ScienceMind

FEBRUARY 2021

KING'S College LONDON

STAFF

THIS ISSUE

Dear Reader,

The month of love is upon us and what better way to celebrate it than to read this month's release! Did you catch a glimpse at all the snow this month? We sure did! This issue is packed with the most ever content we've put into one of our magazines so we're sure you'll find something that catches your eye. There are multiple articles for different sections which will now form chapters. Don't miss our highly anticipated interview with Dr Aileen King! We're sure you'll love it.

If this is your first time reading our magazine...
Science Mind is the award-nominated, student-led science magazine of King's College London, which focuses on reporting recent findings in the main branches of science to students and the wider community. We aim to showcase and develop the written and oral communication skills of students interested in research by concisely explaining complex scientific concepts in the form of lay articles and conducting interviews. Authors can also broaden their knowledge by writing articles for different sectors between issues.

If science communication is a concept that interests you, I encourage you to join the dynamic and constantly expanding team of ScienceMind. We would love to have you on our team!

Yours faithfully,

The Editor-in-Chief
The Founder

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Credit: towfiqu barbhuiya

DEEP DIVE

THE DIABETES MEDICATION THAT COULD ALSO SAVE YOUR HEART

WRITTEN BY RACHEL BRADY
EDITED BY JABARI LAMBERT

About the Author

Rachel Brady is a 2nd year 'BSc Pharmacology' student with an interest in cardiovascular pharmacology and immunopharmacology.

SGLT2 inhibitors, a standard treatment for type 2 diabetes, have been shown to reduce cardiovascular mortality in diabetic patients. Researchers set out to **identify the mechanism** by which SGLT2 inhibitors elicit their cardioprotective effects.

SGLT2 inhibitors work by **inhibiting** sodium-glucose transporters in the proximal tubule to prevent the reabsorption of glucose from the kidney, leading to glucose excretion, thereby lowering blood glucose levels. Interestingly, many treatments for diabetes have been accompanied by cardioprotective effects. However, numerous treatments have also shown to **increase the risk** of cardiovascular events. It is important to note that people with diabetes are nearly 50% more likely to suffer from a myocardial infarction. Therefore, the possibility of any cardioprotective effects of treatments used in diabetes is of great importance.

Since discovering the impact diabetes medication may have on the heart, scientists have screened diabetes treatments to assess their cardiovascular effects. These trials led to the finding that an SGLT2 inhibitor, Empagliflozin (EMPA), **significantly reduced cardiovascular mortality.** Cardiomyocytes do not express the sodium-glucose channels that EMPA works on in the kidney, so alternative mechanisms of its cardioprotective action have been suggested. A recent study found that the cardioprotective effects of SGLT2 inhibitors may be mediated via the induction of autophagy. This cellular mechanism recycles redundant proteins for energy in response to stressful stimuli.

This study used diabetic rodent models of myocardial infarction to assess the impact of EMPA on cellular survival and recovery. EMPA pre-treatment led to a **significant increase** in rodent survival after myocardial infarction when compared to control treatment. Structural changes to the heart, such as left ventricular remodelling and myocardial scarring, which could lead to post-MI complications, were also reduced with EMPA treatment, which confirms previous experiments that found cardioprotective effects of EMPA. The scientists investigated whether these same findings would be true in non-diabetic rodent models of myocardial infarction. Administration of EMPA in non-diabetic rodents **reduced the size** of infarct damage and prevented cardiac remodelling.

EMPA action on sodium hydrogen antiporters

Following the confirmation of the cardioprotective effects of EMPA, the scientists investigated the mechanism by which EMPA acts to protect the cardiomyocytes. In-silico experiments indicated that EMPA binds to sodium hydrogen antiporter in the cell surface of cardiomyocytes, thereby **inhibiting its activity**. To confirm these findings, an inhibitor of the antiporter was used and its effects in cardiomyocytes were assessed. Inhibition of the antiporter mimicked the effects of EMPA in cardiomyocytes and prevented cell death. Inhibition of the channel **blocks** the large sodium influx and the accumulation of calcium, both characteristic features of ischaemic tissue which result in cell death.

EMPA action on autophagy

EMPA is believed to protect cardiomyocytes by downregulation of autophagic processes. Autophagy is the process by which cells degrade proteins to generate energy. In ischaemic tissue, this process is useful, as it **provides energy** for the glucose deprived cells. However, reperfusion of the tissue following a period of ischemia can **lead to injury**. Breakdown of proteins can impair the cell's ability to remove reactive oxygen species, capable of damaging the cell membrane and causing cell death.

The researchers showed that glucose deprivation resulted in autophagy while treating the cardiomyocytes with EMPA reduced the autophagic processes. To further assess whether decreased autophagy plays a role in cardio protection, mice missing beclin 1, a protein integral to autophagy, were given myocardial infarctions. Mice without beclin 1 had **lower mortality rates** and showed fewer signs of heart damage. SGLT2 inhibitors like EMPA have cardioprotective properties in patients with and without diabetes. This research has identified two possible mechanisms by which EMPA acts to generate cardioprotection. Autophagy is a recently discovered process that has promising implications in the treatment of patients post-MI. The discovery of the beneficial effect of the sodium hydrogen antiporter blockade in ischaemic tissue could lead to the development of novel therapies to **reduce** complications following myocardial infarction.

