Medicine Academic Enrichment Session

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13:54

Thank you everyone for joining, we're just going to give everyone a few seconds to come in from the waiting room. Thank you to everyone joining now just gonna give a couple more seconds. Everyone's got connected. So thank you all for coming to the session on bank holiday Monday. It's lovely to see so many of you have. Can I just remind you please make sure that you've only got your last name for the percentage love your surname in your to name, if that's okay. And yeah, I will hand over to your cell is going to be delivering our medicine session and thank you very much. All right, let me share screen. I'll find a button to share screen again. Thank you for joining is Haley satin bank on a Monday, and hopefully you can now see my screen, I'll just enable, so you can see the chat in case anything appears there. Can I get a thumbs up or something from someone that you can see me and my screen and can hear me. Yay. Okay, great. And right I'm, I'm Esther or Esther. I am originally from Latvia, and I did my undergrad, and you're up north in England, and then I'm now doing finishing my PhD actually at University of Cambridge, are working in this MLC importer of molecular biology, which is the ALMA biomedical big biomedical campus in Cambridge. So my background is more biology, it's not medicine but as you will see there's a lot of things, as you probably know already, there's a lot of things in biology, that are sort of intersection through biology and medicine so biomedical sciences and various, you know everything that we study how our body works, how our cell work. And then, you know, it could lead to better human health. So hopefully it's not too disappointing that it's not superduper exactly mentioned but hopefully you'll see the relevance during lecture. And, and yeah, obviously feel free to ask any questions, though, somebody is asking about recording but there's probably a better question for a leave, she can recording in progress. Okay, great.

19:50

I'm perfect.

19:54

But yeah feel free to ask any questions in the chat. I'll try to monitor that or raise your hand or say something, but whatever. During while I talk it's fine just whatever works for you. All right, so we're going to talk a bit about what are circadian rhythms which is the topic of this lecture and also the topic of what I work on for my PhD. And we're going to talk about the relevance to circadian rhythm sort of the body clock how it relates to human physiology, and how it relates with jet lag and shift work so when fly or somewhere where the time the external time is different, how does your time reacts to that. And some bit about molecular mechanisms so a bit more kind of molecular biology, and then a bit more Crona minutes so how can we use this knowledge of various process how various places in the body

are organized around the clock, how we can use that to maybe improve treatments or generally stay healthier. Right, so. Alright, so you will probably feel tired maybe feel tired now maybe you stayed up this weekend they stayed up all night, so why did why does it happen. Well, it's because, in your body there's also kind of a timing mechanism that helps you adapt to the cycles and night. And it's official mission is that it's lost approximately 24 hours. It's endogenous which means that it comes from within your body so it's not something that you just respond to light or something it's it comes from anybody and it's cycles or oscillations and behavior physiology, and it's exhibited by most organisms. Most for humans most obvious one is sleep wake cycle. We're going to start a bit with a few examples in plants actually but we're going to move on then to humans. So, actually the first known. Yeah. Sorry about that, rotating earth just to show good you know we've adapted to have this, these rhythms, because spirits rotate and that leads to cycles something like the first person to describe something that's so cyclical in the 21st Berea Dusty was understanding of classes who are the ship captain. Under Alexander the grade and he noticed that leaves move during the day, in a sort of daily pattern. And what he observed, then you can kind of see on this video here. Or maybe being observed by a houseplant but you need to do a time lapse video where you see that as the time the clock keeps ticking and the leaves open or closed. This is just a zoom up of what just happened with me again. Okay. So Gleaves open close based on that definition that I gave you previously, I know you have reactions button. Can you click a button, which will say, whether you think it has a circadian rhythm, or it's not circadian with nothing there's a button that says yes and the button that says no somewhere there. Yeah, yes, a few yeses. Anyone else some yeses, anyone thinks no. Okay, yes. Okay, well, you can also message me directly, actually, with the answer. One No, if the person says no. If you'd like to write in the chat, any why no mute yourself if you like. So it was actually a little trick question because if you remember I said, I was trying to explain what this endogenous means right, and that is comes from then on this video we come, and on the observations that under assessment. We can't really tell whether it's in comes from within the plant or not because it's, you see that the light is that you see the lighting in the room changes right so maybe the leaves. Oh yes so so I actually got just very perfect, I got a very wrecked answer in the chat as well, directly. I'm not going to say the names, just in case, because you missed me privately but if you like I can obviously means. So,

24:57
one of you said, it comes from within, however it may be due to changes in the environment. Yeah, so I said endogenous must come from within, but here we see light so maybe it's, it's just the plant is responding to light right it can turn its leaves to light. So how do we tell which ones which. Well, if anyone again if anyone has any ideas of how to test this this plant.

