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ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

Moving Beyond Sleep: The Broader Connection Between the Orexin System and Psychiatric Disorders

Opening:

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Chapter 1

Dr. Mignot:

So welcome here. Today, we are going to talk about orexins and the potential of this new neurotransmitter in hypersomnia.

So I'm Dr. Mignot—M-I-G-N-O-T. I work at Stanford University, where I direct the Center for Narcolepsy. I'm trained as a psychiatrist, but I moved to sleep medicine about more than 30 years ago, and I've been mostly practicing sleep medicine, even though you never really leave psychiatry.

And I'm joined by Dr. Roger McIntyre, who is from Toronto, and he's a professor of psychiatry and both a psychopharmacologist interested in depression, bipolar, as well as metabolism. And we are going to discuss the orexin system, and I hope you will be excited about what's coming. So here are both of us.

So the goal of this particular exercise will be for you to try to understand what this orexin is about and how this molecule that's secreted by about 70,000 cells in the hypothalamus kind of controls both arousal as well as REM sleep and how it could contribute to sleep and psychiatric disorders. And you're going to try to also learn a little bit more about how we assess hypersomnia in sleep clinics and how hypersomnia and sleep disturbances could be, of course, crucial to psychiatric disorder. And we'll talk a tiny bit about clinical trials with the orexin agonists. I mean, you already know probably the orexin antagonists, but we'll mostly talk about orexin agonists.

Chapter 2

Dr. Mignot:

So, first, we'll talk a little bit about the neurobiology of sleep and wake and what I guess is important to know when you start to talk about the orexin system in general.

What we like to say as sleep researchers is that sleep is really regulated by 2 main processes, and often we call that the 2-process model. One of them is the circadian clock, which I'm sure you all understand what it is. It's just your internal clock that tells you what time

of day it is. People have the tendency of mixing up diurnal and circadian. It's actually completely different. Diurnal is what happens during the night and day, so you sleep during the night and you're awake during the day, whereas circadian is what you feel independently of sleeping.

So to really dissociate circadian from what is really sleep related, usually what we do is we keep people awake for more than 48 hours, and then we look at things that continue to fluctuate independently of your sleep. And you all know that, in fact, you're awake mostly in the evening thanks to your circadian clock. That's why if you travel to Europe, at the time of your local evening, that it's impossible to sleep. And at the opposite, it's the early morning hours that your circadian clock makes you the most tired, and that's usually into your early morning that you feel that.

So we know quite a bit about the circadian clock. In fact, there's been a Nobel Prize about it, and it was first discovered in fly. And it's quite remarkable that the same processes are actually conserved in humans and mammals. And basically, it works in every cell of your body has a circadian clock, and it's a series of genes that are called CLOCK and BMAL and PER and CRY, and they basically do a loop in and out of the nucleus, and they get phosphorylated outside of the nucleus, and then they re-inhibit themselves, and this whole process takes 24 hours.

So in fact, in each of your cells you have this 24-hour rhythm that is kind of keeping track of the time. And of course, depending of what cells you are in the organism, it may make them more effective at a certain time of the day. For example, the liver, cholesterol, metabolism occurs more during the night, but you release more, for example, your cortisol in the early morning. But there is this—every cell has this little cycle, and the output may be at different times of that circle.

And so that's what the circadian clock does. But all these cells in the body, they are all synchronized by a master clock, which is in the hypothalamus, in the suprachiasmatic nucleus, where the suprachiasmatic nucleus is a little nuclei that receives direct input from the optic nerves, so this way light synchronizes your rhythms. That's why when you move, you can reset your circadian rhythm when you travel to another country.

So the main things that regulate your circadian rhythm are light exposure and a tiny bit of melatonin, but mostly light exposure. But also some other things like food actually is also helpful to move your rhythm around. So that's one of the first things that regulate your sleep.

The second mechanisms that regulates your sleep is how much sleep that you have. You all know that if you don't sleep one night, you are kind of okay. If you don't sleep 2 nights, you become quite grumpy. If you don't sleep 3 nights, you're ready to kill me. I can tell you it's really very difficult to stay awake for more than 2 nights.

And so really that sleep debt, the more you are awake, the more you develop this need for sleep. So those are 2 things. The sleep debt and the circadian clock interact together in a very, very unique way to keep you awake all day and to keep you asleep all night, and that's something that people don't really appreciate. It's not like the circadian clock makes you awake all day. Not at all. The circadian clock makes you awake in the evening. And the way it works, in the morning you wake up, you just slept, so you have zero sleep debt. You are rested because you just slept, so you don't need an extra boost. So in fact, you are awake in the morning because you are rested.

And then, as the day progress, you are accumulating a sleep debt, so you should be more and more tired as the day progress. But that's not what we experience, and the reason we don't experience being more tired is that the circadian clock compensates for the fact that you have been awake for a while and keeps you awake in face of your sleep debt.

So in the evening you're awake because your circadian clock tells you to stay awake, in spite of the fact that you already are sleep deprived for an entire day, and then it crashes. And then the first part of sleep, you sleep because you have your sleep debt that you catch up, so you have a lot of slow-wave sleep. You catch up on your sleep debt. And the second part of the night your temperature drops further, and then you get a lot of REM sleep, and you get some extra sleep, and so you're already rested.