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DEEP DIVE

CANNABIDIOL IN RELIEVING SYMPTOMS OF ANXIETY

WRITTEN BY ZETA IOANNOU
EDITED BY JABARI LAMBERT

Cannabidiol (CBD) is gaining considerable attention in the research community with promising results in a variety of neuropsychiatric conditions (Moazen-Zadeh and Galynker, 2020). In particular, there are several replicated findings for the therapeutic effects of CBD anxiety symptoms. In this article, I will be outlining the **physiology of anxiety** as well as the **effects of cannabidiol therapy** on the mentioned biochemical pathways.

Anxiety is an adaptive, emotional response that naturally takes place upon the detection of a threat by the CNS (Tovote et al., 2015). Despite being a natural biochemical phenomenon, **anxiety can become maladaptive** upon excessive or inappropriate occurrence without the presence of that particular threatening stimulus. (Tovote et al., 2015). Even though the exact pathology and onset of anxiety-related disorders is currently unknown, results from neuroimaging and biochemical studies, suggest that the distinction between adaptive and maladaptive anxiety responses, is governed by regions of the limbic system; mainly the amygdala as well as neurotransmitters of the nervous system such as dopamine (DA), GABA and serotonin (5-HT) (Martin et al., 2009).

The **endocannabinoid system (ECS)** constitutes a very promising therapeutic target for anxiolytic-drug development due to its key role in modulating synaptic plasticity and neuronal activity; both of which relate to anxiety-related disorders (Papagianni et al., 2019, Murrough et al., 2015, Blessing et al., 2015, Izzo et al., 2009). Even though CBD has low affinity for the two main cannabinoid receptors CB1 and CB2 – which are largely responsible for signalling within the ECS – it appears to cause activation of the ECS via inhibition of ECS neurotransmitter anandamide, which in turn leads to a cascade of events which **activates** the CB1 receptor (Blessing et al., 2015, Murrough et al., 2015).

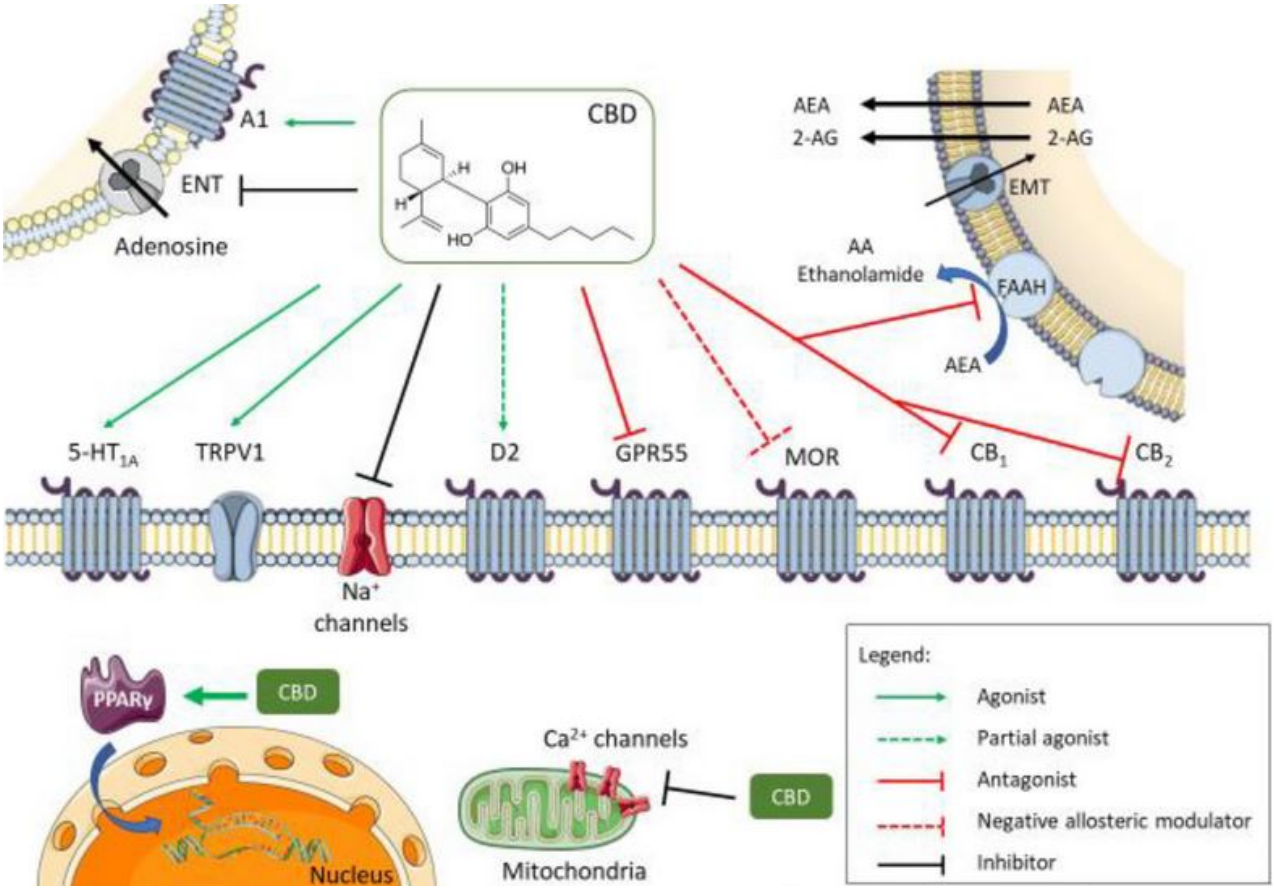

Figure 1. The various molecular targets for CBD. The G-coupled receptors CB1, CB2 and 5-HT1A are the receptors involved in the anxiolytic effect of CBD (Adapted from De Almeida and Devi, 2020).

