[Transcript] Huberman Lab / Ketamine: Benefits and Risks for Depression, PTSD & Neuroplasticity

Welcome to the Huberman Lab Podcast, where we discuss science and science-based tools for everyday life.
I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine.
Today we are discussing ketamine.
Ketamine is a fascinating compound, and it's one that nowadays is being used both clinically for the treatment of depression, and suicidality, and PTSD, and it is also a drug that is commonly abused.
That is, ketamine is often used recreationally, and it has a high potential for abuse.
So today we are going to discuss both the research on the clinical benefits of ketamine, as well as the risks of ketamine.
We are going to discuss the mechanisms of action by which ketamine produces what are called dissociative states.
I will define for you what a so-called k-hole is in scientific terms.
I will talk about dosages of ketamine, I will talk about delivery routes of ketamine, and throughout I will be emphasizing both the clinical benefits and the risks, that is the potential harms of using ketamine out of the appropriate clinical context.
So by the end of today's episode, you will understand thoroughly what ketamine is, how it works in the brain and body to produce dissociative states, and to relieve depression, and you will understand how it can actually change neural circuitry.
This is an important thing to understand about ketamine.
The acute or immediate effects of ketamine, while one is under the influence of ketamine, are just part of the story of how ketamine modifies the brain for the treatment of depression, suicidality, and PTSD.
And by extension, when people use ketamine recreationally, there are those immediate acute effects of ketamine, but there are also long-term changes in the brain that are important to understand.
During today's discussion, we will also be talking a lot about neuroplasticity, or your nervous system's ability to change in response to experience.
And we will be talking about neuroplasticity, not just in the context of ketamine, but as a general theme for how your nervous system changes anytime you learn anything.
And in that discussion, you're going to hear a lot about BDNF, or Brain Derived Neutrophic Factor.
Brain Derived Neutrophic Factor is a critical molecule for all forms of learning and memory and changes to your nervous system.
So in addition to learning about ketamine and how it works clinically and its relevance to recreational use and abuse, you will also learn a lot about neuroplasticity and BDNF and what it's doing in your brain right now as you learn.
Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford.
It is, however, part of my desire and effort to bring zero cost to consumer information about science and science-related tools to the general public.
In keeping with that theme, I'd like to thank the sponsors of today's podcast.

Our first sponsor is Roka.
Roka makes eyeglasses and sunglasses that are of the absolute highest quality.
The company was founded by two All-American swimmers from Stanford, and everything about Roka eyeglasses and sunglasses were designed with performance in mind.
I've spent a lifetime working on the biology of the visual system, and I can tell you that your visual system has to contend with an enormous number of different challenges in order for you to be able to see clearly when, for instance, you go from a shady area to a sunny area, when you look at something up close or off in the distance, Roka understands all of that and have designed their eyeglasses and sunglasses so that regardless of conditions, you always see with perfect clarity.
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Again, that's roka.com, and enter the code Huberman at checkout.
Today's episode is also brought to us by 8Sleep.
8Sleep makes smart mattress covers with cooling, heating, and sleep tracking capacity.
I've spoken many times before on this podcast and elsewhere about the fact that sleep is the foundation of mental health, physical health, and performance.
When we're sleeping well and enough, all of those things are improved, and when we are not sleeping well or enough, all of those things, mental health, physical health, and performance, all get worse.
Now, a key component to getting a great night's sleep is that the temperature of your sleeping environment has to be such that your body temperature drops by one to three degrees in order to fall and stay deeply asleep, and that your body temperature increased by about one to three degrees in order to wake up feeling refreshed.
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I've been sleeping on an 8Sleep mattress cover for about two years now, and I must say it is vastly improved my sleep.
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Okay, let's talk about ketamine.
I realize that many people have heard of ketamine, but most people don't realize that ketamine is very similar to another drug called PCP or Fencycletine, which goes by the street

names Angel Dust or Sherm.
It has some other street names as well.
When I was growing up, I heard a lot about PCP.
They taught us about it in school.
You'd hear about it on cop shows, on television, and the lore was that PCP would eliminate people's perception of pain and would make them violent.
You'd hear these stories in drug education classes that when people are on PCP, they're punching light poles and breaking their hands.
They can fight off eight or 10 police officers who are trying to handcuff them.
I don't know whether or not any of that is true or not, but we heard a lot about PCP and it was associated with drugs of abuse, things like cocaine, methamphetamine.
It was lumped into that category.
Nowadays, when we hear about ketamine, rarely do people mention that ketamine and PCP actually have the same mode of action, more or less.
Okay, I'm not talking about the specifics.
I'm talking broadly, they have the same mode of action in the brain that both of them are dissociative anesthetics.
And nowadays, usually when we hear about ketamine, we are hearing about its benefits.
We are hearing that it can help cure depression.
We are hearing that it can help reduce or cure suicidality, that it can be used to treat PTSD.
And indeed, all of that is true in the appropriate clinical context, at the appropriate dosages and given at the appropriate frequency.
Ketamine has proven to be a miraculous drug for some people, not all people, for the treatment of depression, suicidality, and PTSD.
That said, ketamine also has a very high potential for abuse.
And so it may come as no surprise that we often hear about ketamine nowadays, also in the context of its use at parties.
You hear about people going into so-called k-holes, which is a particular state associated with overdoing the dosage of ketamine a little or a lot.
We'll get back to that a little bit later, what it is, how dangerous it is, et cetera.
In any case, ketamine is an incredible drug, very similar to PCP, Fencycladine, and it is a drug that nowadays there is crossover between the clinical uses of ketamine for treatment of depression, et cetera, and its recreational use.
What do I mean by that?
What I'm referring to is people accessing ketamine legally for the purpose of treating depression, but taking that ketamine out of the clinic, out of the doctor's office, which is a very different set of conditions than most of the studies that have been done on ketamine and its role in depression.
And not surprisingly, if there is increased access to a drug like ketamine, really any drug that has a potential for abuse, then we also see an increase in the number of people that are using that drug recreationally, and some of them do indeed get addicted to ketamine.
So I know many of you are probably wondering, can you get addicted to ketamine?

Indeed people can get addicted to ketamine.
There are some people who like its effects enough that they find themselves compelled to use ketamine even though the use of ketamine is degrading their overall life performance.
So work, school, relationships, finances, et cetera.
That said, ketamine does have these established clinical uses.
So nowadays the landscape around ketamine is so different than it was 10 or 20 years ago when it was lumped very closely with PCP, Fencycladine, and really just looked at as a drug of abuse.
There were some early cases in the 1970s of the use of ketamine in order to treat PTSD.
This was mainly in soldiers in Vietnam or people coming back from Vietnam.
But really the clinical use of ketamine for the treatment of depression, suicidality, and PTSD has really just taken off in the last five to 10 years.
And that's what's brought us to this new landscape of interest and understanding and use of ketamine
in the clinical and recreational context.
So how is it that a drug that at one time was really just viewed as a street drug that was bad, bad, bad is now being prescribed widely and has all this interest surrounding it?
And really this has to do with our understanding of what depression is and what depression isn't.
So I'd like to just take one or two minutes and explain to you a little bit about the history of depression and its treatment.
What we observed starting about the middle of the last century, so around 1950, but really taking off in the early 1980s and 90s is the so-called monoamine hypothesis of depression.
Monoamines, as the name suggests, are synthesized from amino acids.
That's a good way to remember monoamines.
Monoamines include things like serotonin, dopamine, and norepinephrine, although there are other monoamines as well.
Monoamines are neurotransmitters or more specifically they are neuromodulators, meaning they change
the activity of neural circuits in the brain and body.
They can ramp up levels of activity in lots of different brain areas or they can reduce the activity of neural circuits in lots of different brain areas, as well as within the body, right?
Your gut has serotonin and needs serotonin.
Dopamine also plays important roles in the body, et cetera, et cetera.
The monoamine hypothesis of depression is really centered around the idea that it is deficiencies in these monoamines, either serotonin or dopamine or norepinephrine or some combination
of those that gives rise to depression.
In reality, there is very little, if any, evidence that there is a deficiency of monoamines in any form of depression.
However, it is very clear that drugs that increase certain monoamines, so drugs like Prozac or Zoloft that increase serotonin, or drugs like Brupriron, which is often called

Welbutrin, which is its commercial name, which increases dopamine and norepinephrine, can often provide relief for certain symptoms of depression in some people.
However, what we've learned over the last 30 or 40 years is that drugs that are designed to increase certain monoamines in order to treat depression only work in about 40% of depressed people that take them, and they have a lot of side effects.
Now, some people are lucky enough that they can use a low enough dose or perhaps even a high enough dose that gives them relief from their depressive symptoms, but does not give them side effects that make it so uncomfortable for them to use that drug that they would choose rather to not take that drug.
However, a lot of people that do get depression relief from things like Zoloft or Paxil or from Brupriron find that the side effects, which include things like dry mouth, although more commonly reductions or increases in appetite, or vast reductions in libido, or changes in their sleep patterns, et cetera, that those side effects really make it impossible, or at least very uncomfortable for them to take those drugs.
And of course, there are the 60% of depressed people who do not respond to those drugs at all.
Now, I want to be very clear, things like SSRIs, things like Wellbutrin have helped a tremendous number of people get relief from depressive symptoms, and in many cases have warded off suicidality as well.
However, there are also a great number of people who have experienced a lot of side effects and problems from these drugs, hence the desire to find other compounds that can treat depression without creating similar side effect profiles, and that ideally can provide relief not just for 40%, but for all people suffering from depression.
So that's where ketamine enters the picture.
Prior to the 1990s, they were mainly studied in neuroscience and pharmacology laboratories for their abuse properties and for their anesthetic properties.
So ketamine is a dissociative anesthetic.
It's actually used to induce certain forms of anesthesia for surgery.
It's not always used, but it's often used.
This is something that if you've ever had a surgery, you might want to ask your anesthesiologist about what sorts of drugs are you giving me to go under, what sorts of drugs are you keeping me to stay under, and maybe even what sorts of drugs are you giving me to bring me out of anesthesia.
It turns out that when you go into anesthesia, your anesthesiologist is rarely giving you just one drug.
Typically, they're giving you one drug to kill off a little bit of anxiety and maybe eliminate a little bit of pain sometimes, and then they'll give you another drug to drop you into a deeper plane of anesthesia, and then nowadays, there are sophisticated ways to monitor your plane of anesthesia, and there are sophisticated ways to, if necessary, get you out of a deep plane of anesthesia if that plane of anesthesia is too deep.
When I talk about a plane of anesthesia, I'm just talking about going from full wakefulness to a reduction in anxiety to falling asleep to asleep to the point where even if someone were to pinch your toe or your arm, like a really intense pinch, that you wouldn't wake