A second important thing regarding sleep, of course, is there are some sleep-promoting pathways and some wake-promoting pathways. Since today we are mostly talking about wakefulness, some of the major wake-promoting pathways are also monoamines. Not exactly like serotonin, it's not really wake-promoting. However, it's active during wake. Like the firing of all these cells is much higher during wake. But, for example, histamine—you all know that when you take an antihistamine, you fall asleep, so histamine is actually a wake

promoter, and it's more active during the day. Norepinephrine as well. Dopamine, it's actually more active during the day, but it's a little bit complicated because it has a bursting pattern. But all these monoamines generally promote wakefulness, and they are more active during wakefulness and drop their activity during sleep and are completely silent during REM sleep.

So the cholinergic system is another wake-promoting neurotransmitter. There is one system that starts in the brainstem that's very important for REM sleep, and another in the basal forebrain that's important for cognition and wakefulness, and it's also more active during wake, but it's actually silent during non-REM sleep. It's very active during REM sleep, but not during non-REM sleep.

And then finally, so this new kid in the block, I would say, has been discovered recently: this orexin system. It was discovered because it's a cause of narcolepsy, as we will hear, and it's basically an excitatory neurotransmitter. It's a group of cells that's in the hypothalamus. There is about 70,000 of them in the human brain, and then they project heavily in all the monoaminergic cells. So you can look at them as some kind of super excitatory system that excites other systems that themselves help you to stay awake, so it really excites monoaminergic system and makes them even more active and reinforce your wakefulness.

And we know that one of the functions of the orexin system is to be activated when you try to fight sleepiness. So during the day, it kind of goes up to help you to fight your sleep debt that's mounting, and the circadian clock also lift it in the evening. So it goes up during the day, as you will see, and it goes down during the night, which is logical because you are more awake during the day, and you sleep during the night. And it does that by also stimulating all this monoaminergic system.

There is 2 receptors, the receptor 1 and the receptor 2, but right now, as you will hear, most of the drugs that are being developed are acting only on the receptor 2, and it's a main receptor. So, for example, in fish they only have receptor 2, so it's a homologous receptor, and then it was duplicated in mammals, and there is receptor 1 and receptor 2, and they are in different parts of the brain. They are both the same function, but the receptor 2 is more important. It's the oldest, and it has the most effect.

There is also a sleep-promoting area in the ventral preoptic area, which is very well known to be active when you are having non-REM sleep, which I just want to mention. And then otherwise all the wake-promoting pathways are really kind of inhibited during sleep. And as you see, this VLPO, this preoptic area because that's GABAergic, inhibits the orexin system and all the monoaminergic system and cholinergic systems of the pons, and that helps you to fall asleep.

And for orexin, there is one thing that's very particular is not only it regulates wakefulness through all this monoaminergic system, but it also regulates the muscle tone. As you probably know, during REM sleep, you're completely paralyzed, and one of the reasons it does that is that the orexin system, which is silent during REM sleep, it does stimulate some neurons in the brainstem that helps to maintain muscle tone. And then when you don't have orexin, you go more into REM sleep, and it also makes you paralyzed.

So these are the main sleep-promoting drugs that we have. Like, you probably know this about the basic pharmacology. A lot of the drugs that are used today are GABAergic drugs, and they mostly work on GABA-A, and they are modulators of GABA-A. The very old drugs were GABA-A modulators that were extremely strong, and they had the problem of producing respiratory depression, like the barbiturates, and that's one of the reasons they are not used anymore.

Then the benzodiazepine came about, and you probably all know that the benzodiazepine modulates the GABAergic system the same way, allosterically the GABA-A chloride channel. However, it doesn't inhibit it in such a strong way, it doesn't promote the effect of GABA sufficiently strongly that you don't have respiratory depression, and that's one of the reasons that benzodiazepine became really great drugs, because you never die when you take them, which I guess is one advantage.

And then the Z-drugs are slightly safer drugs, but they still work the same way on the benzodiazepine-acting site. It's just they don't have the structure of a benzodiazepine, and they probably act on a slightly different subunit composition of the GABAergic channels because there's a lot of different subunits in this GABA-A chloride channel.

Another type of anti-sleep-promoting drug is blocking histamine. And if you take antihistamine drugs, you all know that antihistamines that are used for allergy can put you to sleep, and a lot of the drugs that we use in psychiatry have antihistaminergic effect, and that's one of the ways that these drugs are very sedative, but actually a lot of patients even take OTC antihistamine to try to help sleep, and many antipsychotic and tricyclics have antihistaminergic properties.

Then there are 5HT2 blockers, which also can produce sleep. In fact, some people try to develop them as sleeping pills, but somehow they make you sleep, but people didn't really like them that much. But they do help to sleep, and I think some compounds can be combination of 5HT2 and H1, and I think that also probably promote even more sleep induction.

Since there is GABA-B agonist. You probably rarely use them, but we'll talk about 1 particular drug, which is called GHB, gamma-hydroxybutyric acid, or oxybate. Gamma-hydroxybutyric acid has a very bad reputation because it has been used as a date-rape drug, so it's very regulated. Nonetheless, as you will learn, it's a very active drug in narcolepsy. It's a very, very effective hypnotic. It makes you sleep very deeply with a lot of slow-wave sleep, and often people feel more rested, and it has definitely a very positive effect in a lot of patients with either hypersomnia or narcolepsy.