25:31
Oh yes could put it into darkness. Well done. Get rid of the stimulus Yes, same thing, control other factors, perfect, and make the environment constants. So, actually this was done then by this guy here, the MME he was an astronomer, but he did exactly what you're suggesting, so he put, he put the planter he put one plant into your cabinet, and he put another plant outside, and he had a tiny hole and let that covenant, so he can still observe the plant. And so he observed it during the day during the night and he noticed that even the plant that was in the cardboard still had asleep, open during the day and closed during night, even though he didn't see any lights and he kind of figured out was able to sense somehow like so there's must be something wrong with him. And then, as I promise. What we're

moving to humans. What happens if you do the same to humans actually in the, oh, oh, sorry I'm losing oh yeah that's just the same constant in the constant slide. There's also the plant will open and close it leaves just the same as in the constant park so it's kind of a complementary experiment to show that that happens regardless of that, if the environmental up constants are the same. So humans are getting rhythms, we can do the same as Marianne did with a, with a plan so we can be in the 70s they could do with human volunteers. So basically there was this so called bunker experiment with German scientists, it's not as scary as it sounds, we're all human volunteers, but they would signing up to live in a closed underground environment they had some, you know all the amenities of the time, and they had their various vital functions monitored to see if humans also you know we don't humans pack cycles on day, week, and sleep in our normal world. But would that continue in a bunker and you maybe you can read here the setup so they measured subjects body temperature. They measured activity patterns like weather, the old version of those Fitbit watches that Now many people have. And they collected some blood, urine tests to see various composition of urine and they lock them, and they, but I delivered food in a nice box. And they also delivered fresh food, other necessities such as a bottle of beer, clearly, very necessitated is just an excerpt from that paper. And what they saw. This is just a plotting data from one of the participants. So you see some variation in the ions in the urine so calcium and potassium. See the volume and the probably the most interesting bits to look here would be the body temperature and sleep wake cycles so the dark bit is when the person was asleep this the light bit is one person for the week. And then the vertical lines denote calendar days right so each day's each line is midnight on each day. So if you look at this graph, maybe again some, some observations from the chat. If you can write, what, what does it tell you specifically about the body temperature and the sleep wake cycle maybe under constant conditions body gets used to it over time. Yes, but to what exactly yes body temperature decreases during sleep, and increasing wakefulness. Yes, that's a good point so it also, like, I guess, for most, most people kind of noticed that especially if you had the temperature measured when you were ill, for example, but you know it's another very prominent key body rhythm in humans and it has a specific phase relationship with with sleep and wake cycles. Yeah, yeah. So, Elena, just kind of was saying to plants in a way that the cycles continue. What can we, and the body temperature also continues its, but it does become more regular with time. Yes, the impact change environment,

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Not so great during the eight and 10. Get off. Be No but, so if I'm mispronouncing your names by the way but this this is a really good point out in the chat that it seems quite constant but it gradually gets later and later and later, right. So thanks everyone for your ideas so we've discovered that there's a body temperature reading that is false during sleep right is when a person is awake. It persists during darkness just like blunt leaf movements persist in darkness as well so those are important points. But then over time as well. We can see that. At first this person you know this Steve just before maybe around midnight sleeps makes up again goes to sleep around midnight, but then they, eight and nine, and nine is already going to sleep later, later and later day 10 is already like it's probably, I don't know 5am 6pm And he just went to sleep. So that kind of tells us that the internal clock, you know it synchronizes with the environment but it's paired the period of internal clock could be slightly different, and then this person actually on average in most humans are slightly longer than 24 hours so if you sometimes feel that you want to stay awake and you want to have 25 hours in the day and not 24 That's is actually some biological truth to it because naturally people do tend to stay up and kind of have print five hour days and gradually drift away from the days on the ground and there are in this

bunker. And you probably know this phenomenon is that, you know, people are slightly different and it's called larks and owls right. Hopefully you can see this question, these, this question, I mean it's very simple. We're going to cover some more difficult, but later as well but for now, I would just want to test this, if we can do an online quiz and have a

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actually maybe not let's not bother with that. If you still see the disc questionnaire Can you post in the chat, whether you're which kind of had you know how many points you got so which bird do you come up as so larks the very early ones Robin's like many hours but you see that there's five questions and for each depending on what time your preferences you get different points you can just quickly add those up.

33:03
So just waiting for you to complete it and writing the perfect one Robin one in the middle. You can't read, sorry, sorry, it's a bit yeah, it's a bit small but there's, there's a P. Golden Orioles yet. The Robbins Robbins nightingales. All right, so we're getting a lot of a lot of nightingales some owls some Robin's a few golden Orioles, not really any logs, I don't think so. I'm gonna do the next slide. So this is actually quite common, I'm assuming a lot of us at work. If you're finishing your GCSE is if I understand correctly, and this is to usually most people are like Robin so this is just plotted in a different way so that this Robin or Lark or owl is scientifically known this prototype so which preference for which time do you have. And, normally people in this the time. Sorry I'm using like cost on that you can see, the times here are the midpoint of sleep so what. When is your, if you divide your sleep into what's, what's there, when do you usually sleep. That's how it's bloated and normally people are sort of around four or five which means they know they sleep for midnight trade more or less. But the interesting thing is it does change with age, Right. Which is not immediately obvious maybe that they, in the work, maybe you know from from the family experiences that young kids you know usually wake up early and go to sleep early, but as you get later as you get into your, you know before, between your pendant 20 People tend to have very later chronotype and actually peak in the, in how late they get, and then after the age of 20, it gradually gets again earlier and that actually the point here. Maybe some of you can guess, with points to women in that usual menopause, age, so this you will have one line from a woman, and which also you can see slightly effects are usually men are lighter than women, but after menopause, it changes slightly. But the interesting point here is to just change the age, and actually, it's especially in the US now this data, started influencing policy in terms of school start times, right, Because if teenagers naturally better and naturally wake up later. Then there's little point of going, making them go to school so early because normally in the US, I think in the UK as well as school starts. Kind of the same both for younger kids and older kids, but the older kids actually struggle more with waking up and it's not because they're so lazy, it's because it naturally because of hormonal changes their current chronotype also changes and in the US where they did trials where they started school times later with for high school kids, they actually performance, improve, just because people's are more alert.