up from that.
Okay, so ketamine has the property of being an anesthetic.
It kills the response to pain, and at certain doses, it can bring you into deep planes of anesthesia at lesser dosages.
It can take you into transition points between awake and deeply anesthetized, and it's really that transition point between awake and deeply anesthetized, which we are going to call the dissociative state.
It's kind of this liminal state, a little bit like dreaming.
It can have some dreamlike qualities to it.
That's the state that has most often been sought after or employed for the treatment of depression, suicidality, and PTSD, which brings up a really important point, which is that when people use ketamine recreationally, it's not clear exactly what plane of anesthesia or dissociation they are actually seeking.
And this is why we hear about some of the desired effects of ketamine that are driving people to use it recreationally, and why we also hear about people having some unpleasant or even very unpleasant or dangerous experiences when using ketamine recreationally.
Because we're talking about a drug that has a lot of different effects depending on the dosages, and as we'll soon talk about, individuals vary tremendously in their response to different dosages of ketamine and the delivery route for ketamine, whether or not it's delivered early in the form of a pill or put sublingually in what's called a troche that dissolves under the tongue or it's injected, whether or not it's injected into the vein or intramuscularly, et cetera.
Each of those can produce very different effects in terms of the speed of onset of the drug and the type of effects that it produces in the brain and body.
So what happened in the early 90s is that laboratories that were studying animal models, what we call preclinical models of things like depression and learning and memory, and to some extent ketamine, but mainly focusing on learning and memory and depression, made an interesting discovery.
There's a certain preclinical model of depression that's pretty common in laboratories that involves taking a rat or a mouse and putting it into a small container, like it looks like a beaker or a jar, sometimes it's a tray, and it has water in it.
And you might be surprised to learn, perhaps not, that if you put a rat or a mouse into water, it will swim, okay?
So it's treading water in order to keep its head above water and not drown.
I realize for some of you, this might be a bit of an aversive topic to hear about animal research, but this is one of the common preclinical models of depression, which is put a rat or a mouse into water, let it swim and see at what point it gives up.
Because what happens is if you put a rat or mouse into water, it will attempt to save its own life by swimming, but at some point it will just give up and it will just start sinking.
And then of course, the researcher needs to rescue the rat or mouse, put it back into its home cage, dry it off, give it some food, et cetera.
This preclinical model is called the model of learned helplessness.

And it's become a prominent preclinical model of depression, because of course, we can't ask mice or rats if they are depressed or happy, I suppose you can ask them, but they're not going to answer in any kind of meaningful way.
So we can only look at their behavior in order to understand whether or not they have a sense of happiness or a sense of depression.
And of course, that's very hard to gauge in an animal model of any kind.
You could make guesses based on other behaviors like are they grooming regularly?
Are they eating regularly?
You know, things that more or less parallel what we think of as health or lack of health in a human who's happy or depressed.
But in the context of trying to understand depression in these preclinical animal models, having a behavior that you can really quantify carefully across a lot of different animals and conditions is really beneficial.
So this thing of putting a rat or mouse into water and seeing how long it takes before they give up to save their own life is called the model of learned helplessness.
And what it allowed researchers to do was to take rats and mice, put them into water, see how long it took before they gave up, and then to give them different drugs to see whether or not any of those drugs either hastened, sped up, or prolonged the duration over which the animal would attempt to save its own life.
This actually has some meaningful parallels to human depression.
One of the hallmarks of depression is that people stop thinking positively about their future.
Depression, of course, can include a lot of other symptoms.
One of the most prominent symptoms of depression, for instance, is consistently waking up around 2.30 or 3.30 in the morning and not being able to fall back asleep again.
Now, keep in mind, it is not the case that if you're waking up at 2.30 or 3.30 in the morning and you can't fall back asleep, that you are absolutely depressed.
It's simply not the case, but that pattern of lack of sleep plus some other things like lack of anticipation of a positive future, inability to imagine the future in any kind of meaningful or positive way, etc., are part of the key features of what we call a major depressive episode.
So this preclinical model of learned helplessness allowed researchers to test a lot of different drugs and establish which drugs at which dosages allowed animals to fight for their life longer when placed into water.
It's really that simple as a model, but it revealed some very interesting things, at least one of which is that when animals were injected with ketamine, this dissociative anesthetic, but they were injected with dosages of ketamine that were below what would induce full anesthesia, these animals would swim for their life for a lot longer.
Now to some extent that ought to be surprising and in fact was surprising to researchers because ketamine is what's called an NMDA receptor blocker.
Now when I say blocker, I'm not getting into the details of what specific form of blocker it is, but I do want to mention that a blocker is sometimes referred to as an antagonist, whereas something that promotes the activity of a receptor is called an agonist.

So if you can just remember that ketamine is an NMDA receptor antagonist or blocker, then you should be fine for the rest of today's conversation.
Now I haven't told you what NMDA is, NMDA stands for N-Methyldiaspartate and you do not need to remember that, but the surprise for researchers was that this drug ketamine is allowing animals to fight for their life for longer, so it has this sort of property of overcoming what we call learned helplessness or a sense of helplessness, a.k.a. antidepressant effects and we also know that it's an NMDA receptor antagonist or blocker and that's perplexing because we also know that the NMDA receptor is critical for changing neural circuitry in the brain.
It's critical for neuroplasticity.
So put differently, here's a drug that blocks the receptor that's critical for neuroplasticity for changes in the brain and yet somehow it's allowing these animals to fight for their life longer.
It's somehow giving them more of a sense of hope, at least that's the subjective interpretation of what one observes when a mouse or rat is swimming for much longer when it would otherwise just give up and sink to the bottom of the vessel.
Now in general, there are two kinds of scientists.
There are scientists that take a look at a set of findings like that and say, oh, here's a drug that's supposed to be terrible for us.
It's an anesthetic and it blocks NMDA receptors and NMDA receptors are good for neuroplasticity and somehow it's also allowing these animals to swim longer and I would say one category of scientists would just look at that and just say, wow, that is a big ball or tangle of confused facts.
How does one even reconcile that, right?
Brain change ought to be good and perhaps even lie at the heart of our ability to recover from depression.
This is a drug that blocks neuroplasticity but somehow is relieving depression.
I'm going to walk away from that.
I'm going to work on something far simpler.
And then there's this other category of scientists which, thank goodness, exists who looks at that apparent contradiction of, okay, there's a drug which blocks plasticity.
Plasticity is thought to be important for getting over depression and yet the drug can provide some relief from depression, at least in these preclinical animal models.
And they say, hmm, I like a good puzzle, right?
The more complex the puzzle, the more interesting and they start digging in with preclinical studies and they start talking to clinicians who are treating patients for depression.
And like I said, thank goodness these sorts of scientists exist and thank goodness they did that because it turned out that when clinicians tried ketamine in depressed patients as a means to relieve depression, it had remarkable effects.
So it was about the year 2000 when the first sets of papers about the clinical use of ketamine for the treatment of depression started to emerge.
Now we have to remember the context in which all of this was happening.
In 2000, drugs like Prozac and some of similar SSRIs, selective serotonin reuptake inhibitors,

things like Wellbutrin, were really hitting the market in full force.
And as we talked about earlier, some people were getting relief.
Some people were getting relief with a lot of side effects and therefore deciding not to take those drugs and a lot of people, the majority of people that were taking those drugs were not getting relief.
So there was a real urgent need to find other drugs for the treatment of depression.
And ketamine, at least based on its apparent profile of being a dissociative anesthetic, would seem like the last drug that you'd want to use to treat depression, right?
It dissociates people, you even hear about dissociation as a symptom of depression.
And yet what happened was a small number of very pioneering clinicians started to explore the use of ketamine in the clinic for the treatment of depression, and in particular for depression that did not respond to any other treatment.
So there was a real critical need to find other compounds and a bit more motivation to test some of these, let's call them atypical compounds for the treatment of depression.
So one of the first landmark papers in the use of ketamine for the treatment of depression is entitled, Antidepressant Effects of Ketamine in Depressed Patients.
This is a paper that I've provided a link to in the show note captions.
It's a small study, okay?
So it doesn't involve many subjects at all, really just has seven subjects, all of whom had major depression, and they did intravenous injections with half a milligram per kilogram of body weight of ketamine.
Now that dosage half a milligram per kilogram of body weight turns out to be very important for today's discussion because it's going to serve as a reference point for later discussions when we get into other modes of delivery of ketamine, such as oral, pill form ketamine or sublingual ketamine.
And as it relates to things like the k-hole or the dissociative state or the various effects that ketamine can have depending on the dosage and the delivery route.
Meanwhile, going back to this study, what they found is that when they injected patients with severe depression with ketamine, the effects of ketamine took place within minutes, within 10 or 15 minutes, and that they experienced a sort of peak euphoric state, okay?
So they're not inducing deep anesthesia, right?
At this dosage, they're getting people into a kind of euphoric, dreamy, semi-dissociative state that occurred within 15 minutes and really peaked about 45 minutes to an hour after they were injected with the drug, and that the total effects of the drug in terms of euphoria were effectively over by about two hours or so.
And that time course of effects makes perfect sense if you look at, say, the half life of ketamine, which is how long it takes for half of the drug to be active in the system, et cetera.
But what was really interesting about this study and others like it is that the patients experienced relief from their depression almost immediately after taking the drug.
So within minutes to hours, and that it persisted for several days after taking the ketamine, okay?
So the dissociative euphoric, dream-like effects of ketamine take place very quickly.

