take into consideration too, which is that there are highly trained guides, meaning people to direct people through the experience. As Matthew Johnson has told me, there is the occurrence from time to time of people having so-called bad trips of having anxiety attacks during the hallucinations and all that. And they have ways to mitigate that and deal with that because the guides are trained. They have all the sorts of medical monitoring devices for heart rate and temperature and things that one would like to see for a study like this, because these are very powerful compounds. I don't want to give away any elements of the discussion with Matthew Johnson, because it will be released in podcast form reasonably soon here, the Huberman Lab podcast. But one of the things that came up and is a fundamental question that I had, that I think probably many of you are asking, is does the experience that one has on these compounds make a difference for whether or not somebody gains relief from depression, from these psilocybin journeys or not? In other words, does it matter what they talk about? Does it matter what they think about? Does it matter if they have a good trip or a bad trip? And I don't want to hold you in too much suspense, I'll let Matthew provide the more thorough answer. But what's really interesting is there are some common themes to psilocybin administration and experience that lead to relief from depressive symptoms, but they are subjectively very varied, meaning that whether or not people feel they had a good experience or a bad experience, whether or not people thought about their parents or thought about the color of the ceiling, doesn't seem to have too much of an impact on whether or not they receive relief during these studies in these clinical studies. It seems like different people can have lots of different experiences and still receive benefit. And that points to something deeper. It points to the fact that these drugs, which is really what they are, are rewiring neural circuitry in a common way despite a diversity of experience while on the drug. And that itself is really interesting. And it takes us back to a place that we've been before in this discussion, which is layer five of the cortex. This area that ketamine seems to impact as well by generating rhythms of the, I mentioned one to three Hertz activity in

layer five of certain areas of the cortex. Well, the 5HT1A receptor is known to be enriched in layer five of the cortex, and layer five of the cortex is a very interesting area because it's an area in which there's a lot of lateral connectivity. So connections between different brain areas laterally, generally is what allows us to merge different senses. So for instance, when we hear a sound off to our right over here, we turn to our right. There's a very hardwired response. And typically we hear something off to our right, we don't look to our left. That's how hardwired some of these circuits are. What appears to be happening is that the activation of the serotonin system and 5HT1A receptor in layer five is offering up or providing an experience whereby the lateral connections are able to engage much more broadly than they would normally. Now that also could be a bad thing. And I asked Matt about this, that sounds kind of spooky. I don't know that when I hear something off to my right, that I want to look off to my left. That could be highly maladaptive, especially if it's a car coming at me from my right. That doesn't seem to be what's happening. It's not really rewiring these deeply reflexive circuits. It's somehow rewiring associations between events, emotional events, past events, current events, and future events in ways that allow people to get some sort of relief or distance from these narratives, these depressive stories about their past and present and allow them to see new opportunity and optimism in the future. It's really a fascinating thing if you really think about it, because I would have thought that simply by ramping up laterality of connections, meaning that cross associations, that things could either be rewired randomly in ways that don't serve us, or would perhaps just cause no effect at all. So it's either going to be bad or neutral, but that's not really the way things are turning out. Again, these are highly controlled studies. I do want to emphasize that ketamine, psilocybin, these things are still illegal. Most all places. There are some regions and cities in the United States where they are locally decriminalized, but they are not legal. They're still illegal. So what we're referring to here are indeed clinical studies in which people are taking them legally. I think it's very likely we will see a shift in the legislature around psychedelics, and in particular, psilocybin in the not too distant future. And I think that for now, what we should know is what Matt told me and what you'll hear far more about, which is that psilocybin. this one where in most cases, two dose treatments done in a highly clinical setting, controlled setting with patients that are carefully selected, can in many cases, the majority of people receive and maintain relief from their depressive symptoms, simply through the experience of this psychedelic journey. I did ask them about micro dosing. I made it sound as if I'd never heard about it