37:01
Yeah so,

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and young children. So there's a question actually in the chat as well. It's, it's another kind of area of research on when this prototype emerged because of, you know, little babies they just sleep and wake up very randomly, so we don't have this clock set up yet and cells from like stem cells or sort of haptics but it gradually emerges with age and then get slowed down. And this question, um, the questionnaire and the things you know we always talk a lot about, about sleep, and that it's kind of important to understand the difference between two kingdoms and sleep and sleep is controlled in a very complicated way No, nobody actually understands why we sleep, we know that we do it, mostly during flight, but nobody really knows why this is a, you don't have to understand what's depicted here but there's different areas, areas in the brain, which all interact with each other with different neurotransmitters and things that control sleep. But I'm very, very simplified currently to be that sleep has two different components so the circadian component is this this body clock that tells okay it's, it's night. We have to go to sleep but there's obviously also your tiredness, which is called this homeostatic homeostatic component to just how tired you are right, because if you've been awake all night or if you've been working very hard or whatever you have to stay awake, you'll be more likely to fall asleep.

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And

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this is how easy you can get to fall asleep. You kind of adds up these two components so you have the processes see the circadian component that is controlled by these hormones as we're going to talk about in a bit more in more detail, you know, just the cycle it goes up and down up during the night, down, and, and already in the evening starts going down, or is this more energetic component so you just get progressed with that most of the day. And you can imagine actually the way. Maybe you've experienced this, that, you know, normally yes you end up going to sleep, you know maybe slightly before midnight when you're very tired and your body clock doesn't sleep. But if you know you have something important coming up for example, you got an evening and you know you have an exam next morning, and you continue to stay awake. So you can imagine that the slight you know your body flex tells you, Oh, you need to sleep. But, you push yourself you and you stay up all night. So again this dark bit is night. And maybe you've experienced this, that after some time that you kind of have to push yourself to stay awake. When the morning comes and the actual exam. Exam comes, you'd feel awake again, and that's because your body clock kicks in, it's like oh, the sun, let's, we have to say. And then obviously you can't sleep again. So, I'm just reading the question in the chat. Yes, hopefully I can send the slicer organizers to look for more detail, cortisol and melatonin for people with insomnia. There's a question about that which we're going to come to in a moment. So, they're going to be. I'm going to have a slide another slight variation about cortisol melatonin and maybe we can discuss that. And so the circadian components is controlled by an area in the brain called Super charismatic nucleus or STM for short. And can you maybe not be able to see it but it's this tiny tiny tiny place just here in hypothalamus, so you may be aware that hypothalamus is this area in the brain that controls a lot of your emotions and temperature control and permanent control, and in this tiny area here, it can communicate with the pineal gland, or here, that releases melatonin. Where do you think Sian, this area in the brain that kind of helps you tell time, Where does it receive input from which other part of the body or brain, and the ideas just come in the chat optic nerves. Yes, an optic nervous comes from.

Which organ. Eyes yes so yeah I sunlight, perfect, perfect. So, yeah, so this, this optic here the optic nerve so it's actually the SCNs I get the very back. I think I have a video here. Yes. It receives input from lot from light because we need to be able to entrain in to actually tell when it's, when it's light and when it's dark. So you'll see item this person and then optic nerves coming all the way back. Meeting this small area in the brain. Pool site. And then, then the SEM send signals to other parts of the brain to pineal gland as well, and then send signals to other parts of the body to organize your physiology, around the clock and here's, here's the bit about hormones as well so somebody was asking about melatonin and cortisol So