They're very, very salient, right?
The person basically is just lying there experiencing this euphoric, dream-like dissociative state, and they get some relief from their depression immediately.
And yet there's persistent relief from that depression, which lasted at least three days out from the treatment.
Now a key theme of today's discussion is going to be that the antidepressant effects of ketamine appear to be fairly short-lived, at least when one is exploring one or two treatments with ketamine.
In other words, the typical contour is that people will take ketamine, get this euphoric dream-like dissociative effect, come out of that feeling some immediate relief from their depression.
This is one of the things that makes ketamine an incredibly attractive drug for the treatment of depression, especially depression that hasn't responded to other forms of treatment, which is that people get relief very, very quickly, indeed the same day that they initiate the treatment.
Now this is especially important when you think about the fact that the mono-aiming hypothesis of depression, which drove the discovery and development of all these drugs like SSRIs, well buttern, et cetera, those drugs often can provide support for people with depression.
Again, only 40% of people get true relief from their depression.
And again, there are some side-effect issues or major side-effect issues in some cases that have to be dealt with.
But even the positive effects, even under the best conditions, oftentimes those effects don't kick in for weeks or months after somebody initiates taking the drug.
Now that might not seem like a long time to wait for some of you, but if you are somebody suffering from depression, even another day, even another hour with depression, seems almost unmanageable.
And sadly, many people who have these forms of depression will go on to commit suicide.
So it is ever so important that there be rapid treatments for depression, even same day treatments for depression.
And based on this study, it appeared that ketamine was, and indeed still remains, that drug.
Now I certainly don't want to position ketamine in your mind as a miracle drug for depression.
In fact, I don't actually believe in miracle drugs.
I don't think that there is any compound that alone can produce all the desired effects that one wants without any negative effects in a way that could warrant calling it a miracle drug.
That's just not how biology works.
There's always an interplay between pharmacology, between our behaviors and what we choose to do or not do.
This is a topic we'll get into a little bit later when we talk about antidepressive behaviors and the role of ketamine in bringing about antidepressive behaviors for the relief of depression.
Now with that said, the study that I just mentioned, as well as many, many other studies

that followed, emphasize that ketamine could provide significant decreases in not just depression and suicidality, but also the feelings of helplessness and worthlessness that are associated with major depression.
And again, it could do that in people that also were not responding to other forms of depression treatment, such as SSRIs, et cetera.
So while we don't want to call it a miracle drug, ketamine turned out to be and remains an incredible drug for the treatment of depression in certain cases.
Now in addition to that, ketamine has been shown in clinical studies to provide relief, not just for treatment resistant depression of the major depression type, right?
Many different forms of depression, but major depression is the one that we're normally thinking about or referring to when we talk about depression.
But ketamine has also been shown to be effective in treating bipolar depression, sometimes called bipolar disorder, although more commonly nowadays called bipolar depression.
I did an entire episode, by the way, on bipolar depression.
If you want to know what it is and what it isn't, how it differs from borderline personality disorder, et cetera, you can go to hubermanlab.com, just put into the search function bipolar and it will take you to that episode.
Ketamine has also been shown to be useful for the treatment of PTSD and for OCD, obsessive compulsive disorder, and for anxiety and for various forms of substance addiction.
So ketamine is not a miracle drug, but it does seem to have broad application and to be very successful for the treatment of a lot of major psychiatric challenges.
Now just because ketamine has shown these incredible applications, it also has some serious problems that are directly related to how it works in the brain, or at least from what we understand of how it works in the brain.
And what I'm referring to here is, yes, ketamine is very rapid acting.
It can often provide relief from depression almost immediately, meaning same day.
However, it is very short lived after about three days or a week or so, the antidepressant effects of ketamine often wear off.
So that creates a situation where people perhaps need to take ketamine every week.
And yet it creates enough of a dissociative state, meaning it takes people enough out of their normal daily routine that the prospect of people taking ketamine every week is actually not that feasible.
And also because of some of the propensity for ketamine to become a drug of abuse, that is for it to be habit forming and or addicting.
One also worries that if people are doing ketamine every week to treat their depression, that they can become so-called hooked on ketamine.
Now fortunately, there have been studies of ketamine and how it works, not just in the short term, but in the longer term that have led to some very important clinical studies that have explored, for instance, people taking ketamine twice per week for a duration of three weeks total.
And what they find is that, yes, after the first time they take it, they get some relief from depression.
They take it a second time that week, they get some relief from depression and they do

the same thing the next week and the next week.
And when they do that, they get relief from depression the whole way through that entire three weeks.
But it turns out that there's also some so-called durability to the effect, such that if people do this twice a week dosing regimen, so ketamine twice a week for three weeks total, they find that when they end that three weeks, they get some ongoing relief from their depressive symptoms, which can extend months or more before they have to repeat that twice a week for three weeks regimen.
Now certainly not all studies of using ketamine for the treatment of depression have used that exact dosage regimen, twice a week for three weeks and take some time off, repeat. Twice a week for three weeks, take some time off, repeat.
Some have explored giving ketamine once per week or even three times per week or doing it once a week for five weeks and then taking an extended period of time off before repeating the treatment schedule.
There are a bunch of different studies out there, but when one looks at all of those studies and mass together, it's very clear that ketamine is providing relief from depressive symptoms immediately and in the days after the treatment, but that when those treatments are stacked fairly closely together, that there is some durability, some ongoing relief from depression.
And what this tells us is very important.
In fact, I hope everybody really highlight this in their minds as they're hearing it.
It's very likely that ketamine is acting by at least two and probably three different mechanisms in order to provide relief from depression.
One of those mechanisms induces relief from depression very quickly and seems to be associated with that euphoric dissociative dream-like state that one experiences when they are under the influence of ketamine.
The second mechanism seems to provide relief from depression in the days and weeks that follow the ketamine treatment.
And there also appears to be a third mechanism by which ketamine can induce long lasting changes in the nervous system.
And it is those three mechanisms, short, medium, and long-term mechanisms that produce the kinds of changes in neurochemistry and more importantly, changes in actual neural circuit wiring that allows ketamine to provide this incredible relief from depression.
So next we're going to turn to what those mechanisms are because in understanding those mechanisms, you will understand how ketamine provides this relief from depression, but you'll also come to understand the more important, broader theme of what depression is really all about at a neural circuit level and how relief from depression is all about neuroplasticity.

sources that include vegetables and fruits every day, but oftentimes I simply can't get enough servings.
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I have more focus and energy and I sleep better and it also happens to taste great.
For all these reasons, whenever I'm asked if you could take just one supplement, what would it be, I answer AG1.
If you'd like to try AG1, go to drinkag1.com slash Huberman to claim a special offer.
From now until August 12th, 2023, AG1 is giving away 10 free travel packs plus a year supply of vitamin D3K2.
Again, if you go to drinkag1.com slash Huberman, you can claim the special offer of 10 free travel packs plus a year supply of vitamin D3K2.
So how is ketamine really working?
We already established that ketamine blocks the NMDA receptor and that the NMDA receptor is critical for many forms, not all, but many forms of neuroplasticity.
Now I realize some of you might be familiar with so-called ligands and receptors, but most of you probably are not.
A ligand is a chemical that binds to a receptor and a receptor is like a little parking spot on the outside of a cell.
There can also be receptors inside of cells, but most of the time, when we're talking about nerve cells, neurons, and you hear the word receptors, you're hearing about receptors on the outside of the cell.
So the NMDA receptor does not exist in our neurons in order to bind ketamine.
It's there actually to bind all sorts of other things that are endogenous, that are naturally made by us, but ketamine has a very high, what's called affinity, has a very high probability of binding to the NMDA receptor if it's introduced to our bloodstream.
So when ketamine is taken in pill form, sublingual form, meaning under the tongue, when it's injected into the muscle or the vein, it gets into the bloodstream and then it's able to cross easily across the blood-brain barrier, the so-called BBB, blood-brain barrier.
The blood-brain barrier keeps a lot of things out of the brain, but ketamine can very readily pass across the blood-brain barrier.
Once it's in the brain, it has a very high affinity for, meaning it knows how to seek out and bind to those NMDA receptors.
Now the simplest way to explain how NMDA receptors ordinarily contribute to neuroplasticity is that they represent what's called an AND gate.
And an AND gate, as the name suggests, is a function in a cell or in a system where two things have to be present.
In fact, for those of you that have a bit of an engineering or computer programming background, you'll be familiar with AND gates.
For those of you that don't, don't worry about it.
I'm going to explain what an AND gate is right now.
An AND gate in the context of nervous system function is when two things are present, like

chemical A and chemical B, both have to be present in order for some process, say neuroplasticity, to occur.
The NMDA receptor, as I mentioned earlier, is a receptor on the surface of neurons and it binds glutamate, which is a molecule that we all make in our brain, and it activates other neurons.
It's what's called an excitatory neurotransmitter.
Now there are lots of different receptors for glutamate, and those receptors are binding glutamate all the time.
However, in order to activate the NMDA receptor, there has to be a lot of glutamate present and it has to happen over a very brief period of time.
So the NMDA receptor is an AND gate in the sense that glutamate has to be present and to bind it, and it has to get a lot of electrical activity, a lot of input in order for that to happen.
So it's a receptor that responds primarily to unusually high or frequent levels of electrical activity.
Most places in real world context, so that it makes a bit more sense.
I like most all of you in moving my arms around a lot throughout the day.
Now as an adult, my motor cortex, the area of my brain that controls motor coordination in my limbs, has connections from my brain to my spinal cord, from my spinal cord to my muscles, and that's what allows me to move my limbs.
Under conditions of just moving my limbs and doing things throughout the day, drinking a cup of coffee or yerba mate, walking outside to view some sunlight in the morning, doing the things that I do every single day and that I already know how to do.
Glutamate is definitely involved in that process.
Glutamate binding to its other receptor types, which are called AMPA receptors for those of you that want to know, that's involved in that process.
It's typical levels of activity.
If however, I were to sit down at this desk and be commanded to or decide to do some specific motor limb movement, let's say move my hand in a three dot sequence for those of you watching, you can see this for those of you that are listening, don't worry about it, it's not very interesting to watch.
The point is just that I'm going to put my finger down in one, two, three points on the desk in front of me and then three, two, one points coming back to me.
Now that's obviously a motor sequence that I can perform.
I just did it, so clearly I can perform it.
But if I were to do that for let's say an hour, what would happen is the neurons that are involved in generating that motor sequence of one, two, three, three, two, one, one, two, three, three, two, one would be active over and over and over again.
And what would likely happen because of that unusual, frankly, motor behavior is that the neurons responsible for generating that motor behavior would be able to detect it as unusually frequent, unusually high levels of activity in the circuits that generate that behavior.
And the increase in glutamate that's impinging on the neurons in that circuit would bind the NMDA receptor, making it change several important things.

