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How do antidepressants really work?

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Antidepressants are some of the most commonly prescribed drugs in the world, with a number of proposed antidepressive mechanisms. A new paper takes a closer look at classical antidepressants like SSRIs & SNRIs, and newer antidepressants like ketamine, to answer the question: is there one underlying mechanism whereby all these different drugs exert their antidepressive effects? (To learn more about ketamine check out MIND's online lecture series on ketamine and our Psychedelic Compendium on ketamine) In this paper, published in *Cell*,the authors argue that across all these substances there is one common mechanism that is essential for their antidepressant effects, which promotes synaptic plasticity in the brain. I interviewed one of the authors, Prof. Eero Castrén, with the goal of understanding what this new mechanism is all about.

Lukas: Welcome to this research interview! Thank you for being here today. We're doing this interview to discuss one specific study you have been involved in. To start off, I would like to know a bit about the background of this research. How did you come up with your research question?

Eero: Well, this is actually something that we've been doing for 20 or 25 years already. So it's a really long-term project. I have an extensive background in neurotrophic factors and neuroplasticity, with a particular focus on BDNF [brain derived neurotropic factor, a protein that is important for the growth of new brain cells] and TRKB [tropomyosin receptor kinase B] receptors [to which BDNF binds]. All the time that I worked in this lab, we have been investigating these molecules and particularly want to find out if psychotropic medication might influence or act upon these receptors. One of the classes of drugs we have investigated are antidepressants, and already found 20 years ago that, when you treat mice with antidepressants, signalling via this TRKB receptor is increased. From that point onwards we spent a lot of time investigating how this happens and which mechanisms are involved. So this recent paper is basically the result of 20 years of work.

Lukas: That is impressive. I suppose this explains why you present the results from so many different research techniques and methods. Could you shortly summarise what these different methods are? And what were the approaches you used to investigate this specific receptor?

Eero: Well, my laboratory is focused on biochemistry and molecular biology, and we have mostly investigated signalling molecules, such as BDNF, and their changes in response to drug treatment. We often look at how phosphorylation [a process in which a phosphate group is chemically added to a molecule with the help of an enzyme] activates these signalling molecules (e.g. neurotransmitters or hormones). In addition, we were doing several different kinds of binding studies, looking at how drugs with very specific structures, such as SSRIs [selective serotonin reuptake inhibitors, the most common type of antidepressant drug], bind to TRKB receptors.

One critical component of this particular study was the modelling. We had the pleasure of collaborating with the lab of Ilpo Vattulainen. He's a very talented physicist and a specialist in investigating the structure of transmembrane proteins through computational modelling [transmembrane proteins are biochemical structures that span the entire cell membrane and have intra- and extracellular functional units]. For our study, his group created models of small molecules like cholesterol and steroids influencing the structure and function of the TRKB receptor. So our work was actually a sort of back-and-forth collaboration with this group. They generated ideas that we would then test in our lab, upon which and they used the results from our lab to improve their model. I think this collaboration was an essential part of this paper, and what I'm most happy about is the model that we ultimately came up with. We managed to design a specific model detailing what exactly happens when antidepressants bind to the TRKB receptor, and this is something we could not have come up with without this cooperation.

In addition to this, we ran studies in cell cultures, where we investigated the effects of these drugs on the growth of neurons and saw that, if we mutated the TRKB receptor, this effect was lost. We also did behavioural studies with mice, in which we saw that a genetic mutation which prohibited antidepressants from binding to the TRKB receptors, led to a loss of their antidepressant effects in these mice. Taken all together, we had a very large repertoire of methods that we used.

Lukas: You already mentioned some of the results you saw from these different methods. Could you summarise the main results for us again? And what were the results you personally thought were the most important?

Eero: As I said, my lab already found some evidence 20 years ago that TRKB signalling is increased by these drugs, and now we have direct biochemical evidence that these drugs indeed bind directly to the TRKB receptor.

The modelling additionally indicated a specific site on the TRKB receptor where antidepressants bind. This binding site is actually at the junction of two TRKB receptors that have come together in a specific way, creating a site for the drug to bind. In the lab, we could verify this binding site using genetic modifications.

Also, imaging studies showed that the presence of the TRKB receptors on synaptic membranes is increased through this binding of antidepressants lending further evidence to the hypothesis that antidepressants bind to them. Usually, TRKB is visiting the synaptic membrane only for a very short time and then it's excluded from the membrane, which means BDNF can't bind to it anymore. But through the binding of the antidepressants this presence of the TRKB receptor in the membrane is increased, which means there is a higher chance of BDNF binding to it as well.

This is something that I found very rewarding because many drug companies have been investigating and trying to find molecules that would directly activate TRKB receptors, in the same way that BDNF activates them. I was always kind of sceptical about this approach, since there is a reason the TRKB receptors normally stay in the membrane only for a short time: The idea is that this short time for BDNF to bind to the receptor allows the brain to select and stabilise only those synaptic contacts and connections that are actively used. But if you directly activate TRKB receptors everywhere you would also stabilise synapses that were not actively used, which would negatively affect the signal to noise ratio in the brain and lead to less optimal performance.