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melatonin is secreted at night, right. So, it's productive is inhibited by light, so when the lights are off its production activates and so only during dark hours you have, we can detect melatonin in your blood, and it helps you fall asleep. Whereas during the day you have glucocorticoids as a, as a set of hormones, cortisol is one specific type of glucocorticoids. It's one of these fight or flight, hormones, which you probably heard about, which activates you know increases your blood pressure, it increases your car trade activates your muscles so you're able to do things and you see that it's kind of gradually it's low in the evening and then increases in an early morning, it's at its peak and then quite high during the day. And as a result of these hormones but also others usually have rhythms in, you know, body temperature and urine volume and blood pressure, etc. And so it's interesting. Obviously these are all correlations, right, that, that you know these hormones come up at this time of the day and the other hormones cut off at the other time of the day for coach so we know that it causes actually increase in blood pressure. Melatonin is really interesting because there's still a lot of research done. Somebody was asking whether it, you know if it's secreted during the night. It's kind of logical to assume okay well it must help us, you know it must make us fall asleep, but doesn't work exactly like that, it's one of these cases where correlation is not exactly equal causation because if you just take melatonin, you're not you're not going to fall asleep immediately. It helps you, it helps with again with temperature control helps with things with some people it does help to fall asleep, but it's not a direct causal link. So there's more research to be done there actually, the role of melatonin as well. But yes eventually these. These hormones, organize our clock of health or physiology, as I mentioned already, body temperature. Say, alertness, you know, again, maybe just on yourself that alertness is higher in the morning, for most people, muscle strength is highest in the afternoon. Actually, if you have a competition, and it's actually better to be on an afternoon slot because it's when your Cincy if you have to go for a run and run fastest, you'll actually be more likely to do that in the afternoon. And there's, Yeah I'll sleep through the night, and I mentioned, cortisol is up in the early morning. And that's where the increase in blood pressure occurs. But this clock of Health has kind of a flip side in clock of disease because when these verses go wrong. They're also more likely to go wrong at one time of the day and not the other. So when do you think the, like heart attacks are most likely to occur during sleep, Morning, afternoon, all possible options, one of these. So, I mentioned better in the previous slide, yes sharpest increase in blood pressure is just actually on this boundary between sleep and awake so this increase in cortisol that I showed you right there's that there's more cortisol produced at the end of the night when we're just awake, it helps us narrow down to fight or flight so it also in a small amount it just activates our body, be ready for the day. But that's also, if you're really hot have a condition where your blood pressure is very high already, or you have other heart conditions, it can lead to this sharp increase extra anchors can lead to myocardial infarctions or heart attack. And even in the lord of any

departments and hospitals they know that that's when most patients come in, actually, early, early morning, and up sleep time. And so for other things as well because our hormones and our other bodily processes vary across the day so do know when they go wrong, it's also different. Again we're going to come to this concept. Later, as well. Only all these pieces are synchronized so you see these metronomes, so it's like many tissues, you know they have the these oscillations and they're all synchronized by, by food and by light. Dare your digestion metabolism your cardiovascular system, your sleep wake system and it all kind of happens in unison like these metronomes sticking together.

47:54
But when the light and the food come different times than expected, then all those synchronized versus go straight, and this is what happens in jet lag. So if you travel to from UK to the US or to Australia, across multiple time zones, and then the time at which we live doesn't always shine in Calgary, and so you're

48:21
not so close anymore. And

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it's no so if you're just traveling that's, that's probably fine right, you get used to it in one or two days, You should again overcome jetlag because your body learns okay now like comes at this time. Your scna receives input from the, from light and it manages over a few days rain train your digestive system and your immune system and your cardiovascular system so is your expect food, the right time and you expect life at the right time. But actually if you do if you switch those timings all the time like what happens in shiftwork, it can lead to some detrimental impact on your health, and on health, shift workers, unfortunately. So, if, especially people on rotational shifts, which means that they work for example you work at McDonald's or something and over at the service station and you need to work one week, you need to work during the night, in other words you need to work during the day. But obviously, people still need to eat when they're awake so they eat during the night, they don't receive light at the right time when they expect. And this has been shown to increase, especially metabolic so some cancers but also especially metabolic diseases such as diabetes and obesity. And I have two examples here to just show on a molecular level, how could. How could that be. So, I think these were in the pre session resources, maybe some of you have already had a look at these graphs so this is from a study a few years ago, when basically they were studying the regulation of food and blue blood glucose at different times of the day and what they did, they gave people exactly the same food to exactly the same calories for breakfast for dinner and monitor their blood glucose and their insulin levels in the in the blood. After the meal, so this blacked out area here is when people ate and then they measured after 30 minutes 60 minutes 90 minutes they continuously monitored their glucose and level of insulin, um, hopefully, you know what, insulin is. But just to remind you, maybe it's a hormone that helps to produce by pancreas and it helps people to absorb glucose from the blood so glucose is what fuels your cells, it helps produce ATP, obviously, but it has to get into cells for them to utilize it and. Insulin helps that process to populate those to get from the blood into the cells. Um, again, maybe if somebody has any observations from these two graphs, what is similarities what is differences between breakfast and dinner and what implications, this could have for any disease maybe that you know, insulin is involved in.

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I'm just gonna stay quiet for a few moments I'm reading your messages but I'm going to, so feel free to send them directly or into the comment chat but I'm reading your messages and I will summarize in two moments when everybody had a chance to look

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differences. Yes, we have some very good answers there. Cool. Yes, so quite a few people both in direct messages and then in the common chat, are saying that,