before. Microdosing, not micro dosing. Microdosing, and his answer was interesting. His answer was that the microdosing effects don't seem to be nearly as impactful as some of these, well, let's just call them what they are. These kind of high amplitude sessions that there are just one or two, there are some studies ongoing where there's more than two, but that the microdosing doesn't seem to compare to these macrodosing, I mentioned the dosages before, this 20 milligrams per 70 kilograms or 30 milligrams per 70 kilograms dosages given several weeks apart. So you'll hear more about microdosing and other psychedelics and their impact on depressive states and major depression in the episode with Matt. But for the time being, it really seems as if, again, we're looking at neuroplasticity, we're coming back to layer five, just like with ketamine and PCP. We're hearing about layer five, we're hearing about rewiring of circuitry, we're hearing about a dissociation or a distancing of oneself from these negative moods and affects and narratives, but there's a key distinction between the ketamine work and the psilocybin work, which is that in the ketamine work, it really is about dissociating from experience during the session with the psychiatrist, whereas during the psilocybin journey, it's really about immersing oneself in the experience and being fully present to that experience. That does seem to be an important component and what the difference is there and why they both seem to provide some relief from major depression isn't clear. I think most likely it takes us back to the fact that this thing we call major depression clearly involves serotonin, dopamine, and norepinephrine. And in some individuals, they may be more deficient in one or several of those or all of those, whereas in other individuals, it might be a different collection of chemicals. And of course there are a tremendous number of other psychedelic compounds that people are exploring for treatment of major depression. But really psilocybin is the one that we have the most data on. MDMA has mainly been explored in the clinical realm for treatment of trauma. There are some trials ongoing for treatment of depression, but the big breakthrough seemed to be happening in the realm of trauma treatment, the so-called maps group that's doing this, again, legally in a clinical setting. And there are other groups that are starting to do it as well. We are going to do an entire podcast about MDMA and some related compounds. So I'll save that discussion for then.

01:47:00 Protocol 8: Ketogenic Diet, GABA (Gamma-Aminobutyric Acid)

One of the most common questions I get for this podcast is about different diets,

different regimes, different nutritional plans, things like keto, ketogenic diet, or vegan diets, or intermittent fasting, or the all meat diet, the so-called lion diet, et cetera. There are actually really interesting data relating nutrition and diet to major depressive disorder. And I think we just need to frame this by returning to something that was said earlier, which is that the ingestion of carbohydrates, in particular carbohydrates and some meats like turkey, that are rich in tryptophan, this precursor to serotonin, are in many ways the self-medicating version of depression treatment. Now, to be clear, I'm not saying that people should use food to medicate their depression. Many people do that reflexively however, they reach for carbohydrate rich foods to blunt their cortisol, because that's indeed what it does. It blunts cortisol when you ingest high carbohydrate foods, in particular starchy foods, and it does increase serotonin, in particular, if those foods rather are rich in the amino acid tryptophan. Now ingesting food is wonderful and important and great, but ingesting excessive foods of any kinds, carbohydrate or otherwise it's not healthy, of course. There have been some explorations of whether or not a vegan diet can improve symptoms of depression. Not a lot of data, not impressive data. There have been very few controlled studies looking at the carnivore or all meat diet. On that, I think there are now some that are starting to spin up, meaning those studies are starting to spin up. However, the ketogenic diet has been explored for its ability to relieve certain symptoms of depression, in particular to what's called maintain euthymia. Euthymia is the kind of state of equilibrium between a manic episode and a depressive episode in a manic bipolar person. We'll return to this more in a future episode, but it basically, maniacs have highs and they have lows, bipolars, either cycle back and forth really quickly. So rapid cycling bipolars or slow, some people So really quickly can be day to day, other people it's month to month or week to week, they're going highs and lows. And you hear about mania and you hear about dysphoria, euthymia is that kind of place in the middle where people feel neither too high nor too low. And there are some interesting studies looking at the ketogenic diet for maintaining euthymia in manic depressives, but also in people with major depressive disorder. Why would this work? Well, we have to remember that the ketogenic diet wasn't discovered so that self appointed nutrition gurus could talk about it online or so that people could make money selling anything related to ketosis. And here I'm not disparaging of the ketogenic diet. It's helped a lot of people. The ketogenic diet was actually shown to be medically relevant for its use to treat epilepsy. It turns out that in epilepsy, or in particular pediatric epilepsy, that a ketogenic diet and the shift of brain metabolism to