The first of which is that your nervous system is capable of changing, but that's an energetically demanding process.
So the incredible thing about neuroplasticity is that when you generate an unusually high or just an unusual pattern of activity, motor activity, or you're hearing a new language, you're trying to learn that, or you're navigating a new city, the neurons are firing in ways that are atypical for them and they are firing a lot more.
And so the neurons are going to bind glutamate, the NMDA receptor is going to be activated, and then downstream of NMDA receptor activation are a bunch of what we call intracellar processes,
a bunch of things that happen in the cells to try and make that behavior occur again and again if needed, but without the huge energetic demand.
You've experienced this before when you're trying to learn something and it feels sluggish, it feels hard, it's frustrating, and then eventually you learn it and it's very facile, it's very easy.
One of the reasons for that is that when the NMDA receptor is activated by these infrequent or unusual patterns of activity, it can then recruit other glutamate receptors, the more typical kind, the AMPA type receptors to the cell surface, and then those receptors can simply bind the glutamate and allow that behavior to occur without this whole process that's involved in neuroplasticity having to engage and do things like build new proteins in the cell, build new machinery, et cetera.
So to just step back from this, the way to think about the NMDA receptor is that activation of the NMDA receptor only occurs under conditions of unusually high or simply unusual patterns of activity that the NMDA receptor, yes, controls neural activity in the immediate sense, like when it's activated, it's changing the patterns of activity in the neuron, sure, but it also can engage gene expression and introduce new receptors to the cell, basically giving the cell the ability to then recreate the same patterns of activity without having to do it in such a metabolically demanding way.
In fact, a good analogy for all of this is the way that muscles can hypertrophy, right?
If you overload muscles properly through resistance training of any kind and then give them a period of rest, there's recruitment of specific things to the muscle fibers as well as recruitment of changes in the nerves that innervate that control the contraction of those muscles and then those muscles grow, they get stronger, et cetera, and they're able to function and use that new strength and new growth.
And you don't have to damage those muscle fibers or trigger those adaptations over and over again to maintain them because you have this new capability.
Now I realize that's a lot of details about NMDA receptors and neuroplasticity, but really if we needed to pick one biological mechanism that resides at the center of many, many important forms of neuroplasticity, it would be the NMDA receptor and its functions that I just told you about.
So now that you have that in mind, that these NMDA receptors are critical at detecting unusual activity, making changes to cells so those cells can then respond to that activity in the future.
You have in mind the conceptual basis for understanding how ketamine works because as I've

mentioned
several times already, ketamine is an NMDA receptor blocker antagonist.
And yet we know that a lot of the changes in the brain that underlie the transition from a depressed state to a non-depressed state involve neuroplasticity.
So what's going on there?
Well, what's going on there turns out to be extremely interesting and you can understand it very easily if you understand that there are essentially two major types of neurons in the brain.
You have those excitatory neurons, meaning neurons that when they are activated electrically, they activate or excite other neurons.
At least they try to.
They release neurotransmitter into the synapse, which is the little gap between neurons.
The neurons on the other side have receptors.
They bind those neurotransmitters, in this case glutamate, which is the major excitatory neurotransmitter in the brain.
And then there is a high probability that those other neurons will be excited that they will be electrically active.
That's one major type of so-called neurotransmission in the brain.
The other major type of neurotransmission in the brain is called inhibitory neurotransmission.
Inhibitory neurotransmission involves neurons that release the neurotransmitter GABA or sometimes also another molecule called glycine, but mostly GABA.
When GABA is released, it has the property of reducing the probability that the next neuron will be electrically active.
In fact, GABA's job is to bind the receptors on the next cell and to make it less electrically active.
So we've got excitatory neurotransmission and we have inhibitory neurotransmission.
And just to place inhibitory and excitatory neurotransmission into context, if you think about a condition like epilepsy, which involves seizures of either the smaller type called petite mall seizures or grand mall seizures, which are the type in which people have body wide convulsions.
They are often disengaged from whatever's going on around them in those moments.
They're shaking quite a lot, et cetera.
There are many causes of seizures, but to get to the heart of what a seizure is, it is essentially runaway excitation in the brain.
A small region of the brain becomes especially electrically active.
And then it spreads out from that foci, that focus of the excitation.
And it recruits a lot of neurons in a fairly nonspecific way, creating these seizure-like motor patterns in the body and patterns of activity in the brain that can involve disengagement from immediate experience and lack of perception.
Sometimes there's aura.
There's a whole discussion to be had about seizure.
And by the way, seizure can occur in a lot of different contexts.
Of course, it can occur in epilepsy, it can occur after a head injury, et cetera.

We'll cover seizure in a future episode of this podcast, of course.
But one of the major causes of seizure, and by extension, lack of seizure, is that ordinarily inhibitory neurons and excitatory neurons are in this kind of push-pull that for somebody that doesn't experience seizures puts the brain in balance so they don't have seizures.
The inhibitory neurons are suppressing the activity of many neurons so that those many neurons don't get runaway excitation.
You don't get seizures.
The excitatory neurons are feeding back onto the inhibitory neurons so everything is kept in balance.
There isn't too much inhibition.
There isn't too much excitation.
Everything's in balance.
Okay, so now you understand that there are NMDA receptors and these are critical for many forms of neuroplasticity.
You also understand that there are excitatory neurons which stimulate the electrical activity of other neurons and that there are inhibitory neurons in your brain that inhibit or suppress the activity of other neurons and that you need excitatory and inhibitory communication between neurons at all times and that it has to remain in balance and that the NMDA receptor is normally just sort of sitting there, not doing a whole lot, unless levels of neural activity are elevated above their normal baseline and then you can get changes in the neural circuits and those changes can be very long-lasting.
Let's not forget the piece of information most pertinent into today's discussion which is about ketamine which is that ketamine blocks that NMDA receptor and there's a conundrum I keep coming back to which is you need neuroplasticity in order to get relief from depression.
What researchers have discovered is that, yes, ketamine blocks the NMDA receptor.
It actually quiets down neurons.
It prevents neurons from being as active as they normally would be and yet somehow almost paradoxically it increases neuroplasticity in brain circuits that are involved in mood, in reward, in self-reflection.
We'll get into what those brain circuits are in a little bit.
The way it works is that ketamine binds to the NMDA receptor present on inhibitory neurons and in doing so dramatically reduces the amount of inhibition coming from those inhibitory neurons onto excitatory neurons.
When that happens, the excitatory neurons in specific circuits of the brain are allowed to increase their activity.
They do what's called bursting.
Bursting is a pattern of electrical activity whereby normally one of these excitatory neurons is releasing glutamate in a pattern that might look or sound like this.
It actually doesn't make a sound in the brain but if you were to record from one of these neurons which people have done many times over and then you were to convert the electrical signal in those neurons to an audio monitor, you would hear the firing, the action potential of those neurons as that, that's what it actually sounds like on the audio monitor.
It sounds like a little bit of static.

But if the normal firing of the neuron is, which is the pretty typical baseline firing of the neurons in the relevant circuits to mood that I'm going to be discussing under conditions where ketamine has been brought into the system, binds that NMDA receptor, blocks the output of those inhibitory neurons onto the excitatory neuron.
Now the excitatory neuron is firing in burst.
And those bursting patterns of electrical activity are the absolute perfect patterns of activity that induce not just short term but long term changes in the neural circuits associated with reward, with dopamine release, with disappointment and with mood in ways that are directly relevant to suppressing or providing relief from the symptoms of major depression.
Now I realize what I just told you is a lot of information.
In fact, what I just described represents essentially what I would teach to an advanced undergraduate slash graduate course, medical school course on neuroplasticity and how ketamine works.
So keep in mind that we're having a discussion here that is at a fairly high level.
And if you could understand even a tiny fraction, even just one bit of what I just described, you're doing great.
If you could understand more, outstanding.
Just to make sure that everyone's on the same page as we move forward because I do want to make sure that everyone understands ketamine and how it works because it does have these sort of cryptic functions of engaging neuroplasticity in ways that aren't obvious.
If you just ask, you know, what does ketamine do when you inject it?
What does ketamine produce in terms of a feeling state?
And then, you know, how does somebody get relief from depression that can all start to get a little bit muddled unless you understand the following.
So I'm going to tell it to you again in just very top contour terms.
Somebody takes a pill or an injection or sublingual ketamine.
It makes its way into the bloodstream and then it makes its way into the brain.
Once it's in the brain, it binds to a particular category of receptors called the NMDA receptor.
The NMDA receptor is a receptor that normally is quiescent.
It's just kind of sitting there.
It doesn't tend to do a lot under normal conditions of everyday life.
However, the NMDA receptor is typical function.
Okay.
So when there's no ketamine in the body or brain is to detect abnormal levels of neural activity and in doing so, recruit changes to cells, receptors, et cetera, literally change the neurons in ways that allow them to respond to that activity in the future without having to be under such big metabolic demand.
And they do that by recruiting more receptors, et cetera, much in the same way as when you overload a muscle in the gym, it will eventually recover, if you allow it to recover, and it will get stronger through the addition of a bunch of new proteins.
The nerve communication of that muscle will change the muscle and the nerve to muscle connection change.