52:49
Oh yeah, very, very good observations, and so they all, you know, always both glucose and insulin come up after a meal, and then come down, but they do it in different speeds so somebody dances a lot in the last messages notice that they come down to same level, but then how they get there is slightly different, I say, eventually, you know, glucose is absorbed and insulin comes down after 180 minutes after three hours after a meal, but it comes down to lower. In, during dinner than during breakfast. Somebody wrote after dinner the glucose levels rise to a higher level. So, slightly higher here and drops lower so let's say after an hour and a half, we already, already, right 100% to two milligrams per deciliter. After breakfast, but after dinner it's still higher. And so the insulin also stays higher for dinner because it's responsible for this glucose in the blood, we need to absorb that and think somebody. Oh yes so instant fluctuation of magnitude, so yeah, so incident response, it helps to absorb glucose also helps to respond to the level of glucose in this negative feedback cycle which we're actually going to mention soon again. And hopefully, don't think anyone named exactly the name of the disease but But you probably heard that insulin is very heavily implicated in diabetes and pre diabetes, which is a disease really, when people cannot regulate their blood glucose usually resolves mostly blood glucose being too high, and your body not responding efficiently to insulin which. So you want to glucose in your cells but you don't want a lot of glucose in the blood because then it will cause various problems, which is what happens in diabetes. So, if you, if your glucose hangs around in your blood for longer. And if your insulin then has to hang around for longer then cells become desensitized to insulin, and then you next only eat even more insulin to absorb the glucose will hang around for longer, and it can damage various tissues especially kidneys. And obviously, you know, we all eat dinner or breakfast. It all happens in, in all of us but if you eat more meals during the night, or if you work shift work and you eat during the night, then you know it will be more, more, more often like this red scenario, and not as often like the screen scenario, and this could be one of the links with increased risk of diabetes and the shift like. And then kind of the next step. This now. Kind of a study in mice rather than in. In humans, but it helps to get this further step so in this in this study they didn't didn't measure glucose, they just made it wait over several weeks. And I'm going to explain what this means. So they had four groups of mice that they fed these in the study. They have a link here, which they fed different diets so there's one. Not they fed mice normal food and add limited means that they had access to food at any time, both during the day and during the night. An important thing to note about myself that they are nocturnal animals so they naturally are active during the night and sleep during the day. And then they had access to normal, normal food all the time. The second group of mice had access to normal food, but in a time restricted manner so this empty scenario where the food was only available during the night, when my active. And then there was had another two groups which ate high

fat diet high fat diet is known to increase weight both in humans and in mouse. And again, they had one group that had access to high fat food all the time, and another group that had access to food, only in during the dark base when they are active. And so they monitor the weight of these mice, which is depicted on the graph here again. So, normal, anytime, normal time restricted pack food anytime fat food time restricted. And, again, maybe some ideas in the chat. What, what would you conclude from this, and maybe any recommendations that you can make for humans, if we assume that humans are similar to this. It's, yeah, so some, some messages you can avoid. Yes.

58:37
Yeah, so yeah some very great ideas in the chat. I'm so important to have a balance that's right to this to two things here right there's a comparison between normal and high fat there's a comparison between time restricted and and at all times. So the fat ones are in, in the red and we see they gain weight quicker, right after like four weeks. They're already higher than say two grams. So that's one thing but even with normal and the within those groups. Sorry, I'm just reading that, the chat, eating regular vegetables.

59:23
Cool. So, the one that increased the most was, as many of you notice was the FAA to the high fat diet, and that he might have at any time they just shoot up, but even Haifa died we know yes it increases weight but if you restrict the food during the time that you're active, it doesn't seem to have, you know, be that much different from normal diet, and many of you wrote that. Yeah, it probably again, is to do with how our body metabolizes food and maybe with that glucose, insulin regulation that was on a previous slide. So, because you have a more efficient, metabolism, when you record the body stores better in a more efficient way, all the nutrients from your food, even if they're high fat. But, of course, normal, normal and time restricted seems to be the best, but the difference between time seems to make even even bigger difference and then fat in this case, in particular. So, and it's so I think there's some slight misunderstanding. Yes, irregular. In this case I don't think they were so interesting irregularity that, then more restricting the food to the active phase of the animals. And actually there's been trials in humans as well, with similar die so it has been shown that if you want to lose weight, for example, this of just eating the same thing, but consolidating the time during which you eat it actually seems to be helping. I mean, again, I'm not trying to give any advice that I was just telling you about the studies like has been recently done in humans that, for example if we, if people eat only during the 810 hours of daytime. It seems better than compared to eating exactly the same thing but at random times. And again, this could be the reason why people who have to eat during the night because of their work, for example, are more prone to diseases like obesity,

1:01:46
right, say. Right. How does it work right now slightly more molecular mechanisms, like I was telling you about how you know the body knows it's the day or the body tries to metabolize things at a particular time of day. How does it happen again. Going to some animal studies, these are studies in Drosophila which are fruit flies, and it's actually one of the first cases where it has been shown that a particular gene is responsible for a particular function. And then, in this case it's first circadian property and discovered a coded period so they noticed that in the same gene they had a mutation. It would affect how the flies behave or half the flies. How the closing, like what's written here is a closing within which