Then, there is gabapentin, and finally the orexin antagonist, which, as you know, will create narcolepsy for 1 night in some ways, and they are quite effective as well, and they are definitely safer than benzodiazepine. And I think in the US, they have struggled a little bit of replacing benzodiazepines as sleeping pills. I think one of the reasons is that they're expensive, and unfortunately, Ambien is just like \$1, so it's very difficult to compete. That's a problem of our healthcare system. If something is cheap, nobody wants to develop a drug that competes with cheap drugs. But for example, in Europe, I think it's being used more and more because they realize that they are much safer than the benzodiazepines, so they are definitely good drugs. They make you sleep.

And, however, today we are talking mostly of wakefulness. Indeed, I think a lot of people, you have seen all these drug about sleep. Yes, there are a lot of people who have insomnia, and there have been a lot of hypnotic and sleep-inducing drugs that have been developed, but there are also about 4% of the population complain of being tired all day long, and we don't have much to offer, to be honest.

Traditionally, what we have offered are really amphetamines, which are dopamine-releasing agents, and sometimes they release also a little bit of norepinephrine, and that's a classic amphetamine. It just basically replaces dopamine and pushes the dopamine to be released, and methylphenidate is a little bit different because it's more dopamine reuptake blocker, but it also releases dopamine.

Then there is pure dopamine reuptake blocker. Modafinil, for example, which a lot of you use, Provigil; it's a mild dopamine reuptake inhibitor. And the good thing about modafinil is that it's very long half-life, and it's very bad drug. I mean, I'm joking, it's a bad pharmaceutical compound, and that's why it's a good drug, because it's a very low potency, and it's very insoluble, and as a consequence it's not addictive. Like the problem with amphetamine and methylphenidate is when you take them a short half-life, you take the immediate release, it can really produce a kick and then a withdrawal, and then that does stimulate people of taking more. And I think in general, when we have trouble with amphetamines, it's most often with a short-acting one. So personally, I avoid using the short-acting only. I like to use long-acting because they're much less addictive.

But the dopamine reuptake blockers, such as modafinil and solriamfetol, which is also a norephrinergic reuptake inhibitor, they produce wakefulness, and they have a relatively long duration of action. So, I think they are safer than amphetamines. Even so, amphetamine and methylphenidate, long acting, the long-acting formulation, I think, are quite also good drugs, and they are not too addictive. Then, of course, there caffeine.

And then finally we will talk a little bit about this, these new drugs, which are orexin agonist, which, as you have seen from the neurobiology, are really uniquely positioned to stimulate all the monoaminergic system and even directly the cortex, so they have really a new type of stimulants, which we believe, as you will see, are very important for narcolepsy, but also will have a lot of application, potentially for the 4% of the population that is tired.

I'm sure that a lot of you already use stimulants in the context, of course, of ADHD, but also even in depression.

Okay, now we are going to go to Dr. McIntyre, that's going to tell you a little bit about the sleepy patient.

Chapter 3

Dr. McIntyre:

Okay. Thank you, Emmanuel. By the way, just a little fun fact—Emmanuel, let's get a little round of applause. I mean, that was to get us started. Come on. Thanks, Emmanuel.

A little fun fact about Emmanuel, and that is that he was the first one to observe that GLP-1s could improve obstructive sleep apnea. So that was a prescient observation, Emmanuel. Who would have known where that would have gone?

Good evening. We're going to have a conversation about the near term, the intermediate term. And what I'm going to do over the next 15-20 minutes or so is I'm going to speak to the orexin signaling system, but more specifically what I'm going to speak to is an aspiration. And the aspiration is that orexin signaling modulation appears to have promise transdiagnostically for discovery and development.

So today we're going to talk about sleep-wake. We're going to talk about mostly narcolepsy in the second part of the presentation from Emmanuel. And you all know that in many countries, including the United States, we already have orexin signaling antagonists FDA-approved, other countries approved, in the treatment of insomnia.

When I came across this system about 15 years ago or so, not too long after they were discovered—these are relatively new systems—I came at it from a different perspective. We are looking at metabolism and inflammation, and at that time I had no idea, as we dug deep into the anatomy of the pancreas, that we're going to find orexin receptors, only to find out these receptors have GLP-1-like effects. And we've been interested in GLP-1 signaling in the CNS as a target, and many of you would know that we've now moved into phase 3, that is repurposing GLP-1/GIP as a treatment for psychiatric disorders.

Given what we now know preclinically and clinically about the incretin system—come back to incretin—we've got good reasons to believe that the first chapter of opportunity is insomnia and narcolepsy, but there's some other opportunities we're going to get into, characterized by conditions of disturbance in reward and motivation like major depressive disorder, substance use disorder, also disorders of arousal, anxiety, and fear, including trauma-related conditions, as well as disorders of cognition, including but not limited to ADHD.

Let's start, if we can. So I know it's the end of the day. I see most of you are wearing your name tags, probably the first time you wore it all day, I know the game. So you guys are hopefully got a little room left for some education this late in the afternoon, this late in the evening.

And what we're looking at here is a little bit death by acronyms. All these acronyms represent different parts of the brain, and I wanted to start off with orexin efferent projections. Much of the research with the orexin system has been asymmetrically evaluating the efferent projections from the orexin-containing neurons in the lateral hypothalamus. Three separate nuclei there.

And I'm going to start, if I can, at this circle. Unfortunately, this slide is a little bit too small for those in the back, but it doesn't really matter. What that circle represents is phenomenologic opportunities: mood, anxiety, substance use, trauma. Let's begin, if we can, with projections, and I'll get into this on a step-by-step basis here.