This mechanism, in conjunction with activity of CBD on 5-HT receptors (Figure 1), is thought to be **key** in the observed therapeutic effects of CBD in anxiety (de Mello Schier et al., 2014).

In a double-blinded study, 40 healthy subjects separated into four groups of 10 who received either oral CBD, diazepam, ipsapirone or placebo. **Diazepam and ipsapirone are commonly prescribed drugs for acute anxiety** (Zuardi et al., 1993). The volunteers were subjected to a simulated public speaking test (SPST) to compare the anxiolytic properties of the assigned drug.

The authors concluded that acute administration of CBD **may be appropriate alternatives** for patients experiencing sedative effects from other anxiolytic drugs commonly prescribed such as diazepam; **diazepam showed significant sedative effects mentally and physically** in the subjects involved in the study (Zuardi et al., 1993).

Due to CBD not being associated with adverse side effects such as potential dependence and tolerance or sexual dysfunction as opposed to other pharmacotherapies for anxiety with **limited efficacy** (e.g. benzodiazepines, serotonin-uptake inhibitors and monoamine oxidase inhibitors), CBD is constituted a **very promising anxiolytic drug** (Murrough et al., 2015, Griebel et al., 2013, LeDoux et al., 2016). Further studies are needed to **determine the long-term safety and efficacy of CBD therapies** and a more standardised dose-effect response; especially when considering the complex legalities surrounding CBD's therapeutic status for anxiety (Skelley et al., 2020).

About the Author

Zeta Ioannou is a 1st year 'BSc Biomedical Science' student with interests including drug discovery and development.

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THREADING WATER

THE ROLE OF VITAMIN D DEFICIENCY IN THE PREVALENCE OF AUTOIMMUNE DISEASES

WRITTEN BY ROSA TSUCALA & CHARLINE HENDRICKX
EDITED BY TAMAS BODO

Introduction

Calcitriol, the active form of Vitamin D, is a hormone that contributes to immunomodulatory, anti-inflammatory, antioxidant and anti-fibrotic actions within the organism. The purpose of this article is to set forth the relation of activated Vitamin D to autoimmune diseases (AD's) and present the prospective applications of vitamin D for their treatment. AD's are a category of non-communicable diseases caused by the generation of autoantibodies against self-antigens, which results in an internal inflammatory response. Examples of AD's include Myasthenia Gravis, Hashimoto Thyroiditis and Diabetes Mellitus type I. The question of interest is **"What is the role of vitamin D in the pathophysiology of autoimmune diseases?"** and **"Can Vitamin D be utilized for their treatment?".**

Vitamin D Structure and Function

Vitamin D is a secosteroid hormone (its structure comprises a broken ring) and exists in two forms: D2 (ergocalciferol) and D3 (cholecalciferol), as seen in Figure 1. The primary supply of vitamin D to the organism is through the skin after sun exposure, and the secondary source is the diet. When the inactive form of vitamin D enters the organism, it is transported to the liver, acquiring the structure of the intermediate 25-hydroxyvitamin D (25-OH D). 25-OH D is then transported into the kidneys and is converted to its active form, 1,25-hydroxyvitamin D or calcitriol.

Accumulating evidence has shown an inverse relationship between vitamin D serum levels and the development of AD's. The effectiveness of vitamin D could be attributed to its structure. 1,25-hydroxyvitamin D has the unique ability to pass the plasma membrane and enter the cell to bind to cytoplasmic Vitamin D Receptors (VDR). The 1,25-hydroxyvitamin D-VDR complex acts as a transcription factor and modulates calcium homeostasis and intestinal absorption.

The VDR receptor is present in many cell types, such as lymphocytes and dendritic cells. This suggests that vitamin D can have systemic effects and prove beneficial to many cell types. Moreover, evidence has indicated that vitamin D influences both innate and immune systems.

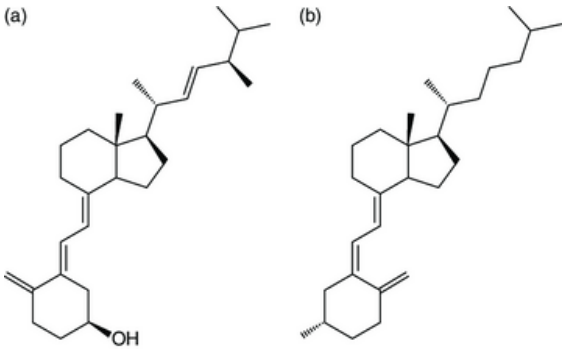

Figure 1. The two different forms of vitamin D, D2 (ergocalciferol) indicated by (a) and D3 (cholecalciferol) indicated by (b). Source: Ledesma-Amaro, Rodrigo & Santos, María de los Ángeles & Jiménez, Alberto & Revuelta, José. (2013). Microbial Production of Vitamins.