is something that happens for that larval stage of the blind, so they emerge from that pristine growth emerge from that feedback. And this mutations and it happens at a particular time of the day. So, this is four days here it happened, mostly, you know, four times in this normal scenario here. If this gene is mutated, who just happens randomly, but also they can mutations that help, that all these four cycles squeeze into three days, or the other way around. During the four days, you only have three cycles of this equation. And these two scientists cannot come benzer they match, so called Passion mapping so they know that this is a gene cough period. And interestingly, much later when we now can sequence also human genes. They're also humans with mutation in period in. And this leads to so called familial advanced sleep phase disorder where kind of humans do the same thing as here in C, so they are, they have a faster cycle they usually like go to sleep around 5pm and wake up at 3am. And that's that's the day basically let's say from midnight to 3am and they have to constantly adjust it otherwise they seem perfectly fine but it's the same gene in humans that seems to also affect human behavior. And gradually, over the course of molecular biology investigations. These three people mentioned even received a Nobel Prize for it and 2017, they figured out what this this particular protein do so hopefully you all know that, you know, a dean is a portion of our DNA that encodes for a particular protein so period is both a gene, and a protein gets made from the theory of gene. And in fruit flies. We know that this, so there's another one, timeless, but basically they get transcribed from DNA then they get translated into protein again some terms that you probably heard, but interestingly they then suppress their own transcription to something similar happens in mammals as well, too. This is just a generalized scheme over the cogs and Gears of the flock, so you have a thing that represses production of itself. In case of mammals and replaces mostly period protein. So it does, it gets produced but then once there's a lot of it, it stops production itself, so it's levels goes down, and service goes down, then this inhibition this blockage no longer happens and then experience again. And then it gets translated it's getting a protein. It's got too much of it, it's not producing again, and by some other modifications, this person takes 24 hours. And that's how cells are able to keep time and then some other, there's a lot of regulation going on. And, including those hormones that we've heard about that essentially can feed back onto this mechanism, and then period and other genes can also then control other other genes that will then control again, hormonal productions and other things in the cell periphery that's at least a little bit clear, but I can show you. So this is just another schematic of the same thing. So we have these crying per genes, and they, these squiggly lines representing the rhythms and then they control the genes and we can observe that in individual cells so this is what the lab that I work and we do a lot. So you see light that comes up and down. These tiny dots here so this is a well cells and this tiny dots are each individual cells, and the light that comes up, It comes up when period protein is, is there in the cell. It's not normally light up but this is just a technique that we use in in biology and molecular biology to monitor some proteins. So

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we have this period gene that we can fuse with luciferase is the same protein that in, you know in fireflies fireflies glow. So they produce this enzyme separates it makes them glow. But we can take that and using molecular genetic engineering techniques fuse it to something else to make the other whatever something else we're interested in, in this case period protein we can make it glow. And this can help us study this in a dish. And then we can find, for example drugs that might be affected, etc. These genetic circuits could then control other processes. For example this is a family of enzyme that metabolizes drugs and deliver and if we know that they're linked in the same circuit. Then we can know

what time of the day, maybe these drugs are metabolized better or worse in the lead back for. Same with this enzyme HMG co reductase, which is an enzyme that produces cholesterol. So, cholesterol again probably you've heard, is a lipid that is required for normal functioning of the body is mostly produced by the body. But unlike what sometimes you're led to believe. So, what you eat, does influence your levels of cholesterol but cholesterol also produced in your body. But if it's so much of it, it can cause again, cardiovascular disease and coronary heart disease. So a lot of people who are at risk of these diseases take drugs called statens and statens inhibit an enzyme in your body that produces cholesterol also eventually lowers cholesterol, but we know that this enzyme called this complicated name HMG COA reductase is controlled by the circadian network so it's more active during the night. And so you know that that's why people could take seconds which is like millions of people, it's one of the best, most sold drugs in the world, but they're directed to take this drug, just before bed, because we know that this ends, you know, it will be more efficient just before, during the night, when cholesterol is produced, and so you want to inhibit the production of cholesterol, at that time rather than, you know, if you, if you don't produce cholesterol. During the day, you take an inhibitor well it doesn't, you know, it's anyway not producer called them to help much, but if you take it in the time when the process is happening, then it can help. And this is the idea of so called Quantum medicine or during a therapy, where you have a treatment or illness or disorder that takes into account the study of circadian rhythms so you can help increase the efficiency efficacy of the drug like in the case of statins, or you can also try to reduce drug side effects.

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Okay, question sorry I was talking a lot, hopefully it is some of it was clear, maybe one question about Curlew medicine. So, remember we discussed. Now, like 30 minutes ago something we discussed the high blood pressure and when it's tires and the cortisol and everything. So there's a drug called Verapamil which is actually an ion channel blocker and is prescribed to treat to lower blood pressure to treat conditions when blood pressure is increased. How could you improve the, what can you recommend to people to, to companies that manufacture this drug, how can we improve the efficacy of it, knowing what we covered in the first half again maybe wait a few ideas. So there's one idea to take it in the morning, which makes sense. So, if the blood pressure increase happens in the morning, but this type problem there that the blood pressure increase that we covered happens in that when you wake up, it kind of happens, just as you wake up, it helps you wake up, so by the morning it's already might be a bit too late, Because you've already woken up to take the drug. Oh. So what else could you do,

1:12:11
yes.

1:12:15
Oh yes, There's some very good good suggestions there so first of all, yeah, you'll need a proper clinical trial somebody suggesting take people with high and low blood pressure and then there's a great suggestion. Recommend could be taken just before you go to bed and if it's Capital One, that can be slowly released late night that made the capsule not as easily the soul but exactly same, same idea, I see, does it before bed make it really slowly yes yes yes Well done everyone as a work quite a few people who said that. So yes, you also with rugs, they have different by availability, they have different kinetics of absorption in the gut and they don't act immediately. So there could be depending on the