The orexin system has projections, as you saw already hinted at, that being the wake-promoting parts of the brain, but I want to actually start thinking about other psychiatric disorders, other potential targets.

So if we look at the far left, we have orexin efferent projections to the paraventricular nucleus of the hypothalamus. So this is the apex of the counterregulatory response. This is where CRH is produced. So already we stop for a moment and we say that's interesting that one of the most well-characterized efferent projections is the synaptic connection linking the orexin system to the apex, that being the paraventricular nucleus. We also see the amygdala, well known for its role in fear, and the bed nucleus of the stria terminalis. The bed nucleus of the stria terminalis is critical for anticipatory anxiety.

So we have this anatomy linking orexin to areas of brain relevant to stress response, to fear, to fear consolidation, but also to anticipatory anxiety.

To keep going, what we also have is projections of the orexin system to the paraventricular thalamus, relevant to motivation. We have the striatum, including the ventral tegmental area and the nucleus accumbens, but also cognition and endocrine centers, that being the hippocampus, as well as the prefrontal cortex.

So these data, along with separate lines of research looking at some of the preclinical behavioral models, provided the impetus for

many sponsors to begin studies evaluating orexin antagonism, specifically orexin 2, but also orexin 1, but more orexin 2, as a potential treatment for major depressive disorder.

Seltorexant would be the lead candidate. It is a selective OX2 antagonist, and it is now in late phase 3 as an adjunctive treatment in adults with major depressive disorder. And there is a campaign that would suggest, although I don't think it's definitive just yet, that orexin 2 antagonism holds greater promise in major depressive disorder than does orexin 1, but I think that's still to be fully ascertained.

Now, to keep going, we know that the orexin system is playing a role in arousal. Emmanuel spoke to that. It also plays a critical role in autonomic function and autonomic dysfunction, and that's probably critical to the stress response. So alongside its effect on the hypothalamus, specifically the paraventricular nucleus, it also regulates sympathetic and parasympathetic flow.

This was a study done in menopausal women experiencing insomnia. This treatment—this orexin antagonist, suvorexant—was helpful in these women, but what caught my eye was not so much that, that is, the effect on sleep parameters, which is important, but what caught my eye was the effect it had on vasomotor symptoms during the night. And this is aligned with multiple lines of research that this particular signaling system plays on autonomic nervous system activity known to be highly impaired in depression, anxiety, and stress-related conditions.

So what we have here is a number of columns. I'll just try to maybe summarize it if I can. There's been a number of different models around this. So we know that the orexin signaling system is playing a role in the stress response. We know that from projections to stress response centers, various nodes and circuits and networks. We also have in depression, anxiety, we have in trauma models a number of different reports. This is some data from our lab and a couple other labs showing an increase in orexin activation in select brain regions in conditions of trauma or conditions of chronic uncontrollable stress.

And I think everyone is aware that in PTSD, complex PTSD, about 60% to 70% of people have insomnia. We know that a cardinal feature is dysregulated arousal. Of course, that's transdiagnostic.

And what's also, I think, interesting is the projections of the orexin outputs from the lateral hypothalamus are also into key areas that we are targeting with some innovative therapeutics, including some of the empathogens.

For those maybe a little less familiar, orexins play a critical role in modulating cognition. We're going to say more about this in a moment. They play a role in memory consolidation, memory acquisition, and also a role in fear extinction.

And what's so interesting is that the projections of the orexin system is right across the board, right across not just the conventional and traditional structures that we have considered in PTSD, such as the bed nucleus, such as the amygdala, but also in other node regions like the hippocampus, which I think has really now caught on. And we have a number of studies that have now started in phase 2 evaluating orexin signaling modulation for PTSD.

Now, Continued Place Preferenced is a model of drug and alcohol or substance misuse. Generally speaking—again, sorry, the slide doesn't project so well—all this is to say is that we have, in fact, now evidence to suggest that orexin signaling modulation may affect reward salience. And reward salience can be evaluated using Conditioned Place Preference. This is, in fact, some mirroring models looking, in this case, at suvorexant affecting reward, and specifically reward-related memory. And this is, in fact, in keeping with the physiology of orexins. Yes, being responsible for arousal, but also being responsible for reward. In fact, they are referred to as reward motivators in the CNS.

So the notion being that if, in fact, this is the case, can we consider orexin signaling possibly in the treatment of alcohol, substance, or tobacco use?

What's also very interesting to me, as we followed very closely this area for quite some time—again, I'll show some metabolic data in just a moment—is the effect that it has on protein markers of Alzheimer's disease. Orexin does decrease hyperphosphorylated tau. It increases clearance of amyloid. And for the longest time, Emmanuel, we thought this was just simply through facilitating glymphatic clearance. We do know that other interventions that increase glymphatic clearance don't have the same effect on amyloid and tau, and there's been some really nice new data to suggest that actually the orexin signaling system is actually decreasing the microglial conversion from M2 to M1, that is creating a pro-inflammatory microglia. That's one theory.

But the other aspect, which is interesting, is new data suggesting that the orexin system is increasing microglial phagocytosis of hyperphosphorylated tau, as well as amyloid protein in the brain.