predominantly one in which ketones are being metabolized rather than more standard glucose tight metabolism, can greatly reduce the number of epileptic seizures that these children experience. It's not always the case, but it's often the case. And so you talk to a neurologist or a neurosurgeon who's specialized in epilepsy, in particular pediatric epilepsy, and they'll tell you this, "Oh yeah, the ketogenic diet, in many cases, not all, "can be very effective for this treatment." How? How is it that a ketogenic diet reduces seizures? Well, the way it reduces seizures is by increasing what's called GABA transmission. GABA is a substance that is naturally released in our brain. It's an inhibitory neurotransmitter, meaning that when it's released into the synapse, it has the tendency to reduce the firing, to reduce the electrical activity of the next neuron or sets of neurons. There are various compounds that increase GABA, in particular, GABA in the forebrain. One common example would be something like alcohol, drinking alcoholic drink or two will increase GABA transmission, ironically will lower your social inhibitions by increasing your neurochemical inhibition. It basically suppresses the self-monitoring pathways. And if people drink enough, it will suppress all pathways and people will urinate themselves and fall over. It will eventually inhibit all sorts of pathways. So the GABA system has a rich array of effects all over the brain and body. But alcohol tends to activate the release of GABA. You might say, well then why not just take alcohol to suppress seizures? Well, that be a terrible idea because there tends to be a rebound excitability after alcohol stops having its effects on the GABA receptors. And so then there's an excitability for which an epilepsy would be terrible. The reason why the epileptic diet is useful for epilepsy is that increases what we call the tonic level, the sort of the ti, the level of GABA in the brain, and that suppresses some of the hyperexcitability, that is the characteristic feature of epilepsy. And there are other drugs, for instance, the benzodiazepines and things of the Xanax, variety, Valium, and so forth. Those increased GABA transmission. Those drugs also have a lot of potential for abuse and addiction, et cetera, and they're problematic for other reasons. But the ketogenic diet, by way of increasing ketone metabolism or shifting brain's metabolism over to ketones tends to modulate GABA such that GABA is more active and adjust the so-called GABA glutamate balance. This is getting technical, but glutamate is an excitatory neurotransmitter, GABA is inhibitory neurotransmitter, and their balance is vital for neuroplasticity, for maintaining healthy levels of activity in the brain, et cetera. And so there is decent evidence that people with major depressive disorders, in particular, the people with major depressive disorders that are refractory, meaning they don't respond

to classical antidepressants, can benefit, it seems, from the ketogenic diet. Now this is not always the case, but for those of you out there who are struggling with major depression, and for which drugs have not worked, please talk to your psychiatrist. I don't know how many of them are up on the literature about the ketogenic diet or the EPAs and the rest. Psychiatrists vary in terms of how involved in the current literature they tend to be, but there are many excellent psychiatrists out there. Most of them in my experience, are actually quite avid learners about what's happening and what's new in this realm that they call psychiatry. So it's really interesting that eating in a particular way, lowering carbohydrates to the point where you rely on ketogenic metabolism in the brain, increases GABA and can provide some relief for depressive symptoms. And that in particular, that seems to have positive effects in people that are refractory or don't respond to classic antidepressants. And that would include things like fluoxetine, et cetera. I'll make one final point about ketogenic diets and GABA and depression, which is that it's also been shown that for people that respond well to these drugs that impact the serotonin system, dopamine system, or norepinephrine, the ketogenic diet, there may improve the ability for those drugs to work at lower dosages,

01:54:50 Summary of Protocols Covered

which is reminiscent of what we saw with the EPA supplementation. So today we've covered what at least feels to me, like a tremendous amount of material. This topic of depression is indeed an enormous topic to try and get our arms around. We talked about the symptomology, we talked about some of the underlying neurochemistry and biology, and then we talked about approaches to deal with it that are really grounded in the neurochemistry in biology. I just want to recap a few of those tools and what those things are. First of all, we talked about making the effort to not overwhelm the pleasure system. That might seem counterintuitive. To not overly seek out pleasure, or else one can find themselves in a place of depression. I mentioned way back at the beginning of the episode, a young man who I know to be really struggling with depression, and it is thought, and we don't know for sure, but is thought that some of that depression was probably triggered by an overindulgence in video games and other highly dopaminergic activities to the point where those activities eventually were countered by the pain balance that Dr. Anna Lembke described. And he now has to do those activities repeatedly and for many, many hours each day, just to feel okay, not even to derive