Effects on Immune System

Calcitriol regulates several chief mediators' action in the innate immune system (the rapid, non-specific immune system). It has been found that the expression of vitamin D receptors (VDR) is regulated by the activation of toll-like receptors (TLRs), and TLRs are activated via bacterial stimuli. Therefore, bacteria will activate TLRs, and in turn, TLRs will increase the expression of VDRs and vitamin D activity.

It has been shown that vitamin D affects natural killer (NK) cells which are cells that limit tumors and microbial infections. It was observed that calcitriol regulates NK cells cytotoxicity, cytokine secretion, and degranulation, explaining vitamin D's anti-tumor effects. Vitamin D and its receptor also work on the adaptive immune system (slow, specific immune system). Studies have shown that vitamin D and VDRs affect B and T lymphocytes by inhibiting their differentiation, promoting their apoptosis, decreasing their immunoglobulin production, and promoting a more tolerant immune status. Vitamin D also inhibits the secretion of proinflammatory cells and stimulates the production of anti-inflammatory cells. These observations may account for vitamin D's protective effect upon ADs.

Vitamin D and autoimmune diseases

So, what is the link between vitamin D levels and ADs? Investigations demonstrated that low levels of vitamin D are indeed associated with an increased risk of infections and ADs. For example, there are high occurrences of ADs in northern countries, such as multiple sclerosis, which seem to correlate with low levels of vitamin D. Scientists have also discovered a strong association between Autoimmune Thyroid Diseases (AITDs) and vitamin D deficiency.

AITDs is a group of T-cell mediated disorders, more prevalent in females, which have detrimental effects on the thyroid gland (see Figure 2). In addition, low vitamin D levels have also been associated with Systemic Lupus Erythematosus (SLE), a chronic inflammatory disease affecting bodily tissues. There are also associations between ADs and VDR polymorphisms that display VDR's crucial role in regulating immunological responses. Certain VDR polymorphisms have been identified as the onset of specific ADs such as polymorphism with BsmI or TaqI that leads to thyroid disease or FokI polymorphism with diabetic nephropathy, and many other VDR polymorphisms that ultimately lead to changes in vitamin D regulatory effects and thus changes in the immune response.

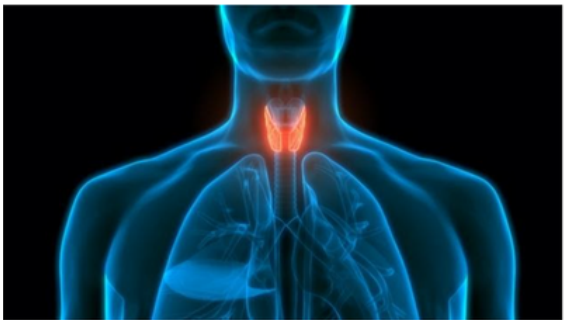

Figure 2. The thyroid gland.

Could vitamin D be utilized for the treatment and prevention of autoimmune diseases? Having in mind the aforementioned, vitamin D could be utilized for the improvement of AD treatment, however, it has not yet been established as a primary treatment method.

Conclusion

Overall, vitamin D deficiencies have a strong correlation with the development of many ADs, such as thyroid diseases and systemic lupus erythematosus. Moreover, VDR polymorphisms have also been associated with an increased risk for AD development. In order to establish treatment methods utilizing vitamin D, further experimentation is required. In the meantime, vitamin D supplementation in doses of 1000 IU daily would be suggested to attain sufficient vitamin D levels, which is likely to reduce the risk of developing an AD.

About the Author

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SHALLOW DIVE

HOW COULD MALE CONTRACEPTIVE PILLS WORK?

WRITTEN BY SOUMIYA DRIR SADAOUI
EDITED BY TAMAS BODO

Unplanned pregnancies account for a total of **40-45%** of all pregnancies worldwide. These have resulted in an ongoing global health issue that presents **health and socioeconomic risks** to families and communities. Nowadays, both men and women possess an interest in the development of safe and effective **contraceptive options for men** in order to offer further options than the now available: condoms, introduced in the 18th century, and vasectomies developed in the 19th century. The factors that have led to decelerating clinical development in this field include a notable **pullback of financial support** in the last decade, social concerns raised against unfamiliar novel treatments, and the biological nature of human bodies. The latter is significantly important as men, in contrast to women, cannot fall pregnant, and hence the assessment post-treatment is challenging to quantify. Moreover, **while female contraceptives suppress one ovum's fertilization per menstrual cycle**, male contraceptive methods aim to stop sperm ejaculation (15-200 million sperm/mL), which could require treatment of 5 to 8 weeks to be effective.

There are ongoing clinical trials that study the **suppression** of testicular testosterone and sperm production. The studies have shown that this can be achieved by hormonal male contraception therapy, denominated androgenic-progestin birth control. These are pharmacologically referred to as **steroid drugs**, and they are being developed as both **'male pill'** and as **long-acting injections**. Alternatively, there are also ongoing studies on non-hormonal male contraceptive methods that target the suppression of proteins involved in sperm maturation and motility to suppress sperm transport through the vas deferens.