You're going to hear a bit more about this in a moment from Emmanuel. This is one of the orexin OX2 modulators. This is oreporexton. This was a secondary analysis conducted in adults with narcolepsy, and this was looking at memory, executive function, and processing speed, showing benefit across these measures. Again, this was secondary. To what extent is this direct and independent? To what extent is this pseudospecific? That's to be determined. But this is very much aligned with also additional study with alixorexton showing benefit on the BC Cognitive Inventory, also in people with narcolepsy.

So, and again, aligns with the preclinical behavioral models and also the pharmacology of the orexin system being potentially beneficial here. So it raises the question whether or not this system could be potentially helpful in the treatment of ADHD.

So I start off with major depressive disorder and substance use disorder, disorders of altered reward function, altered motivation function. We move into cognition conditions, and of course, we have the trauma-related. But this, I think, is an incredible opportunity.

This was a study done with daridorexant. This was an orexin signaling done in ADHD, and this is one of the very few studies, in fact, to look at cognitive functions in this group, showing benefit in a variety of cognitive measures on the far right in persons. But again, it's hard to know to what extent or to which this is actually a direct or independent effect.

This is actually just a cue for me to mention to you that there is, in fact, now an appetite to explore the therapeutic potential of the orexin agonists as potential treatments for ADHD, given the cognition data seen earlier, along with some of the preliminary work done with ADHD.

Now, just to sort of round the horn here a little bit, just to bring everybody to a similar kind of perspective on this, orexin is produced in the lateral hypothalamus. In the lateral hypothalamus, we have the suprachiasmatic nucleus, we have the arcuate nucleus, and it's probably not as well known that much of peripheral metabolism is regulated centrally in the hypothalamus, and to some extent in the hippocampus.

The orexin neurons are exquisitely sensitive to glucose. And in fact, when glucose levels begin to drop, they fire. When you have hyperglycemia, it inhibits the orexin neurons, so they are regulating centrally peripheral glucose homeostasis.

Secondly, they also regulate the autonomic nervous system, as I said earlier, as well as the hypothalamic-pituitary-adrenal axis. In other words, the counterregulatory system.

So from a central perspective, they are regulating glucose homeostasis, but they also have an effect peripherally. And the effect peripherally is, is that they have an effect on fat patterning, more specifically the conversion of white adipose tissue to brown adipose tissue. And brown adipose tissue is more thermoenergetically active; it's more energy efficient.

They also have an effect where they can increase insulin sensitivity; that is, they affect tyrosine hydroxylation right in the insulin receptor on the surface. But the part that got us initially interested in this is the incretin effect that the orexin system have. OX1 and OX2 are located in the beta cell of the pancreas. They do facilitate glucose-stimulated insulin secretion and do suppress glucagon.

And what's interesting is that they have a kind of a bimodal effect. So in situations of hypoglycemia, that will trigger activity of the orexin system to increase glucose availability. In situations of hyperglycemia, they decrease glucose availability through these mechanisms that I'm mentioning.

The other aspect about this as well is that there's now some interesting data that in situations of hyperglycemia, they do directly reduce gluconeogenesis. This was a study that was done with lemborexant in rodent models. These are diabetic mice. And in these diabetic mice given lemborexant, lemborexant compared to vehicle was able to decrease glucose. Insulin held stable throughout, suggesting a direct effect on the insulin receptor with these particular treatments.

So just to sort of maybe put this into a kind of a maybe a framework, what does this mean for repurposing or considering the study of the

orexin signaling modulators in psychiatry? Well, there is in fact one suggestion. One suggestion could be is that we have now several assets that are in phase 2 or phase 3 in depression and bipolar depression that are targeting metabolic systems. And drugs that target metabolic systems have a fairly consistent effect on hedonic tone. So as we think about drug development in psychiatry, it's also about targeting specific domains like anhedonia. And so it could be put forward as a hypothesis that, in addition to having an effect on alleviating depressive symptoms, perhaps through their effects on metabolism, there could be a reason to believe that they could have an effect on hedonic tone. And that is, of course, a hypothesis, but one that's supported by many lines of research.

So to summarize, we're here to talk about orexins, the relatively new kids on the block—1998 makes them fairly newbies. We're talking about narcolepsy in just a moment. We know they're fit for purpose in insomnia, but there is an appetite to repurpose these agents or to develop these treatments, either agonism or antagonism, frankly, across conditions of reward, conditions of dysregulated stress response like anxiety, PTSD, as well as cognitive function. So it's a very, very exciting time for the orexin system.

Folks, thank you very much. Thank you. Emmanuel is going to come back. And Emmanuel, we're going to hear about hypersomnia and narcolepsy.

Chapter 4

Dr. Mignot:

Thank you, Roger.

Yes, there is no doubt that the neurobiology of orexin is quite complex and exciting. It's definitely regulating mostly wakefulness, but also a lot of other aspects, in particular metabolism, as we heard. So I want to point out that certainly we have a lot to discover right now. Most of the clinical trials have only been done in patients with narcolepsy type 1, which are people who don't have orexin. So obviously it works because they don't have orexin. You give them an orexin agonist, that's a no-brainer, I would say. It's a bit like giving insulin to someone that's diabetic.

But the real question is what's going to happen when you start to give this drug in people with normal orexin, like you and me, or people who are tired for other reasons. And we know it works, but exactly what position it's going to take in our practice, whether or not it will have metabolic effects that are a little unique, whether it will have some antidepressant effect. We see very dramatic changes in patients with narcolepsy type 1, but of course they don't have orexin, so it's very logical that we will see a lot of dramatic effect. What will happen in people with normal orexin, we're just starting to discover.