pleasure from them. And worse, many other activities, practically all other activities have lost their zest, they've lost their excitement and his sense of pleasure for them. And so there's a really active campaign now to reset that system. So, number one, don't overwhelm your pleasure centers either through activities or compounds. Might seem counterintuitive, but you're setting yourself up for anhedonia and depression if you do that. It's not just about addiction that too, but it's also about setting yourself for anhedonia and depression. How often can you engage in these activities? Well, that's going to differ from person to person, everyone's slightly different, but you should really mind your extreme highs and your extreme lows and be cautious about those. We'll probably have a Dr. Lembke on again at a future time to try and get some more specifics about that. But if you do feel like you need to reset that system, it really does seem like a 30 day complete detox from whatever activity or substance that is. And ideally it doesn't continue after that 30 days, especially in conditions of drugs of abuse. Second of all, talks about the norepinephrine system and how the norepinephrine system is really deficient in many forms of major depression. And in depression, there is now more deliberate pursuit of nor epinephrin inducing activities that are healthy, that aren't adrenaline seeking per se, things like cold showers, things like particular patterns of breathing that engage and tend to make us more alert, things like exercise that will increase our levels of noradrenaline. I'd be remiss if I said that these activities could completely eliminate depressive symptoms in people with major depressive disorder. I don't think that's the case. And again, I want to acknowledge that people with major depressive symptoms often don't have the energy, the willingness, or the capacity to engage in some of these activities, but things like cold shower, deliberate cold showers, things like regular exercise, they aren't just feel good activities. They actually engage the norepinephrine system and keep that system tuned up and allow us to increase our norepinephrine levels at will on a regular basis. And their mood enhancing effects are real effects at the level of neurochemistry, then we talked about EPAs, Essential Fatty Acids, and it's clear that for most people, getting above 1000 milligrams and probably even closer to 2000 milligrams per day of EPAs can be beneficial for mood, especially in attempts to treat or offset major depressive disorder. Are there side effects? Well, you need to explore those for yourself and with your doctor, everyone has a different health background. For the margins of safety, for most people would probably be quite large, but for some people that might not be the case. So definitely check with your physician. We also talked about exercise and how EPA and exercise on a regular basis can offset

these inflammatory pathways. I want to mention something I've mentioned on a previous podcast, but in terms of keeping the Inflammatone, all these molecules that create inflammation, and then the inflammation can limit the amount of serotonin through the pathways we described. In order to do that, it's also very, very useful to ingest two to four servings of fermented foods on a daily basis or near daily basis. These are data that were published by the Sonnenberg Lab at Stanford recently in the journal Cell, Cell Press Journal, excellent journal that ingestion of these fermented foods really keeps the gut microbiome tuned up, so to speak, well in order to offset these inflammatory cytokines, keeping inflammation at bay, it just turns out to be a really good thing in order to keep our mood in a good place. So EPA, exercise, fermented foods, creatine as a potential source of relief from depression or offsetting, or keeping us away from major depression or relapse into depression. And then we talked about the prescription compounds and the compounds that are being used mainly in the course of studies and of psychiatry and depression, things like ketamine, PCP, psilocybin, and related compounds. And then lastly, we talked about ketosis, which may not be right for everybody,

02:00:10 Support & Additional Resources

but might be right for certain individuals out there who are grappling with this. If you're learning from this podcast and hopefully enjoying it and applying some of the tools that we describe, please subscribe to the podcast on YouTube. That really helps us. As well, please leave us a comment and some feedback for future episodes and topics that you'd like to see us cover. You can do that on YouTube, in the comment section. As well, please follow us on Instagram. It's Huberman Lab on Instagram. There, I provide some recaps of some of this material. I also provide some original material that doesn't show up in the podcast. Please also subscribe on Apple and Spotify, if you haven't already. And on Apple, you have the opportunity to leave us up to a five-star rating, as well as a comment and some feedback. Please also check out the sponsors that we mentioned at the beginning of the podcast. That's a terrific way to support what we're doing. We also have a Patreon, it's patrion.com/andrewhuberman. And there you can support the podcast at any level that you like. Throughout the course of today's episode and in previous episodes, I mentioned supplements that may be appropriate for you. If you want to check out the supplements that I take, you can go to thorne.com/u/huberman.

That's T-H-O-R-N-E.com/u/huberman. There, you can see the supplements I take. If you want to try any of those supplements, you get 20% off any of those supplements. And if you navigate from that location in the website to any other locations in the Thorne site, you will also get 20% off any of the other supplements that Thorne makes. We partnered with Thorne because they have the absolutely highest levels of stringency in terms of the quality and quantity of the supplements that they put in their formulations. And last but not least, I want to thank you for embarking on this journey of trying to understand what is depression, how does it work, and how to treat it. And thank you for your interest in science.