It gets stronger and sometimes it gets bigger and stronger in the same way a neuron can change the way it functions in response to experience and neurons don't know experience of life in any other way, except the patterns of electrical activity and chemical activity that impinges on them.
Okay.
Now ketamine, the drug binds to and blocks that NMDA receptor.
So the obvious conclusion would be that ketamine prevents neuroplasticity and that's not what happens.
We know that ketamine actually induces neuroplasticity and it does so specifically in the brain circuits
that control mood, the net consequence being improvements in mood.
How does that happen?
It happens because ketamine binds to and blocks those NMDA receptors on inhibitory neurons.
The inhibitory neurons are the neurons that normally suppress the activity of other neurons.
So when ketamine binds to the NMDA receptor, the activity of those inhibitory neurons is reduced and as a consequence, excitatory communication between neurons in those mood related circuits
increases.
And it increases in a way that recruits neuroplasticity that strengthens those connections and makes them more likely to be active in the future.
Now it is not the case, at least at clinical doses, that ketamine induces seizures.
It certainly can at higher doses, but at clinical doses, when ketamine suppresses the activity of those inhibitory neurons and the excitatory neurons ramp up their activity, they're ramping up their activity a lot and enough to create changes in those neural circuits associated with mood.
And the changes are in the direction of making those neural circuits more likely to generate positive mood and less likely to generate negative mood.
We'll get into the specifics of those circuits in a little bit, but ketamine is not creating the kind of enormous increases in excitatory communication between neurons that leads to that runaway excitation.
Now the point of the discussion we just had over the last 10 minutes or so was several fold.
First of all, I do believe it's important to understand the key components of neuroplasticity, which is this remarkable feature of our brain and nervous system that we all have, right?
This ability to change our own brain circuits.
No other organ in the body, as far as we know, can direct its own changes, but we can direct our own brain changes.
And the NMDA receptor is absolutely critical for that.
I also think it's important to understand the difference between inhibitory and excitatory communication between neurons, because that's just central to understanding brain function.
Brain function is a series of accelerators and breaks.
It's not all about neurons stimulating other neurons.
It's also about neurons preventing the activation of other neurons.

That's just central to everything, not just preventing seizures, but it's central to learning.
It's central to vision.
It's central to hearing.
It's central to creativity.
It is at the core of brain function.
And the other reason to have the discussion we just did is that ketamine has this incredible property.
It can literally change the neural circuits that generate mood, that generate your feelings of well-being.
But it does so through a somewhat convoluted pathway, right?
It blocks the receptor that everyone thinks is involved in neuroplasticity.
And in doing so, it actually creates neuroplasticity.
Now even though I just described all of that to you over the last 10 minutes or so, keep in mind that what I just described to you as a process that actually occurs in the brain takes many, many days.
It involves cells changing gene expression, making new proteins, new receptors.
Anytime we say neuroplasticity, even when you read about so-called short-term neuroplasticity, it is happening over the course of at least many, many hours and more likely many days or even weeks.
So the process I just described of how ketamine creates neuroplasticity through blockade of NMDA receptors is very likely to be the process that explains the longer-term changes in mood and affect that are associated with ketamine therapy for the treatment of depression.
Now it is possible that ketamine blocking the NMDA receptor is also responsible for some of the immediate effects of ketamine that people experience when they take the drug.
The dissociation in some cases euphoria and that sort of dream-like state that it can put people into.
That is possible, but it's very clear that the NMDA receptor blockade is critical for the neuroplastic changes that are going to occur over the days and weeks following ketamine treatment.
And if you think back to our earlier discussion when we were talking about the two time a week over three week type regimen of taking ketamine or some variant on that, now it might start to make sense as to why, yes, there is immediate and short-term benefit of taking ketamine for depression in the clinically appropriate setting.
Of course, I'm not talking about recreational use right now, but that also there's some durability of those effects that even after the three weeks of taking ketamine twice per week, people often will experience weeks or months of relief from depression when they're not doing the weekly ketamine therapy sessions.
So that longer-term relief that I'm referring to as durability of the treatment is very likely to be the consequence of actual neural circuit rewiring.
Now there's an additional and very important facet to this whole discussion about neuroplasticity in response to ketamine treatment for depression.
If you recall the burst firing that induces that plasticity, I told you it induces plasticity, but I didn't tell you how.

Now you already could imagine some of the mechanisms that could be insertion of those new glutamate receptors, those amper receptors that we talked about.
However, even for that to happen, a bunch of other things have to happen first.
But one of the key ones to understand is the thing I mentioned at the beginning of today's episode, BDNF, which stands for Brain Derived Neutrophic Factor.
Brain Derived Neutrophic Factor is an incredible molecule.
I should mention that it's one of many growth factors in the brain and it has its own set of receptors.
This is something called the TrackB receptor, TRKB, TrackB receptor.
When BDNF binds to TrackB receptors on neurons, it does a lot of things.
It sets off a whole cascade of things, including the insertion of new glutamate receptors so that those neurons become extra sensitive to any input they get.
So that's one form of change that BDNF can create.
BDNF can also alter the overall shape of neurons.
It can cause neurons to grow new branches so that it can receive new inputs from other neurons.
Anytime BDNF is discussed in popular books or the popular press, people will talk about it as quote unquote, fertilizer for neurons.
I don't really like that term because it really undervalues the total number of things that BDNF can do.
BDNF actually can act as its own kind of neurotransmitter.
It can actually stimulate other neurons and it does a bunch of other things.
For sake of this discussion about ketamine, understand that that burst firing of neurons, that very high frequency firing of neurons, can invoke the release of BDNF in ways that make those circuits very plastic very quickly.
In addition to that, there's some evidence that ketamine itself may be able to cause release of BDNF directly without having to go through all of the mechanisms that I overwhelmed you with a few minutes ago.
Or hopefully didn't overwhelm you with, but that I taught to you a few minutes ago.
Now what's especially exciting about BDNF in the context of ketamine therapy for depression is that it appears based on both preclinical and clinical studies that BDNF isn't just one of the ways in which ketamine can invoke neuroplasticity and these improvements in mood.
It may actually be required.
It may be the central process to all of that.
Now it can still be downstream of all that NMDA receptor stuff that we talked about before, but there are several lines of evidence that suggest that ketamine induced release of BDNF is one of the core mechanisms by which ketamine can relieve depression.
Now there are several lines of evidence to support what I just said about BDNF in the context of ketamine.
First of all, in mice that lack BDNF, they have no BDNF.
They can't make BDNF because they don't have the gene for BDNF.
We call those BDNF knockout mice.

In those mice, if you give them ketamine and you put them into that learned helplessness task that we talked about a bit earlier, where you put them into water and see how long they swim, normally ketamine would allow a mouse to swim longer, to fight for its life longer.
Well, it no longer does that in a BDNF knockout mouse.
And the only thing that's different about that mouse as far as we know is the lack of BDNF and there are ways to make sure that it's lack of BDNF in the specific neurons that are relevant to everything we're talking about, not just that their limbs don't work as well, et cetera.
In other words, all the appropriate control experiments have been done.
That's preclinical data because it comes from animal models.
In addition to that, depressed people who have a mutant form of BDNF.
So these humans are not knockouts for BDNF.
They can make BDNF, but the BDNF doesn't function normally.
In those people, they have a very reduced response to ketamine treatment for depression, suggesting that BDNF action is at least one of the critical functions that allows ketamine to relieve depression.
And as I mentioned earlier, ketamine can actually invoke the release of BDNF and get this, there's some evidence that ketamine itself can bind to the track B receptor.
That is, it can bind to the BDNF receptor, it can mimic BDNF.
So this is an entirely different way of thinking about ketamine than we normally hear about.
In other words, we hear a lot about ketamine and ketamine therapy.
We also hear fortunately about some of the problems of ketamine abuse and we will talk about some of those concerns a little bit later.
And we hear about BDNF, this so-called brain fertilizer, but rarely if ever do we hear that ketamine itself can mimic the effects of BDNF in the brain.
But researchers and clinicians are definitely paying attention to this.
And it's starting to raise what I consider a very exciting model of how ketamine could provide relief for depression, which is that it's acting as a growth factor in the brain, or at least it's mimicking the action of growth factors, allowing the specific neural circuits that control things like mood, outlook on the future, self-reflection, etc., allowing those circuits to change in ways that provide significant relief for major depression.
And in doing so, and this is a very important point, it appears that ketamine is relieving depression in ways that are entirely different from any other kind of treatment.
Now in an earlier episode about psilocybin and its potential role for the treatment of depression, I went into a lot of depth about how psilocybin can induce neuroplasticity to provide relief for major depression in certain individuals under certain conditions.
I do want to highlight that because indeed it's another case where neuroplasticity is involved.
But in that situation, as some of you may remember, or if you don't, don't worry, I'll tell you right now, it was a pretty straightforward model.
Psilocybin looks a lot like serotonin chemically, except that psilocybin binds a particular receptor when that receptor is bound, it allows these brain-wide changes, those brain-wide changes seem to change one's reflection on oneself, so-called ego dissolution, changes in mood

that are stable over time, etc., etc., it was all pretty straightforward.
With ketamine, it's clear there are multiple mechanisms involved.
And perhaps most importantly, with ketamine, it's that immediate relief that occurs day of or close to day of treatment, and in the days afterwards, and it's that long-term relief that very likely is the consequence of NMDA receptor suppression, burst activity in neurons within these mood-related circuits, BDNF being released and changing neural circuits, strengthening
them in order to give elevated mood as a consequence of that bursting activity, and ketamine mimicking
BDNF.
In other words, ketamine acting more or less like a growth factor in the brain in order to make sure that whatever changes occur in those neural circuits to elevate mood are durable, that they really are reinforced and last over time.
I'd like to just take a brief break and thank one of our sponsors, which is Element.
Element is an electrolyte drink that has everything you need and nothing you don't.
That means plenty of salt, sodium, magnesium, and potassium, the so-called electrolytes, and no sugar.
Now, salt, magnesium, and potassium are critical to the function of all the cells in your body, in particular to the function of your nerve cells, also called neurons.
We now know that even slight reductions in electrolyte concentrations or dehydration of the body can lead to deficits in cognitive and physical performance.
Element contains a science-backed electrolyte ratio of 1,000 milligrams, that's one gram, of sodium, 200 milligrams of potassium, and 60 milligrams of magnesium.
I typically drink Element first thing in the morning when I wake up in order to hydrate my body and make sure I have enough electrolytes.
While I do any kind of physical training and after physical training as well, especially if I've been sweating a lot, and certainly I drink Element in my water when I'm in the sauna and after going in the sauna because that causes quite a lot of sweating.
If you'd like to try Element, you can go to DrinkElement, that's lmnt.com slash Huberman, to claim a free Element sample pack with your purchase.
Again, that's DrinkElement, lmnt.com slash Huberman.
Usually I've discussed two major mechanisms for how ketamine can induce neuroplasticity, leading to improvements in mood and affect that gives relief for depression.
Those two mechanisms are linked, or at the very least are happening in parallel, they're happening at the same time in the brain.
Just to make matters more interesting, there's an incredible twist into this whole thing of how ketamine works.
When I say how ketamine works, I'm not just talking about how ketamine provides relief for depression.
I'm also talking about why people use ketamine for recreational purposes, and it is the following.
Yes, ketamine has all these impacts on excitatory neurons, inhibitory neurons, BDNF, etc., etc.
But ketamine can also bind receptors in the opioid pathway.
What is the opioid pathway?