What we now see as a result of the antidepressant action, is that the TRKB receptors are more active and stay in the membranes for longer, but they still need the release of BDNF to have any effect. This means that, even though synaptic TRKB receptor presence is increased across the board, only those synapses are strengthened where BDNF is being actively released, i.e., the active connections are strengthened. For me this is very gratifying because I always thought this kind of action would be a dream come true and it turns out that antidepressants might actually fulfil this dream. We suspected something like this for quite some time, but we had no idea how this could happen, and now we have a model and we're testing this model and hoping it will stand the test of time.

Lukas: Is this "dream come true" also what you are hinting towards when you state that antidepressants are "smart drugs" in your paper? Could you explain in what sense antidepressants are "smart"?

Eero: What I mean in this particular context is that the drugs themselves do not activate the TRKB receptors, but they increase the probability of BDNF binding to it. Antidepressants only provide an opportunity for BDNF to bind, which means that the activation of the TRKB receptor still is dependent upon neural activity. And neural activity is in turn influenced by your own actions, so you can actually influence the outcome of this drug treatment through behaviour. This is what I mean by "smart drugs". This kind of action being a dream come true means that these substances are not imposing things on you, but basically giving you an opportunity to influence the structural function of your nervous system through your own actions.

Lukas: That is very exciting! In the study, you further report that this occurs across different types of antidepressants [SSRIs, SNRIs, Ketamine]. Do you think that this effect might also be the cause of antidepressant efficacy of other drugs? Meaning that all substances with potential antidepressant effects would work through this same mechanism.

Eero: Essentially all the antidepressants drugs that were investigated have been shown to involve signalling via TRKB receptors. I think that BDNF and TRKB are only mediating the process of activity-dependent synaptic selection and stabilisation. If you can activate this same process using other molecules, then I think that this molecule might also be an antidepressant. I don't see any reason why in principle you could not come up with another molecule that would fulfil the same type of physiological effects [promoting neuroplasticity] but using different molecular pathways. It seems that TRKB and BDNF signalling have evolved to fulfil this particular function and that's why acting on TRKB receptors seems straightforwardly to produce these effects. As I was saying, so far it looks like essentially all the drugs that are antidepressants seem to be doing this thing.

Lukas: Let's turn now to the implications of your findings. What do you think your results mean for the interpretation of the antidepressant effects of SSRIs, which classically has focused on the role of serotonin? Do your results imply that serotonin signalling is actually not necessary for the antidepressant action?

Eero: Serotonin is a very important and very old neurotransmitter that has existed for a very long time in animals and even in plants. It definitely has many effects in the brain and it's very clear that these

antidepressant drugs actually influence serotonin transmission, there is no question about this, but our data suggest that serotonin may not be needed for the antidepressant effect. We saw that when we genetically manipulated TRKB receptors in mice and then put these animals into behavioural tests, the antidepressant effects seem to be lost. From that point of view it seems to us that TRKB is a critical mediator for these behavioural effects, but there is definitely serotonergic action going on as well. Such effects occur together, and I think more work is now required to look at what the specific effects of antidepressant drugs actually are. It could be that different drugs have slightly different ways of affecting TRKB but also of affecting monoamines including serotonin, which could indicate in which situations to use which drugs.

Lukas: In addition to neurotransmitters, in your paper, you also mentioned the effects of cholesterol in the brain. Could you clarify the difference between cholesterol in the brain and in the rest of the body?

Eero: Cholesterol is often considered a bad guy that you need to get rid of, but in fact cholesterol is an important part of the fatty membranes that are surrounding all cells. It also plays an important role in coordinating many proteins and different factors.

Interestingly cholesterol does not pass from the rest of the body to the brain, which means the brain is dependent on its own cholesterol synthesis. This is mostly done by astrocytes in the brain, which transmit the cholesterol to neurons that take advantage of it. It has been shown before that cholesterol is important for connectivity and synaptic function in the brain, and if you'd reduce it too much then you would have problems with synaptic function. Basically, the high cholesterol in the body has nothing to do with cholesterol in the brain and does not get transmitted across the blood-brain barrier. Even though it is kind of considered a bad guy, it is definitely necessary for proper function of the brain.

For example, we found that cholesterol also acts on TRKB and our results actually imply that antidepressants can bind to TRKB only because cholesterol supports this binding and it is required for the antidepressant effects.

Lukas: I have one final question for you: What comes next for you and your lab?

Eero: There are a number of things we are doing. One of these, which is quite natural now that we have found this binding site and have a model of it, is looking for drugs that can be designed for this particular site, with potentially higher affinity than common antidepressants. One result of this could be altered versions of classical antidepressants that act faster. The other thing that we are investigating are natural substances in the body, other than BDNF, that interact with TRKB, such as cholesterol. This is also something that we would like to investigate more in detail and understand better.

Lukas: Perfect! Thank you again for your time and all the best for the future.

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