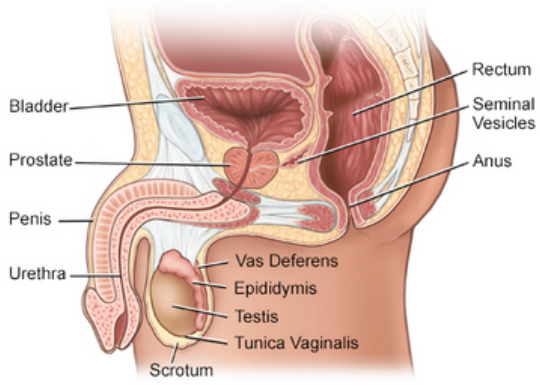

Figure 1. Anatomy of the Male Pelvic Area.

The male's hypothalamic-pituitary-gonadal axis is composed of a classic **negative-feedback loop** (a stimulus resisted through a physiological process that returns the body to homeostasis). The gonadotropin-releasing hormone (GnRH) from the hypothalamus **stimulates the production** of gonadotropin hormones.

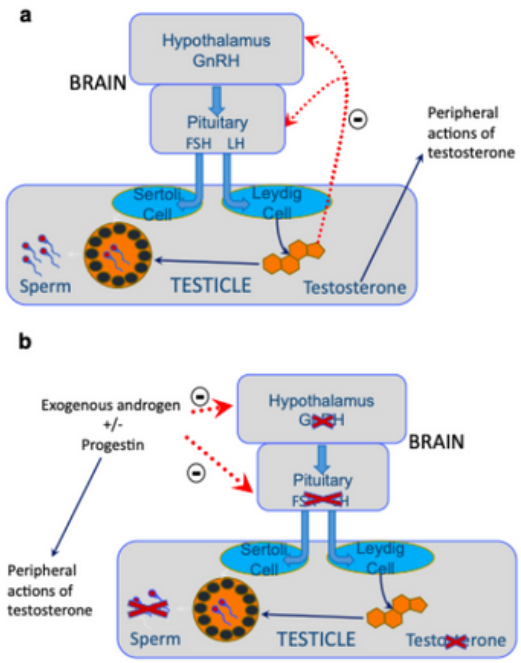

Figure 2. Hypothalamic-pituitary-gonadal axis physiology with contraceptive agents (Thirumalai and Page, 2019).

The hormones then stimulate sertoli and leydig cells within the testes, which **support** both sperm and testosterone (T) production, respectively. This results in **high** intra-testicular testosterone concentrations, which is **crucial** for normal spermatogenesis (production of sperm). The androgenic-progestin birth control drug **binds** to androgen receptors in the brain and **inhibits** GnRH production, and therefore gonadotrophin hormones, which results in intra-testicular testosterone synthesis and spermatogenesis. The role of progestin is to **inhibit** gonadotropin hormones more profoundly and rapidly. In contrast, non-hormonal male contraceptive methods **target** either: the **interruption** of sperm maturation within the testes, the **interruption** of the effective transport of sperm by modifying sperm motility or by reaching the ovum, and finally, the **inhibition** of sperm-egg fusion.

About the Author

Soumiya Drir is a 2nd year 'BSc Pharmacology' student interested mental health, endocrinology and neuropharmacology in general.

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SHALLOW DIVE

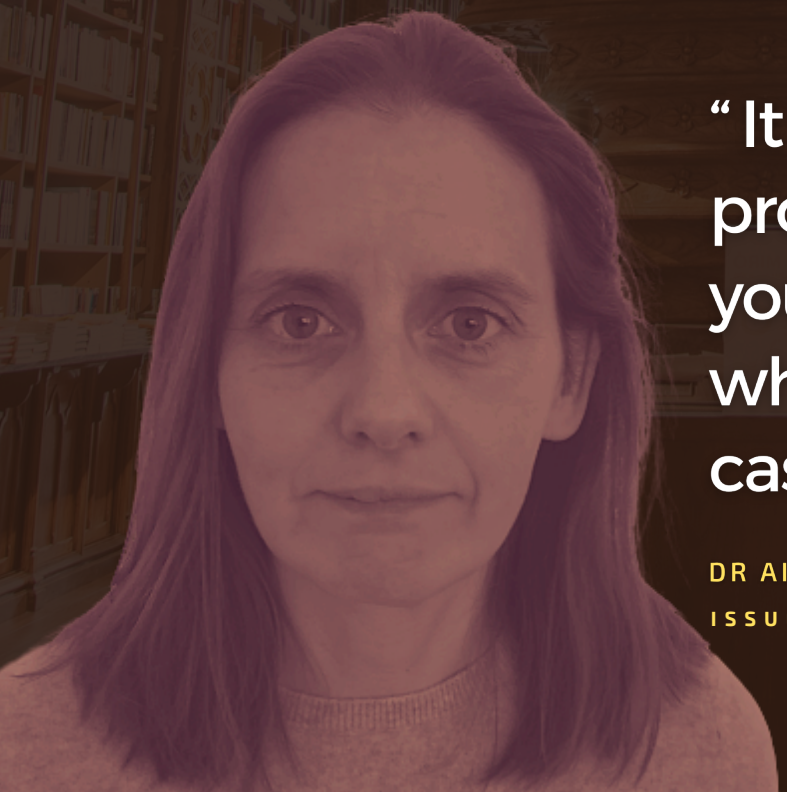
New Players in the Fight Against Diabetes:

DR AILEEN KING DISCUSSES ANIMAL MODELS AND ISLET TRANSPLANTATION

WITH PETR BORODAVKIN & AAIMAN BHARMAL

Aileen King is a Senior Lecturer in Pharmacology at King's College London. Her research interests focus on diabetes. Aileen is a member of the Pharmacology and Therapeutics teaching department at KCL where she holds the role of senior tutor. She was awarded the British Pharmacological Society's Integrative Pharmacology Fellow Prize in 2009 for her excellent contribution to teaching. She is a member of the BPS animal welfare and in vivo pharmacology sub-committee.