dosage and individual patterns as well, that's a good point. You could take a creative formulation of the drug that's not released immediately so that reaches highest level in your blood. By the time that you wake up. Yes, thank you very much for some great ideas, and this actually what is this different formulation of the RAF Milan, it actually what is happening that they directly take it. I think just for bed and it's but it's concentration in the blood reaches its peaks just around five 6am. And then of course you can. There's some ideas about individual patterns so that's also another concept that gaining popularity at the moment about personal medicine right that, you know, different people have different traits and different genetic makeup but also different patterns and your chronotype which would become blocks and that was also can affect when the drug is more efficient or causes more or less side effects in you particular. So it's also something that's currently cited or maybe we can, you know, study the people or make them take this questionnaire or measure the Mulla Mulla turning in their blood to see when they in particular have will probably have higher efficacy of a particular drug. Right. This is a final example I think that I'm showing you from another study the geneticists. And this is, I'm going to explain these graphs. So, this is same, same concept we're trying to find the time when a drug or combination of drugs is more effective, but this time for cancer. Does anybody know. Okay, now let's let's, let's have a look at the graphs first. So there's one, this one on the left is showing number of side effects. And this one on the right is showing the survival of patients, and you're comparing two conditions. One is called Cronos, so that one that's Corona therapy where, You know these these drugs are infused by intravenous injections, but they can be done either continuously or. So, what's written here concentrating fusion or they can be done at a particular time. And we're comparing the number of reported side effects here after the number of courses so let's say each week, a patient receives a course, and then at some point after several courses they usually start develop side effects have probably had. And then this is survival I think this actually is a mouse study. So they, again they give these different treatments and then they measure how many patients or mice survived. And hopefully you can appreciate that in both of these graphs. The Crono regime seems to be doing better because, Here for example after seven courses in the constants in the black one, after especially after eight courses you already have 20 patients reporting side effects, but it's just half as much up to the end of the course. In the corner one. Similarly with survival. the blue line, like looks after 13 after two years you know there's this many people on the normal regime that's survived but a slightly more in the Krainer regime. Do you know what generally anti cancer drugs do. Maybe if anyone happens to know what what cancer is as what's common between many types of cancer. Stop repetition of cells, yes somebody's saying inhibit tumor growth,

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kill cancer cells, yay, toxins into cancer cells. Yes, but what so okay so cancer cells are cells that divide uncontrollably right and that's why tumor grows, disrupt DNA of cancer to prevent replication, yes. So that's one of the more specific replies, very good. So, to inhibit to cancer cells growing up. But in order to grow, they need to grow, they grow like almost exposure they divide, and divide they need to replicate that DNA and DNA replication is very complex process, but that's what normally, a lot of cancer drugs target this process because in the normal normally adults especially south divide but very, most of cells divide quite slowly. But cancer cells like very fast so they need to replicate their DNA all the time. And if you inhibit how specifically inhibitors of DNA replication. It will mostly kill cancer cells, not only because there's some cells in the body that also divide like a painter hairs grow and immune system cells renew very quite rapidly. That's why people who undergo chemotherapy or radiotherapy,

you've probably seen in movies or hopefully just in movies and not in real life that has Fallout and immune system is compromised during cancer treatment and that's exactly because those are the cells that divide quickly just as cancer cells do but it's mostly the cancer cells and we'll see that we want to target in in chemotherapy. So, this process of DNA replication is known to happen. Also, at a particular time of the day. Anyone can guess which time of the day DNA replication normally happens. And why not not specifically I'm not, obviously. Okay, who thinks it's during the day, yes or no. Who thinks it's during the night. I'll say, first day, yes or no. Does DNA replication happen a lot during the day, yes or no. Have the buttons to press. Yes. A few yeses.

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Okay, there's not that many so maybe mostly things, thinking that's. Oh, that's some complicated hypothesis about the night and blood pressure. So, no so this, this is mostly. Oh no there's somebody. Yeah and I just when most growth and repair happens yes make sense and mitosis in DNA replication happens to like yes, well then, so a few people are saying no, now so this is, this is the, what in fact is happening so you know your body is preoccupied with develop things during the day, with more metabolite metabolic active things in here that helps you move, they do you know replication and cell division do happen more during night. One other reason, it's thought to be behind this is that UV radiation from the sun, right, we know that sun. If you are locked in the sun, that can cause damage because of the UV radiation from the sun, and especially DNA is very sensitive to that. That's why a lot of like solariums and being too too much in this under direct, direct sun is could lead to various complications as well, because your DNA in your cells really don't like you, me, and that's why they usually try to replicate, when the sun is not out, which is during the night, and kind of researchers have investigated those pieces and then thought okay, well maybe, then we need to give the drugs, during the time that cancer cells divide between, which is why this thing works. And those now more trials happening about various treatments, how to make them more efficient or less harmful for body, depending on the time they're given. Right. And that is more or less everything I wanted to tell you, I'm going to recap some examples so circadian rhythms is something that happens, not only on the level of organisms so your sleep breakout cycles but also in your cells and tissues. They're normally synchronize with each other and main synchronizing keys are light and food. But it comes in a step back, and unexpected times, like during jetlag or shift work. So, then the body can not deal with the environment, effectively, which could result in especially metabolic diseases. And this knowledge of how circadian rhythms organized physiology can help IT system, improve existing treatments, and some areas of biology we covered was about studying gene functions in these model organisms and how genes can be regulated and being circuits with each other, which is something that you study a lot in, if you could study Biology at undergraduate level, either in medicine or pure biology. That's where you will learn about gene regulation a lot. And we can study the expressions of how genes produce proteins, could be observed using these list of phrase things, hormonal and levels and regulation can be studied by various blood tests, but we can do it at different times of the day, and it may be, you know, also when, if you ever had blood tests or other tests usually tell you oh you need to do this in the morning or you need to do this at night because we know that levels vary.