So I think I'm going to use this to just tell you a little bit what we see in a sleep clinic in terms of patients who are tired and will have a sleep problem. So we call these general patients with hypersomnia or hypersomnolence. In fact, we should differentiate hypersomnia and hypersomnolence.

In fact, narcolepsy, which is an archetype of disorder with a lack of orexin, is a disorder where you have hypersomnolence. So people with narcolepsy, they wake up in the morning, they are okay, but then after 1 hour or 2 hours, they feel they need to take a nap again, and then they have this terrible sleep attack. They can't really keep their eyes open, and then they will sleep, and then they feel better after a little nap. Whoop, back to normal. And then it doesn't last. A few hours later, they will again kind of have that. And then this sleep attack, they feel better, but also they go into dreaming very quickly, so often they have these very vivid dreams during the night. Sometimes they are so real that the patients themselves don't know if it happened or not. I mean, I have countless patients that told me in the morning they wake up and they have dreamt that someone entered the house and broke the window and stole things, and they wake up, and they are really in disbelief that this has not happened because it was so strong that they really believe that this has happened. So they have these very, very intense dreams, and sometimes, again, it's almost bordering into a hallucination. When they fall asleep, sometimes they just dream so quickly that they see things, or when they are very tired, they may kind of barely close their eyes and start to have a dream. So it can be quite scary.

And also, as you probably all know, during dreaming you are paralyzed. You're completely paralyzed. All of us are, but of course we don't remember. Most of the case, we don't remember our dreams, unlike narcoleptics, which are often very strong memories of their dream, as I mentioned. But some people—actually it's quite frequent, even in psychiatric patients. It's more frequent with depression. People wake up from dreams, and they are still paralyzed. So during dreaming, you are paralyzed because otherwise you will be acting out your dreams, which would be very bad. And in fact, it happens in a different disorder called REM behavior disorder, which is a

precursor of Parkinson's disease.

But in patients with narcolepsy, often people would wake up, and they can't move, and it's very scary because they are still paralyzed from REM sleep, and then suddenly they may start to dream again.

I must reassure you, some of you must have experienced that. I've experienced it twice. People with depression often actually experience quite a bit of sleep paralysis, but it's usually rather benign.

But then there is this very odd symptom for narcolepsy type 1, which is maybe the most important symptom, because if it's present, then you know that the cause is a lack of orexin. It's basically cataplexy. It's very odd. It's when patients get emotionally excited, when they're happy about something, and generally it's really laughing or joking. It's not like laughing itself. It has to be funny. It's so particular. It's something that has to be funny to your own self, and often it occurs with a family member, someone you really like, like something that's personal. But a good joke, a patient with narcolepsy cannot give the punchline of a joke that they find funny. Suddenly they [choking sound]—they collapse. They don't hurt themselves, but they can't talk, and then they last a few seconds, and then they come back up.

It can be quite subtle. I mean, it's not like patients will do that in front of you. In fact, it's generally inhibited by stress, so it more often happens with family members, but it's absolutely typical. If someone tells you they have this kind of symptom when they are laughing or joking, or in certain emotions, you are sure that they have narcolepsy; this muscle weakness, especially in the face, but also sometimes in the leg, and all these symptoms of a rapid REM, et cetera.

So interestingly, people with narcolepsy also gain a lot of weight. So there is definitely some metabolic aspect when they start narcolepsy, especially when narcolepsy is very abrupt. In children, sometimes they gain 10 pounds or 20, or they can gain 40 pounds, actually. They can really become huge, and it can be very, very bad for them. So the faster the onset, the more weight gain they have.

And the cause of this disorder is the lack of orexin. We know that the cells that produce orexin are dead, and they are killed by an autoimmune process that's triggered by the flu, so that's what we have learned later.

So really, I like to say that narcolepsy type 1 is a little bit like type 1 diabetes, except that instead of killing your insulin-producing cells, you kill your orexin-producing cells in the brain.

Now, there are a lot of other patients that have a little bit of a flavor like narcolepsy. So this will be hypersomnolence. So these people, they just feel very tired during the day, they have to nap. But when they nap, they feel better. I call them narcolepsy-like, and they don't have cataplexy, and those we call narcolepsy type 2. And sometimes they have REM sleep symptoms, and that's one type of sleepiness. And I have to say those kind of sleepiness, they look almost like sleep-deprived patients because if they take a nap, they feel better, and that's a big differential diagnosis. You have to make sure that these patients are not sleep deprived because if you sleep only 5 hours, you're going to behave like this. You will [groggy sound], and then you take a little nap, and you feel better. So you have to eliminate sleep deprivation, but otherwise we call this narcolepsy-like, and they can react quite well to things like modafinil and a small dose of stimulant or harder treatment that we use for narcolepsy.

For narcolepsy type 1, there is a genetic marker which is present in 25% of the population, but present in 99% of the population with narcolepsy because it's an autoimmune disease, so it's very strongly associated with HLA. So it's useful to eliminate narcolepsy because if it's negative, you know this patient doesn't have this lack of orexin, but if it's positive, it doesn't mean much because 25% of you will have it. So it's useful to eliminate narcolepsy.

And sometimes we do a lumbar puncture because we can measure the orexin in the CSF, and that's the best test. Then if the orexin level is 0, we know that the patient has narcolepsy type 1.