Don't worry, here I'm not going to hit you with a lot of details, but we've all heard of the opioid crisis by now, or at least most of you have.
The opioid crisis refers specifically to people taking exogenous opioids, taking opioids, so taking pills that activate particular receptors in the brain that lead to analgesia in some cases, so pain relief that lead to changes in mood.
There's a lot to be said about the opioid crisis.
It's called a crisis for a reason.
Many, many people are addicted to those compounds.
That's a discussion for another time.
Keep in mind that the receptors those drugs bind to are opioid receptors, and those receptors that you and I all have, by the way, do not exist in order to bind drugs that are made by pharmaceutical companies.
They exist in our brain and body to bind to the so-called endogenous, naturally made opioids that we all make.
Those receptors have different names.
The mu-opioid receptor, the kappa-opioid receptor, etc.
They tend to have the names of Greek letters to differentiate them.
Now, ketamine can bind to various opioid receptors.
When opioid receptors are bound, we know that creates certain effects, things like pain relief, things like changes in psychic states, dissociation, for example.
If enough of them are bound, you can get euphoric states.
Under certain conditions of high dose binding of ketamine to those opioid receptors, you can start getting into planes of anesthesia where people lose consciousness and actually have no response to pain whatsoever.
If you recall the clinical studies we talked about earlier, where ketamine was used to relieve depression, well, the dosage used in that study, as you recall, was half a milligram per kilogram of body weight.
That is the dosage that will induce these dissociative, mild euphoria, those sorts of states of mind, but where people are still conscious.
When you start getting to dosages of ketamine that are in the range of one to two milligrams per kilogram of body weight, now you're talking about anesthetic doses.
When that happens, you're going to get full parking, full saturation of all the potential receptors that ketamine can bind to, those NMDA receptors.
It's going to block those.
It's also going to bind to the so-called mu-opioid receptors and maybe this other type as well for those of you that want to know, euphysianados, also the kappa-type opioid receptors.
What we've got here is a drug, ketamine, that is hitting two different systems, the glutamate-related system, and the endogenous opioid system.
And researchers and clinicians have logically started to ask whether or not some or all of the effects of ketamine are due to the opioid system, and they want to know which effects those are.
Now this is where things start to get really interesting, both in the context of clinical treatment of depression and recreational use.

First of all, when people take ketamine, again, it enters the bloodstream and it goes into the brain, but it is metabolized to something called HNK, which is hydroxynor ketamine. Now I don't expect you to know what hydroxynor ketamine is, and I don't expect you to care about it until I tell you what I'm about to tell you, which is that hydroxynor ketamine has an incredible specificity for the mu-opioid receptor and maybe that kappa-opioid receptor as well.

In other words, when we talk about ketamine, that's the drug people take, but when it goes into the body, it's converted into yet another drug, and that other drug, hydroxynor ketamine, is selectively activating the opioid system.

So this led researchers to ask it a very important question, which is, when a human being takes ketamine in order to treat their depression and they get some relief from depression, is that the consequence of neuroplastic changes in all those NMDA glutamate-BDNF-related circuits that we talked about before, or is it the consequence of something happening in the opioid system?

You can't ignore the fact that ketamine has this property of binding to these opioid receptors because they have such a powerful effect on our thinking, on our mood, on our state of consciousness.

It's entirely reasonable that the opioid system could be a major player, if not the major player, in this whole depression relief thing and maybe even in the creation of dissociative symptomology when people take ketamine recreationally.

So what researchers slash clinicians did is they undertook a series of experiments where they gave people ketamine for the relief of depression, but they also blocked the opioid receptor system, and they did that using a drug called naltrexone.

So what I'm about to describe to you is a study done by my colleagues at Stanford School of Medicine, namely Dr. Nolan Williams and Alan Shatzberg and colleagues entitled, Attenuation of Antidepressant and Anti-Suicidal Effects of Ketamine by Opioid Receptor Antagonism.

And as a consequence of me reading you that title a moment ago, you now already have the conclusion of the study.

What they observed is that when people were given ketamine, they got relief from depression. That wasn't surprising.

Again, many studies had shown that before since the early 2000s.

If however, individuals were given naltrexone to block the opioid receptor pathway and they were given ketamine, well, then the antidepressant effects of ketamine were no longer observed.

Now that suggests that it is the opioid receptor system that's responsible for the antidepressant effects of ketamine.

And perhaps this HNK, this hydroxynor ketamine, which is the metabolite of ketamine, is the way in which ketamine normally relieves depression.

Now a lot of people took note of these studies because after all, there are probably dozens if not hundreds of studies looking at the effects of ketamine on all that NMDA receptor stuff and indeed neuroplasticity and mood related circuits can't be discounted as one way in which ketamine provides relief from depression.

But what was very interesting is that in people given ketamine and naltrexone, those people still experienced the immediate effects of ketamine, the mild euphoria, the dissociation,

the feelings that one would normally expect when people were under the effects of ketamine, but what they didn't get were the longer term changes in mood that we would call relief from depression.
Now of course the goal of modern psychiatry is to treat depression, not to block the effects of these drugs that are capable of treating depression.
Now what the study does, and by the way, there are several studies like it that support these general set of findings that part of the critical role of ketamine in providing relief from depression is to activate the opioid system.
But what this study does is it really points to the fact that when we say ketamine treatment or we talk about somebody taking ketamine recreationally for that matter, we have to pay attention to what's happening while they are under the influence of the drug.
We also have to pay attention to what's happening in the days and weeks after they're under the influence of the drug and perhaps most importantly, this calls to mind a really important idea which is that whether or not you're talking about ketamine induced relief from depression or psilocybin induced relief for depression or MDMA induced relief for PTSD, a topic that I covered on a previous episode of this podcast, we have to step back and look at the idea that the effects of the drug that people experience, whatever those may be because obviously it's going to depend on what particular drug they took, those immediate effects may not actually be related to the long term clinical benefit of those particular drugs.
Now I realize that many people might not like that idea and frankly, I don't actually think that's the way that it works.
I don't think it's going to be an either or situation.
However, because drugs like ketamine, psilocybin, MDMA have such profound effects on people's psychic states when they are under the influence of them and because at least in the proper clinical setting and use, they do seem to provide impressive relief from a lot of these psychiatric challenges like depression and PTSD.
People naturally correlate those two things.
They couple those two things.
In fact, they collapse those two things and presume that their experience of what they saw, what they heard, how they felt while they were under the influence of the drug was actually the stimulus that created the relief from their clinical condition like depression.
But what these data on combined treatment with ketamine and naltrexone to block the mu opioid receptor really show us is that that may not actually be the way that it works.
It may be that the effects of a drug like ketamine that one experiences while interesting, perhaps even profound, perhaps great insight comes to one when they do that therapy in the proper context.
It is not clear at all that it is that experience and the effects of those drugs in those immediate minutes and hours.
That's actually what's causing the relief from depression.
Now, again, I don't think it's an either or I like to view the whole situation more or less as a sort of wave front that the experience that one has subjectively while

they are under the influence of a drug like ketamine or psilocybin or MDMA sets off a series and in fact, multiple series is that a word multiple types of processes in the brain, some of which rely on things like NMDA receptor, BDNF, et cetera, type neuroplasticity, others which rely on the opioid receptor pathway, and that each of these have different time courses such that some provide immediate relief in the days and hours after treatment, some in the weeks after treatment and some more durable long lasting changes that can occur over months or maybe even years.

And a really important thing to underscore in the context of all this is that throughout today's discussion, we've been talking about drugs and receptors and relief from depression. But what we're really talking about here are people who get relief from depression and almost with certainty when they get relief from depression, they are also starting to do other things.

They are going back to work, they are engaging in relationships again, they are viewing themselves differently again.

Hopefully they're getting morning sunlight and exercising and eating well and doing all the sorts of things that we would call anti-depressive behaviors.

And it is impossible to separate the positive behavioral consequences of a drug treatment for depression from the drug itself in a way that lets us say, okay, ketamine relieve depression and then as a consequence, people went and did a bunch of behaviors that were healthy for them or stopped engaging in behaviors that were unhealthy for them.

So we can think of behaviors as pro-depressive or anti-depressive.

In fact, we know that one particular behavior that is viewing blue light in the middle of the night between the hours of say 11 p.m. and 4 a.m. is known to invoke a pro-depressive circuit.

It involves a structure called the habanula.

I've talked about this on previous podcasts.

It tends to lower dopamine and increase cortisol and the day is following that exposure to sunlight, et cetera, et cetera.

So there are pro-depressive behaviors and there are anti-depressive behaviors.

We know that viewing morning sunlight, getting regular and sufficient amounts of quality sleep, proper nutrition, proper social engagement, there is now a plethora of quality research pointing to the fact that those are true anti-depressive behaviors.

So we can never separate out the effects of a drug from the effects of a drug that feed back on and combine with the effects of the drug that one is hoping for, in this case, depression relief.