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And

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we can use trials ideally randomized control trials where we can improve existing treatments. Maybe by studying at what time of the day we get them. Thank you have any other questions I tried I know there's a few maybe that I missed but I tried to answer some during the lecture but if you have any other questions, just feel free to put them into chat now. We have a few more, yeah we have like 10 more minutes for anything that you'd like to discuss, or

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if not taking

1:24:01
this medication play a role in type two diabetes Yes, of course. So there's various depending on the stage of diabetes, there's various medications that people take. And this I think Glucophage is one of the most common ones which just uses another pathway to activate glucose uptake from the blood so it's not by glucose utilization themselves. I don't know I have to admit it or know exactly what they're these drugs are given at a particular time of the day. I'm not aware of, but yes, there's various medications that are aimed at decreasing the levels of glucose in the blood and efficient utilization as well. So, stop there. Anything else.

1:25:15
It's a great question about controlling when you eat as well as controlling lifelong preventive measure people at risk this type two diabetes, whether that's been looked into, and, yes, that's a, that's generally considered again because of the way metabolism is organized and it's more efficient during the day I don't know any specific studies that looked into very long term effects like if you're a, you know, our age like teenager, or early 20s Whether I think the overall health will definitely be improved by not by consolidating their metabolism and eating during the day more than just before bed, and it will help prevent Type two diabetes but it's, it's obviously very busy, there's a very complicated there's many factors that are genetic factors or other factors. So, it's, you know, not not 100% Sure. And another thing I guess it's worth mentioning that people with people, for example at work night shifts you know they don't always have a choice, it's not their fault that they, you know, sometimes situation forces people to do various things and or it's a job that they particularly like that happens to happen during night so what's currently also being looked at is various tweets when they can take together to kind of adjust your body clock in a way that it does help metabolism during the night. Um, what does my PhD in circadian rhythms look like in particular that's a good question. So I studied it in in in in cells so like, like I showed that, that video was salts flashing up and down. So not on an organismal level and my PhD looks at how proteins are made and broken down in cells and one that also has a rhythm and whether that has an impact on other things, and we just call this Brutus is called preaching homeostasis so in your body in all cells. Proteins are the things that perform most functions and you want them in the right time in the right place, and you want to renew them because over time they can make damage so constantly proteins gets broken down and recent size. Actually I think it's estimated that around six years it takes for all your body not only protein but all your body parts to renew. So yeah this brutal process of protein in your is what I'm looking at is body clock, less constant and blind people. This is a fascinating question so whether the communication trigger the eyes and hypothalamus and how it's affected in blindness so there's, if you want to look up there's a researcher called Russell foster he's an

expert in this, and I think they've studied a lot of blind people. Maybe I've also put a podcast. In, I think in the extra resistance, I'm not sure maybe he speaks, there as well. But they do so. There are other cells in the eye, that sense like to, obviously you have your cones and rods right that that kind of render the images that you see. So, in depending on the type of blindness that people have, they they have, they could have damaged circadian rhythms or absent even circadian rhythms. If they have damaged in those other cells that helped you relate the signal to the SEM, but if they only have problems with vision and don't have the damage in those other particular cells called retinal ganglion cells, then they could be okay. So yeah, it depends on which cells are play apart and then obviously light is one of the main synchronizing stimulus, but things like food also help so if, if a person who can't see and even has a damage in those retinal ganglion cells, but still has regular patterns of eating or physical activity that will help them stay sort of entrained to the day and night. There's a Christmas cheer on the SDN would you struggle to sleep. So it's a good question as well. SDN is very very tiny so I don't know any particular cases of tumors, specifically in that area, but there's been studies in mice where with lesions in that approximate area and they do indeed lose rhythms so normally mice would be more active during the day, during the night, and mice with lesions with damaged dress and I just randomly active so and that's how they first discovered that this is a particular area where which synchronizes the body clock. It's because of these mice that couldn't normally organize their behavior.

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There's more questions to think about cancers in the eye. I think normally they, again, it really depends on when and other diseases of the eye. Normally it wouldn't affect person circadian rhythms but maybe if they are somehow damaged those retinal ganglion cells or if they are located very nearby then what could happen so it depends on the location.

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Oh, anything else. I don't know if Haley wants to say anything at the end. If not, I guess that's it. I'll I'll try to actually contact her and see if I can put up my presentation if anyone's interested, and yeah there's a podcast and some videos in the resources that you should have access to, if you're interested in this topic more. Yeah, thank you very much for listening and thank you for your participation and questions. It was really great to have you, hopefully. Yeah, you enjoyed it and enjoyed the rest of the program as well.

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Thank you so much, that was a really interesting session. And yeah, if you send me over the PowerPoints I'll put them up on the website so you can all access that. But thank you very much.

1:31:42
I hope everyone's kind words in the chat, it's really nice to hear that you enjoyed it. Okay I hope everyone has a great rest of the day, and thank you again for your time. Thank you. Thank you.