But another way to confirm narcolepsy that we do more often, because people don't like lumbar punctures, is a sleep test where we basically put the patient in a sleep lab. We measure how fast people fall asleep and go into REM sleep. Sometimes patients with narcolepsy go straight into REM, which I told you is very abnormal. In a normal person, you first have non-REM sleep. You remember, you catch up on your sleep debt first. The REM sleep normally occurs only in the second part of the night, driven by your circadian clock. But here is a patient with narcolepsy, sometimes they go straight into REM. That's very, very unusual. Only maybe 1% of the population has that. But patients with narcolepsy, frequently they go straight into REM.

And otherwise, we give them naps during the day. It's called the multiple sleep latency test. And then patients, when they're tired, they go to sleep very quickly. If you're sleep deprived, for example, you would fall asleep very quickly in each of these naps, and the patient with narcolepsy, not only they will fall asleep very quickly, but they will also go into REM sleep, which is very unusual in normal people.

So that's a way we diagnose patients with orexin deficiency. First, you look at cataplexy. If they have cataplexy, you pretty much know that they have narcolepsy, and then you confirm it with a sleep test where you see that the patients go quickly into REM sleep. We also have other techniques now using machine learning where we can almost analyze the sleep at night and directly tell that they have narcolepsy type 1.

But again, there is also this milder form of narcolepsy, which is called type 2, or idiopathic hypersomnia, and those are actually 2 different presentations. There is a group of patients that are like narcoleptics, but they don't have cataplexy. So basically, there are these people who have this overwhelming sleep attack. "Oh my God, I can't stay awake." And then they sleep, but they feel better after a little nap. It's almost like they're sleep deprived, and they look more like narcoleptic, and that's one possibility.

Or there is also idiopathic hypersomnia, which is much more frequent in the context of psychiatry, where instead of having this nap where they feel that they feel better after a nap, they just feel tired all the time, and they have trouble waking up in the morning. That's called sleep inertia. It's completely different. It's not hypersomnolence; it's actually hypersomnia. They need a lot of sleep.

So you see a lot of these patients. They cannot wake up in the morning. Alarm clock, alarm clock, alarm clock. Then they drag themselves outside. They are like zombies. They take tons of coffee, and then they continue, and then they drag all day long. And then maybe in the middle of the day, if they try to nap, they sleep 2 hours, and they still feel tired. They have even more trouble waking up, and then it's almost like sleep is even worse. And then when they go to bed, they sleep for a long time. So this is a true hypersomnia. It's different from hypersomnolence, and it's more different from narcolepsy. We call this idiopathic hypersomnia, and I think that's what you see a lot more in the context of psychiatry.

Sometimes depression can manifest like that. Like people have trouble waking up in the morning, they just feel like in a fog all the time, and then when they sleep, they may feel a bit better, but usually not very much better, and then often they nap for long periods of time, and they have a true hypersomnia. So we call those idiopathic hypersomnia.

And I have to say that for idiopathic hypersomnia, it's sometimes a bit difficult to differentiate from depression. But in depression, in theory, people don't sleep as much.

Then there is a third presentation of sleepiness, which is called periodic hypersomnia, very particular. I think it's a form of bipolar disorder. It's a teen or an adult, and suddenly they're totally normal, and then suddenly they sleep for 20 hours a day for like 10 days without stopping, and when they're awake, they are weird. So it's like they are in a fog. Oh, they are really actually. Usually they go to an emergency room because they are confused. They just don't even know where they are. They answer like with monosyllable. Sometimes they are very almost like frontal, so they may eat like chips with honey, or they may undress themselves. That's why there's hypersexuality or disinhibition, but most of all they feel in a bubble, and they often don't even remember what happened during these 2 weeks. And then suddenly it's finished, and they're totally fine for like months, 2 months, 3 months, 6 months, and boom, it restarts again. It's completely unpredictable, and this happens for 10 years, and at the end it kind of burns out. It gets better around age 30, and usually they kind of grow it up, and it's very particular.

Chapter 5

Dr. Mignot:

Okay, so the way we diagnose narcolepsy, I think I mentioned that we really do an MSLT, this nap test, and then we try to prove that people are tired. And in this nap test, we measure the sleep latency, and if you are sleep deprived, definitely you fall asleep much faster than a few minutes. Like, you fall asleep in a few minutes. And then if you go into REM sleep, you have narcolepsy, narcolepsy type 1. And IH, you usually fall asleep, but you usually don't have REM sleep. But the most important is really this nonrestorative aspect of sleepiness.

And right now the way we treat narcolepsy or hypersomnia, we have drugs that we use that make people sleep at night. That's called

sodium oxybate. It makes people sleep very, very densely, and then they feel better. It also works in idiopathic hypersomnia. These people with sleep inertia, we give them this strong drug twice during the night, and then they feel better in the morning, and they are less tired.

Or we use like amphetamines or modafinil, like you do. And of course, in the future, when they lack orexin, we're going to use orexin agonists. And when they don't lack orexin, we're starting to explore orexin agonists. And they work, but you need higher doses.

And in fact, that's what you see here. When these orexin agonists were discovered, the first things that people said is it's going to be fantastic in narcolepsy because it's like insulin in type 1 diabetics. And indeed it's incredible. I mean, they take it, they are completely awake. They are cognitively much better. We have the feeling that all the drugs we were using before, they were really insufficient.