Okay.

So I've been bookending this conversation about ketamine at two very divergent levels, meaning we've been talking about high level stuff, relief from depressive symptoms.

We haven't been going into a lot of detail about that, but that's pretty high level.

We're talking about thought changes, behavioral changes that we're calling anti-depressive.

Changes in mood and affect that are positive, positive anticipation of the future, et cetera, et cetera.

And then we've also been talking a lot at this other end, which is very reductionist

down at the cellular and molecular level, we're talking about receptors and binding of receptors and neuroplasticity and track B and all that stuff.
We've completely neglected, meaning I've completely neglected until now, what bridges those two levels of understanding and what bridges those two levels of understanding are the neural circuits that actually change when one takes ketamine.
Whether or not those changes occur quickly, whether or not they take a longer period of time, whether or not they involve an MDA receptors or the opioid receptor systems or both.
We know that certain neural circuits change when people take ketamine in these patterns of dosage and frequency of about half a milligram per kilogram.
And again, that's the injected form twice per week over three weeks.
And then they get some durable resistance to depression.
Fortunately, we can talk about those neural circuits without having to bring about a lot more nomenclature, a lot of new language.
And I say fortunately, because I realized today you've been hit with a lot of new terms.
Now I've already mentioned one of the key brain structures and that's the habanula.
A few moments ago, I talked about the habanula in the context of people who get too much bright to light exposure in the middle of the night.
That activates the habanula.
It's a sort of a disappointment circuit.
We can call it that because we know that it leads to pro depressive symptoms in animal models and very likely in humans as well.
And it does so we know by reducing dopamine and increasing cortisol.
There's evidence that when people undergo ketamine therapy, connections between the habanula, what we can broadly just talk about as a structure involved in generating a feeling of disappointment, the connections between the habanula and the reward circuitry of the brain, which I've talked about several times before on this podcast.
But for those of you that aren't familiar with it, this is the so-called mesolimbic reward pathway as areas like the ventral tegmental area, the nucleus accumbens.
Don't worry at all about those names.
Just know that this is a brain area that is chocoblock full of neurons that release dopamine, which is a molecule that tends to increase mood, increase motivation.
In many ways, we can think about it at least for sake of this discussion as antidepressive.
So what we've got is a structure, the habanula that normally provides inhibitory and now you know what that means.
Every input to this reward pathway that releases dopamine.
And when people take ketamine, that inhibition is lessened such that the reward pathway is more available for engagement through daily life activities.
Now I say available for engagement through daily life activities for a very specific purpose, which is that all of the changes in neural circuits that we're talking about, that can come about from taking a drug, well, those changes don't actually do a whole lot unless those circuits are reinforced by particular behaviors.
So this relates back to what I said just a few minutes ago about pro depressive and antidepressive behaviors.

Somebody can take ketamine and potentially get relief from depression, but if they continue to engage in pro depressive behaviors, they are not going to get much if any relief from depression.
Conversely, if somebody takes ketamine and they are reducing the amount of output from this disappointment circuit, this habanula to the reward circuitry of the brain, and they do engage in behaviors such as seeking out work that stimulates them, seeking out social engagement, taking good care of their body, their mental health, their physical health, et cetera.
Well, those circuits are not designed to respond to ketamine.
They are designed to respond to particular patterns of thinking and behavior.
So again, we can't forget that when we hear that a drug causes plasticity in a given neural circuit, what it's doing is it's biasing the balance or the probability that those neural circuits will be engaged by certain activities, but one still has to engage in those activities.
Now fortunately, when people tend to have elevations in mood, they tend to move around more when they tend to move around more.
They tend to engage in more things when they tend to engage in more things.
If they have a positive outlook on life, presumably they are engaging in adaptive things, things like social relationships, job-related, school-related, goal-related behavior.
So it's important to understand that a discussion of neural circuit changes in response to ketamine is really a discussion of neural circuit changes in response to ketamine that shift one's overall system toward having yet further neural circuit changes in response to daily activities and thereby bolstering health, or in this case, mental health.
Now it's also important to understand that rarely, if ever, does a drug provide relief for some sort of clinical challenge in just a one-track kind of way.
The way to think about this is that most mental processes and certainly things like depression are a two-way road.
You have pro-depressive behaviors in circuits and you have antidepressive behaviors in circuits.
And so perhaps it won't be surprising to you that there's evidence that ketamine treatment can reduce the output from the habanula to the reward pathway, this disappointment to reward pathway, weakening that, making the reward pathway more available for engagement through thoughts and behaviors that are antidepressive.
And in addition to that, it can further bolster the neuroplasticity within the reward pathway itself, in particular with connections with the frontal cortex.
And for those of you that aren't familiar with the frontal cortex, your frontal cortex does a lot of things, but one of the things that your frontal cortex is absolutely critical for is for establishing context-dependent strategy, meaning for allowing you to say, okay, in a given circumstance, what should I do to get the results I want?
In another circumstance, what should I do to get the results I want?
It's not strategizing of the manipulative type, although I suppose it could be.
It's strategizing of how do I get what I need from this social connection?
How do I get what I need from my goals and exercise?
How do I get what I need from my goals in terms of work or school, et cetera?
Your frontal cortex is that part of your cortex that's always churning ideas.

It's always wondering, am I doing well, am I not doing well, and is adjusting your behavior accordingly.
So it's now established that ketamine can improve connectivity.
That is, it can strengthen the connections between areas of the brain that are associated with context-dependent strategy building and these reward pathways.
In other words, it makes people more sensitive to whether or not they are getting the results they want from their efforts and to how to adjust their efforts so that they do get the results they want from those efforts.
And there's other evidence that NMDA receptor blockade is not the way that ketamine provides relief from depression.
Namely, there's a drug called memantine.
It's used actually to treat Alzheimer's and it too is an NMDA receptor blocker and it has no antidepressant effects.
Now as you recall, ketamine is a dissociative anesthetic and one of its primary effects is to create this feeling of dissociation.
For those of you that aren't familiar with what dissociation is, dissociation is where people feel separate from their body.
They can still think, but it's as if they are observing themselves.
In fact, in anticipation for this episode, I consulted with several different colleagues in the Department of Psychiatry at Stanford School of Medicine and one of them described the effects of ketamine as described by a patient of theirs who had taken ketamine for the treatment of depression.
And that patient described it as observing themselves, thinking, observing themselves, doing things, even though they were lying completely still.
And perhaps most importantly, describing themselves as being above their body and actually looking down on themselves from the third person perspective.
Now that I realize is a foreign experience to most people, but of course there are people who experienced dissociation even while not on ketamine.
And as many of you know, dissociation is actually one of the primary symptoms of PTSD and trauma.
So this raises a sort of conundrum.
Why is it that a particular state of mind that's associated with PTSD and trauma and in some cases depression itself, which is induced by a drug like ketamine, can provide relief from depression.
And that all goes back to the neuroplastic changes that we talked about earlier and more likely the changes in the mu opioid receptor system that we talked about earlier.
But nonetheless, the dissociative effects of ketamine are so profound for people that take them that I thought I'd spend a minute or two explaining what likely causes that dissociative third personing of self effect.
And in so far as we know, it has to do with an uncoupling of certain brain circuits in particular neocortical brain circuits.
The neocortex is the part of the brain, the lumpy outside part of the brain that's associated with action planning.
It does a lot of things really.

It's involved in sensory perception.
It's involved in speech generation, many, many things.
But the neocortex has connections to other regions which are called subcortical regions.
And it seems that when people take ketamine or fancyclidine PCP, there's an uncoupling of those networks, a quieting of those networks that starts to create a different dominant rhythm in the brain.
Some of you may be familiar with rhythms in the brain, so-called alpha rhythms or alpha patterns of activity.
That's just dominant patterns of activity associated with particular brain states.
So for instance, alpha brain waves are associated with an alert but calm, relaxed state of mind where thoughts are sort of free flowing.
It's a little bit dream-like, but it isn't really like a dream where anything can happen.
It has a structure to it.
When people take ketamine, the alpha pattern of activity is completely abolished, at least for the duration of time that they're under the influence of the drug, which typically is about an hour to two hours or so.
And a different pattern of brain activity, which is called the theta pattern of brain activity, starts to really emerge.
It's as if it gets unveiled.
And that theta pattern of activity is the one that's associated with a dream-like state.
It's the one that resides more or less at that liminal border between wakefulness and sleep.
If you've ever been falling asleep and you were thinking something like you were running and you kicked your leg, it's very likely that you were in theta pattern of activity in your brain at that moment, just prior to when you woke up.
Whereas when you're more alert, you see patterns of activity that are higher frequency, things like alpha, beta rhythms, and so forth.
So ketamine produces particular patterns of brain activity and this sense of dissociation when it's taken at subanesthetic doses.
If you recall the clinical studies we talked about earlier, they injected half a milligram per kilogram of body weight in order to provide depression relief for those patients.
When people take ketamine, they will take it by different routes of delivery.
And now here we have to expand our conversation to include both the clinical context, research studies, and recreational use.
Now, I do that because typically when people take ketamine in a study, in a clinical study, they will get an intravenous into the vein or an intramuscular into the muscle injection of half a milligram per kilogram of body weight ketamine.
However, when people are taking ketamine recreationally or when they are accessing ketamine legally
by prescription and taking it at home, which is becoming a more common practice, they will often take it orally in pill form or they will take it sublingually by putting it under the tongue or in their cheek and then that so-called troche dissolves and the ketamine goes into their system.