In 2020, the WHO released a ranking of the most frequent causes of death globally, in which Type 2 Diabetes Mellitus (T2DM) was placed in 9th position. Accounting for nearly 1.6 million deaths in 2016, T2DM cases have skyrocketed by nearly 70% since the year 2000, while its comorbidities such as obesity and high blood glucose have been costing millions of pounds to the healthcare systems worldwide. However, the following statistics are no way near being gone unnoticed.



"It helps you solve one problem, but it gives you another problem, which is usually the case in science."

DR AILEEN KING

Academics and medical medical professionals are fighting a challenging battle to come up with novel treatments to combat the rising impact of T2DM. Dr Aileen King has been looking into the pathology of the condition for over 10 years in an attempt to discover potential ways of its management in humans. In that time, her research has yielded fruitful results, with the pinnacle being the KINGS mouse strain -named after Dr King.

"This mouse has a mutation in its insulin molecule, which leads to something called endoplasmic reticulum stress. This means the mouse can't produce insulin as efficiently as it should, and its' insulin-secreting cells go into apoptosis [cell death]." she explains. More intriguing, however, is the fact that the mutation only makes the male mice diabetic. Dr. King shared with us that female mice only experience glucose intolerance but do not in fact become fully diabetic. These findings closely resemble the current epidemiological impact of T2DM in humans, as the prevalence of the condition rises in women after menopause. Dr. King feels that this correlation may provide us with a potential solution for diabetic patients in the future: "I am really intrigued how you can have the exact same mutation and the male mice get really diabetic and females don't. If we understand why the females are less likely to have their beta cells fail, we could have both males and females after menopause in the future."

"Our model is also of particular interest because this mutation is also found in humans" she added, underscoring the relevance of the model in the pursuit for new treatments for diabetes.

Although having been utilized in drug development and disease modelling by academics for decades, the use of animals for scientific procedures is still a sensitive topic for some, as the ethical side of the process remains in the spotlight. According to Dr. King, the gap can be bridged through openness of research specialists towards the general public: "Some people don't realize how regulated it is. There needs to be three licenses in place and a government inspector can show up to the lab anytime to see what you're doing and check whether you have permission to perform the procedure. If you are not open, people will use their imagination." Another important detail Dr. King pointed out is that animals must be treated to the highest standard in order to ensure the researchers get the most accurate data, so it is in their best interest to make sure the animals are taken care of: "If the animal is in a lot of distress, their blood glucose will increase because of the effects of adrenaline and cortisol. I think it's important when you're working with animals that you actually like animals, because then you automatically treat them with respect-it's hugely important."

Besides, the impact of Dr King's work on T2DM extends beyond animal models. Another promising area of her expertise is the optimization of beta-cell transplantation for diabetic patients. Although the first successful procedure in humans dates to the year 2000, there still remain a series of hurdles which hinder its use on a broader scale. The main one is the rejection of the implanted beta cells by the immune system of the recipient which destroys them, rendering the transplantation unsuccessful. As a consequence, patients might be forced to go through immunosuppressant drug therapy to nullify the risks of the implants' rejection.

"The risks of immunosuppression are actually higher than insulin. If you are well-treated with insulin, you're expected to have a long and healthy life, so giving them a drug that may increase their chance of cancer is not great" summarises Dr. King.

Her approach to the procedure aims at circumventing the need for immunosuppressant drugs by making the implanted cells unreachable to the immune system of the recipient. More specifically, the beta cells are put into molecular cages that prevent the cells of the immune system from attacking them, while still allowing small molecules such as insulin, glucose, and oxygen to pass through.

"The cages are made from a seaweed polysaccharide called alginate. It's safe and completely inert, and if you're a mouse it can cure diabetes!" reveals Dr. King, suggesting that although there is much more that needs to be done, the procedure has further potential in humans: "The islets are not always happy in those cages, so you may end up needing more beta cells for transplantation. It helps you solve one problem, but it gives you another problem, which is usually the case in science" she concluded.

About the Author

Petr Borodavkin is a 3rd year 'BSc Biomedical Science' student familiar with T2DM and BPD.

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Aaiman Bharmal is a 1st year 'BSc Pharmacology' student interested in drug discovery and development.