However, we have discovered that it also wakes people up in normal people. If you have orexin, you just need to give about 3 to 5 times higher doses, and it also wakes up people the same way as amphetamines do. And that's where we believe that there may be an opportunity for other people who are tired for other reasons.

Right now you use modafinil, I think, quite often when people are tired following residual sleepiness in depression. I mean, at the sleep clinic, we hope that we'll be able to use—right now we use amphetamines as well, or sodium oxybate, this strong sedative, which actually can work quite well, but you have to be careful because sometimes it induces anxiety.

And then we are very excited about the possibility of using orexin agonists.

Indeed, there are clinical trials that show you that these orexin agonists are incredibly effective in narcolepsy type 1. Like you have, for example, this test where you ask people to try to stay awake as long as they can, doing nothing. This is a torture for narcolepsy type 1. If they have nothing to do and you ask them to just—they cannot read; they cannot watch TV; they just sit and try to stay awake, I can tell you, a narcoleptic type 1 that doesn't have orexin falls asleep in 2 minutes. Impossible.

With this, all the treatments we had before—amphetamines, sodium oxybate, these drugs that make them sleep more at night—we could raise this to about 10 minutes. And that's the best, or 8 minutes trying to fight the sleepiness.

But normal people can still wait for 20 or 30 minutes doing nothing. And with the new drugs, these orexin agonists, they can stay awake for 20-30 minutes without any problem. So it completely normalizes them.

And we see also a complete reversal of all kinds of symptoms. For example, I have a lot of patients that started new hobbies. They restarted to do golf, or to dance, or to date, or whatever. I mean, their life before with the treatment was much more constrained, and we see a transformation of their personality with these drugs.

However, you have to realize they don't have orexin, so obviously it's kind of replacing an entire neurotransmitter in the brain. So it makes them more awake in an incredible way, and it also changes back their personality to something different.

The question is, will you see some of these effects in people with normal orexin? And I think we are starting to study this, but we don't have a lot of data. But there is some hope that indeed it does the same thing.

So as you have heard, these orexin 2 agonists have a very clear and strong efficacy on sleepiness, both subjective and objective. Now, what's exciting is that it looks like these compounds also have a positive effect on cognition.

So this is a slide, for example, where we see the effect of alixorexton on cognition, and based on the PGIS, and as you see, the patients are really increasing their general cognition and improving with the treatment over time.

The next question, of course, is what is this cognitive effect? Is it just because people are more awake, or is there an independent effect? This is very difficult to test, but there have been studies with TAK-861, oreporexton, which have tried to do a mediation analysis to see how much of the cognitive effects are mediated by the effect on sleepiness. Is that because they are more awake that they're more cognitively effective in life? And the cognition was measured with a PVT, which is a test of attention. And when you do this mediation analysis, you find that about 65% is secondary to the improvement in sleepiness in NT1. So that suggests that a large portion

of the cognitive effect is actually independent of sleepiness. There may be effect on sleepiness and effect on cognition that are independent.

What about the safety, tolerability of these drugs? We find that all these drugs have the same side effects, which are urinary urgency, people need to go to the bathroom more frequently; there is sometimes insomnia effect; some people have reported minor visual disturbances. But what's exciting, there is no effect on blood pressure and heart rate. These effects are generally transient. People get used to it.

There is also some question of what would be the long-term effects. Initially, when these patients take this orexin agonist, they're immediately extremely awake, and that works for about a week or a few days, and they sometimes even don't sleep the first night. And I don't think it's insomnia; it's just that they are so awake that it's really exciting for them, so they usually don't complain. And then after a few days it gets better, and then they start not to have this insomnia. And then sometimes they still have remaining a little bit of insomnia, but it goes largely away. And then after about a month it's stable, and it seems that it stays stable, the effect on all the symptoms of narcolepsy, for many months. And now we have about 2 years of follow-up for some of these drugs.

The next question with that is, what about narcolepsy type 2? Narcolepsy type 2 is not due to orexin deficiency, and you have heard that with the first drug, 925, TAK-925, which was never developed because it's an IV formulation, this drug is effective not only in narcolepsy type 1 at low dose, but at higher dose on narcolepsy type 2, idiopathic hypersomnia, as well as sleep deprivation, so subjects that have normal orexin.

So this has been explored with alixorexton in narcolepsy type 2, and what you see is that it's clearly also effective on the MWT. For example, these drugs have a dose-dependent effect on the sleep latency in the MWT, but you see that you need a higher dose than what has been used in NT1.

And finally, so alixorexton is still under study for idiopathic hypersomnia. So now that it has been shown that it's active in narcolepsy type 2, where we generally have normal orexin levels, it's being explored in Vibrance-3 in the treatment of idiopathic hypersomnia, which also has normal orexin level, and it's being enrolled in the US now. It's just starting, and of course, it's MWT and DSS, as for the narcolepsy type 2 study. But as you see here, they're using a slightly higher dose because they felt that potentially the dose that was used in NT2 maybe was slightly on the lower end.

So we are very excited to hear what's going to happen with these drugs, these orexin 2 agonists, in patients who have normal orexin levels, such as NT2 and IH, but it seems that they will be effective.

Dr. McIntyre:

Thanks, everyone, for being here. We stayed a little late. Thanks to the sponsor. Enjoy the rest of your time here at ASCP. Thank you.

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