Now, an important thing to understand is that when people take ketamine orally, only 25% of the active form of ketamine makes it into the bloodstream.
And when they take it sublingually, typically only about 35% of the total amount of ketamine they take is converted into metabolically active ketamine that acts on the neurons in their brain.
So when you hear about the dosages used in studies, they are going to generally involve injections of ketamine and far lower doses of ketamine than when you hear about people taking ketamine orally or sublingually.
So for instance, I weigh 220 pounds, that's 100 kilograms.
So if I were to be in one of these studies, which I have not been, but if I were, I would be given 50 milligrams of ketamine by way of injection.
However, if I were going to try to achieve the same amount of active ketamine in my bloodstream and brain as I would through injection, I would need to ingest three times as much ketamine by way of pill and perhaps a little bit more by way of sublingual ketamine if I wanted to get the same effects.
So if I were to take 50 milligrams by way of injection in a study and I went to a different study and they said, okay, we want to recreate that effect.
We're going to give you a pill.
Typically they're going to give me 150 milligrams of ketamine in a pill form or 200 milligrams of ketamine in the Troche sublingual form.
Now it's really important to understand this dose dependence according to delivery business because I realized that nowadays, especially a lot of people are taking ketamine through legal sources.
So they're accessing it legally, but they're taking it outside the clinic and more typically they're taking it not by way of injection, meaning they're taking higher dose ketamine and they're taking it sublingually or orally.
So it's very important to understand this dose dependence according to mode of delivery business.
Now in anticipation of this episode, I put out a request for questions about ketamine on Twitter and I got many, many questions, some excellent ones therein, but one of the more common questions was what is a k-hole in scientific terms?
A k-hole is what's used to describe the subjective experience of when somebody takes ketamine typically recreationally and they end up in basically a pseudo anesthetized state.
What that means is that they took a dosage that for them put them beyond the boundary of the subanesthetic dose and has them transitioning into the anesthesia level dose of ketamine.
Now I mentioned everything I did about dosages before because it's very important to know that different people, even if they are of equivalent body weight, are going to respond to ketamine differently depending on how quickly and how thoroughly they metabolize ketamine.
So in the clinical context, injections of ketamine into the vein or into the muscle are done at this half a milligram per kilogram dose and they have clinicians there, they have researchers there who are paying attention to whether or not the person is in a dissociative state if they're still conscious and to see whether or not the person is going into full blown anesthesia.

Now that's one of the values of doing ketamine in the context of a legal clinical setting.
However, I'd be remiss if I didn't acknowledge that a lot of people are getting ketamine legally, but then taking it at home, hopefully not alone, hopefully there's someone there to monitor them or their in session with their physician over zoom.
That's actually happening more and more these days through telehealth, but that itself also has certain risks, right?
Because if the person needs something and they don't have someone there immediately in the room to take care of it, that could be a very problematic situation.
And of course there are situations where people are taking ketamine recreationally, regardless of how they're acquiring it, they're taking it and they are guessing how they're going to respond to it based on some crude understanding of dosages.
But when people talk about a k-hole, what they're talking about is taking ketamine at a dose that for them takes them beyond the mild or perhaps even an extreme dissociation and starts placing them into full blown anesthesia.
And that itself actually can be dangerous.
Going into anesthesia like planes of consciousness while not always deadly can be deadly.
And it certainly can be and has been deadly when people start to combine it with other drugs, in particular drugs like barbiturates or alcohol.
So I want to be very clear that the dosage range is that you hear about when hearing about ketamine are extremely broad and so is the variability to any one given dose.
And so too is the response to a given dose in a given person, depending on the route of delivery.
You need to be very careful about the ability of ketamine to take you into deep, deep planes of unconsciousness and in some cases death.
And of course, as with any sedative, one needs to be extremely cautious about doing anything like driving or even walking in traffic or walking anywhere in some cases, if one is under the influence of ketamine.
Additionally, for those of you that are seizure prone, either due to epilepsy or prior head injury or maybe you're seizure prone and you don't know it, ketamine can induce seizures and it should be completely obvious to you now why that's the case.
And then blocks and MDA receptors on inhibitory neurons and quiets their activity, which of course can lead to runaway excitation in the brain if you are seizure prone.
When I put out the request for questions about ketamine on social media, I also got a lot of questions about the different forms of ketamine.
When I say different forms that included questions about whether or not intranasal was better than oral was better than sublingual, et cetera, et cetera.
To be fair, with one exception, the different modes of delivery probably relate more to dosage that actually gets metabolized than to anything else.
What I mean by that is most people don't know how to equate the clinical dose of half a milligram per kilogram of body weight into a dosage to take orally or sublingually or in some cases, by the way, people will take it rectally.
And the reason people take ketamine rectally is that rectal administration bypasses the liver and indeed ketamine can be hard on the liver to metabolize.

It can dramatically increase liver enzymes.
So oftentimes people that are taking ketamine frequently and don't want to create damage to the liver, they will opt for rectal administration.
Now I realize that unless it's somehow related to your profession, anytime somebody says intrarectally, it raises a few eyebrows and people, you know, kind of lean back a little bit and I get it.
In a future episode of the podcast, I promise to distinguish between the different modes of drug metabolism depending on whether or not people take something orally, sublingually by injection or rectally.
Another common question I got when I solicited for questions about ketamine on social media was about the R versus S versus RS forms of ketamine.
And I must tell you that sent me down a deep, deep rabbit hole of research in which I discovered very contradictory evidence.
For instance, I could find papers, I did find papers that said that the R form of ketamine had a much greater affinity for the NMDA receptor than did the S form of ketamine.
I also found reviews that said the exact opposite.
Okay.
And there I was sitting with the two reviews in front of one another wondering if there was something wrong with my visual system until I called a colleague, Dr. Nolan Williams who's a triple board certified neurologist psychiatrist at Stanford School of Medicine whose laboratory specializes in the use of ketamine for studies of treating depression and for treating depression in the clinical population.
So I asked him, what's the deal here?
I'm getting very contradictory evidence.
And he spelled it all out for me.
It appears based on the clinical data in humans and on binding studies that the S form of ketamine is more potent.
That is it can more robustly bind to the NMDA receptor.
And in addition to that, the S form of ketamine tends to produce less dissociation at a given dosage than does the combined SR form of ketamine or pure R ketamine.
He also added and sent me a study that I'll link in the show note captions that there was recently a clinical trial of R ketamine.
So pure R ketamine alone and it failed to relieve depressive symptoms.
So I said, great.
Thank you so much.
This is now all made very clear to me that S ketamine is the preferred form.
It produces less dissociation and it provides better depression relief.
And then he said, no, actually it's a little more complicated than that.
It appears the situation is the following, the combined SR form of ketamine seems to be the most potent for relieving depressive symptoms.
The S form of ketamine is second best in terms of providing relief from depressive symptoms and is the one that's most commonly prescribed nowadays by nasal spray by oral dosing by sublingual dosing.

And it's what is typically given by way of injection in clinical studies where they do injections and it appears that the R form of ketamine is the least potent and effective in treating depression.
Now I realized that by putting this out into the larger world and assuming that there are experts in ketamine out there, either by way of use or by clinical study of their own, that I will get a lot of comments back saying, no, actually the R form was more effective for me than the S form versus the SR form, et cetera.
Just to reiterate from the clinical trials that have been done, we know that the combined SR form is more potent and effective than the pure S form, which is still more effective than the pure R form.
So that's what we know now based on the clinical studies.
But of course, I acknowledge that anytime a drug is out there as a clinical tool and it's being used recreationally, that people are going to explore and they're going to experiment and they're going to find what works best for them.
So I certainly invite feedback about what has worked best for you, hopefully in the clinical context.
So whether or not people have used ketamine prescription from their doctor, whether or not they participated in a clinical study or whether or not they're doing it recreationally, I imagine that I will hear about those experiences and I will take note of them.
Another commonly asked question I received was, what about micro dosing of ketamine?
There's a lot of interest in micro dosing nowadays.
People are micro dosing psilocybin, people are micro dosing, all sorts of things, hoping to get some of the same effects as the macro doses, but by using dosages of compounds that are below what would induce, say in the case of psilocybin hallucinations or in the case of ketamine below what would induce the kind of dissociation and euphoric effects that one would have to lie down for a few hours and disengage for the rest of the day.
I consulted with my clinician colleagues about this and they told me that at present, meaning as of yesterday, there is zero published clinical evidence that they are aware of and by way of extension that I am aware of in which micro dosing ketamine has been effective for the treatment of depression.
All of the positive effects on depression that I've talked about during this episode are gleaned from studies where people used this half milligram per kilogram dosage of ketamine or it's equivalent by way of some other route of administration, not injected but oral or sublingual.
So are there any benefits to micro dosing ketamine?
As far as the scientific and clinical literature that's published as of today is concerned, the answer is no.
Okay, so today we covered a lot of information, we talked about what ketamine is.
Remember ketamine and PCP, angel dust, very similar compounds both block the NMDA receptor.
We also talked about what sorts of subjective effects that produces dissociation and mild euphoria and third personing of self, that's the dissociation when taken at low dosages and when taken at higher dosages, it can induce full blown anesthesia and put people into subconscious states and there's actually a potential even for seizure and death if the

dosage is high enough for that person.
Again I want to emphasize that people's dosage sensitivity varies tremendously, route of delivery will impact that and on and on.
We also talked about how the NMDA receptor itself and the activation of this incredible molecule BDNF brain-derived neurotrophic factor seem to be important for at least some of the antidepressant effects of ketamine, both in the days and weeks following ketamine administration.
And in addition to that I described how ketamine impacts the opioid receptor system and how we simply cannot overlook the involvement of the opioid receptor system in producing the antidepressant effects of ketamine.
And we also talked about the brain circuits and the brain waves associated with dissociative states and the depression relief that seems to arrive for many people who take ketamine.
And I tried to highlight some of the unique features of ketamine, first of all that it does seem to provide depression relief where other approaches have not but that the depression relief tends to be pretty short lived unless it's applied in this multi times per week over multiple weeks kind of fashion to produce what I call durable changes which almost certainly involve changes in neuroplasticity that is rewiring of brain circuits.
And another key point that I highlighted is that we always have to remember that when thinking about how chemicals like ketamine or any other substance for that matter can modify brain circuits in order to change them and provide relief from depression or some other psychiatric challenge that always, always, always there is a requirement for engaging in antidepressive behaviors as a way to further reinforce whatever positive changes have come about through the drug treatment.
As a friend and colleague of mine who's expert in this area once so aptly said better living through chemistry still requires better living.
Thank you for joining me for today's discussion about ketamine.
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Thank you once again for joining me for today's discussion.
And last but certainly not least, thank you for your interest in science.