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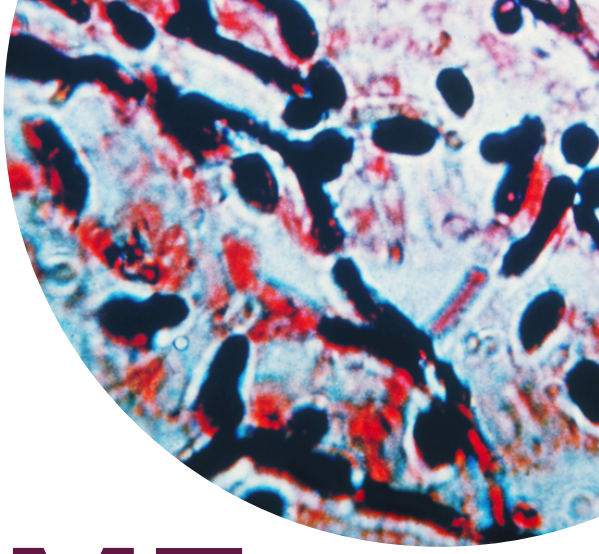

THREADING WATER

BATTLE FOR THE MICROBIOME

WRITTEN BY SEAN CRAWFORD
EDITED BY JABARI LAMBERT

People with cystic fibrosis appear to be protected from thrush infection. Frequent infection with opportunistic bacterial pathogens appears to protect against fungal infection, including thrush caused by yeast like organism Candida albicans.

In the previous issue, I summarised the clinical presentation of thrush as well as ground-breaking research by KCL scientists which characterised the thrush fungus' secreted toxin, candidalysin. Briefly, thrush is an infection caused by the yeast like organism Candida albicans transitioning from its yeast like state to hyphal form which is associated with the development of white plaques on the vaginal or oral mucosa which can be intensely itchy or cause a burning sensation. KCL researchers initially discovered in 2016 that candidalysin toxin secreted by the candida yeast was required for the fungus to colonise and damage epithelial barriers.

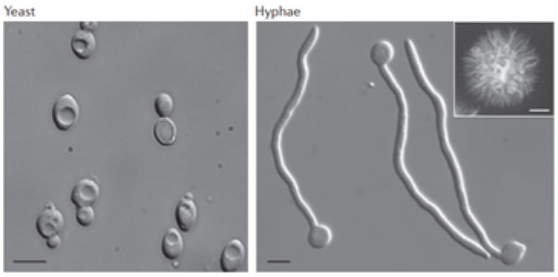

Figure 1. Scan depicting the morphology of yeast compared with hyphae.

It was found to damage cells by forming pores in the cell membranes. In 2020, King's scientists demonstrated that the toxin also forms pores on neuronal cells. Therefore, disruption of sensory neuron or nerve membranes by candidalysin thrush toxin is a plausible way in which thrush could cause symptoms suggestive of nervous system involvement. Those living with cystic fibrosis often suffer from pneumonia caused by opportunistic bacterial pathogens galvanising on the thick, sticky mucus that clogs the airways and is characteristic of having cystic fibrosis.

Frequent hospitalisation with lung infection severely affects the quality of life of people with cystic fibrosis, including shortening their lifespan to about 50 years in the UK. It has been realised since the early 1990s that people with cystic fibrosis who are hospitalised for serious bacterial lung infections seldom develop thrush infections, despite aggressive antibiotic therapy. This was a surprise finding because antibiotic treatment would logically be associated with an increased risk of developing fungal infections due to alteration of the microbiome in favour of thrush causing Candida yeast.

Infection by B.cepacia bacteria appears to offer a particularly significant degree of protection against thrush infection as well as candida related fungal sepsis. B.cepacia pneumonia is particularly difficult to treat due to its innate resistance to many of the antibiotics in clinical use, such as streptomycin, requiring a complex cocktail of antibiotic drugs to treat. Despite prolonged treatment with various antibiotics in hospital, this subset of cystic fibrosis patient seldom develops superficial thrush infection and the threat of fungal septicaemia is negligible.

It appears protection against the thrush fungus is gained by the diffusible signal factor of B.cepacia bacteria. Diffusible signal factors are chemicals released by bacteria to gain a competitive edge over fellow microorganisms in their vicinity.

Figure 2. People with cystic fibrosis must socially distance from others who share their condition due to the high likelihood of one harbouring bacterium that could prove fatal to the other. The male lead in this 2019 romantic drama happens to suffer from chronic B.cepacia infection.

They simply act to interfere with the growth and spread of their fellow competitors. The diffusible signal factor released by B.cepacia is a fatty acid called cis-2- dodecenoic acid, it is a lipid or oil like substance.

In addition to decades of clinical data showing that a B.cepacia lung infection offers protection from thrush, Liang et al based in Jiangsu, China demonstrated in 2018 that B.cepacia derived cis-2- dodecenoic acid was sufficient alone to cause symptomatic relief as well as elimination of vaginal thrush in a mouse model.

The researchers found that application of the molecule protected epithelial surfaces from damage as well as interfering with candida albicans switching from its harmless yeast form to hyphae forming thrush causing state. The secretion of candidalysin toxin, which KCL scientists have shown is essential for presentation of thrush infection as well as a possible way in which the thrush fungus could activate human nerves to cause symptoms, was also reduced by application of the bacteria derived chemical. As a fatty acid molecule, B.cepacia derived cis-2-dodecenoic acid is likely to intercalate amongst cell membrane lipids. This suggests its protective, anti-thrush effects could come from associating with human cell membranes. This may provide the cells with protection against the membrane damaging effects of candidalysin which is essential for the thrush fungus to latch onto epithelial surfaces. Alternatively, the molecule could interact with the membranes of fungal cells to obstruct the transition to the disease-causing hyphal phenotype.

Indeed, Liang et al confirmed topically applied cis-2-dodecenoic acid was able to suppress yeast like cells from transforming into thrush causing hyphae, suppress production of candidalysin toxin and prevent fungal cells from adhering to mouse vaginal epithelium. This led to the clearing up of the vaginal thrush infection in the mice. In the future, cis-2-dodecenoic acid should be investigated for ability to protect human cells from thrush toxin effects while stalling the growth and pathological transformation of the usually commensurable organism. Following on from the work by King's scientists recently, the fatty acid could be tested for its ability to protect neuronal cells against the effects of thrush toxin. If neuronal cells are protected by cis-2-dodecenoic acid this would imply potential for a treatment that provides symptomatic relief of itch before then eliminating the thrush infection. Current topical treatments such as ketoconazole cream only act to suppress fungal cell growth and replication so ability to tackle the troublesome symptoms with the bacterial derived substance would represent a breakthrough.

About the Author

Sean Crawford is a 3rd year 'BSc Pharmacology' student with interests in neuropharmacology.

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DEEP DIVE

RED SAGE COMPOUNDS SUPPRESS IMMUNE RESPONSE

WRITTEN BY KIRA LINKE
EDITED BY JABARI LAMBERT

Many important medical strategies are derived from the natural world, and red sage appears to have untapped potential for treatment of immunological diseases. Red sage, Salvia miltiorrhiza, is native to China and Japan, where it is used in traditional medicine for cardiovascular and cerebrovascular disease. Scientific research has not found significant efficacy in this. However, Salvia miltiorrhiza contains unique tanshinones that demonstrate immunosuppressant properties. Tanshinones are a class of chemical naturally found only in Salvia, and all of which are produced in S. miltiorrhiza. In particular, production of the interleukin-12 (IL-12) and interferon-γ (IFN-γ) are inhibited. IL-12 and IFN-γ contribute to the differentiation of T-helper cells into Th1 cells, which are involved in autoimmune disorders like multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease, as well as acute allograft rejection, unexplained recurrent abortions, and in some chronic inflammatory disorders with no specific known cause.

IL-12 induces the production of IFN-γ and has a demonstrated role in pathogenesis of autoimmune disease in rat models. Progression of autoimmune disease is accelerated by additional exogenous IL-12, while inhibition of IL-12 can prevent graft-versus-host disease. Thus IL-12 activity has been conclusively linked to immune activity. IFN-γ is a regulatory molecule and has similarly been linked to autoimmune disease pathogenesis. It, too, has been demonstrated to accelerate disease progression when concentrations are increased, but less research has been conducted on IFN-γ than IL-12. Nevertheless, control of IL-12 and IFN-γ is an important aspect of treatment for many immunological diseases. A study published in the journal Immunopharmacology by a collaboration of South Korean scientists examined the ability of three tanshinones found in S. miltiorrhiza to decrease concentrations of IL-12 and IFN-γ, including levels of gene expression for IL-12-producing promotor gene.

They isolated tanshinone I, 1,2-dihydrotanshine, and cryptotanshinone from the root of S. miltiorrhiza and tested the effects of each individually. First, mouse macrophages were stimulated with bacterial marker molecules. In the presence of a tanshinone, the concentration of IL-12 produced was significantly lower. 1,2-dihydroxytanshinone had the most significant effect. The inhibitory effect was shown to be dose-dependent, but a cytotoxic effect was observed above 1μM. RT-PCR results showed that the levels of gene activation for IL-12-producing promoter genes were significantly reduced, suggesting that the effect of tanshinones occurs on a translation level.Next, IFN-γ levels were examined using ELISA assay. Again, inhibition was significant and dose-dependent, where 1,2-dihydrotanshine caused the most significant reduction in concentration.

Tanshinone I, 1,2-dihydrotanshine, and cryptotanshinone have demonstrated promising immunosuppressant abilities, and may be able to assist people suffering from Th1-mediated immunological diseases in treating or at least managing their conditions. Considering that these compounds are found only in Salvia, they also provide another fascinating insight into the incredible interactions between nature and people, and the power to use that for our benefit using precise scientific techniques.

Figure 1. Red sage (*Salvia miltiorrhiza*) in the wild.

About the Author

Kira Linke is a 1st year BSc Pharmacology student interested in immunopharmacology,

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THREADING WATER

NOVEL ANTIBODY THERAPY COULD IMPROVE ATOPIC DERMATITIS AFTER A SINGLE DOSE!

WRITTEN BY CHETANA PRABHU
EDITED BY JABARI LAMBERT

Atopic dermatitis is a lifelong condition associated with the immune response of the body towards certain allergens. Any contact with an allergen, causes the immune system to act quickly to produce chemical messengers to mediate an immune response, causing itchy or painful rashes to appear on the skin. The allergen moves through the slightly porous skin and is picked by an antigen presenting cell causing type IV hypersensitivity, which is mediated by the T cells of the immune system which eventually produces inflammatory substances like histamine and leukotrienes. There are multiple ways to get the dermatitis flare-ups (itchy skin rash with redness) under control such as orally administering the affected individual with an immunosuppressant drug or with the use of natural topical alternatives. Some of the current immunosuppressant drugs include- Azathioprine and Cyclosporine, whereas the natural treatment includes coconut oil, vitamin supplements and ancient mind-body practices.

In cases of severe dermatitis, steroid based drugs may also be prescribed, however, they can have serious side effects if not taken with caution. Side effects can range from upset stomach, vomiting, increased risk of infection and certain type of cancers.

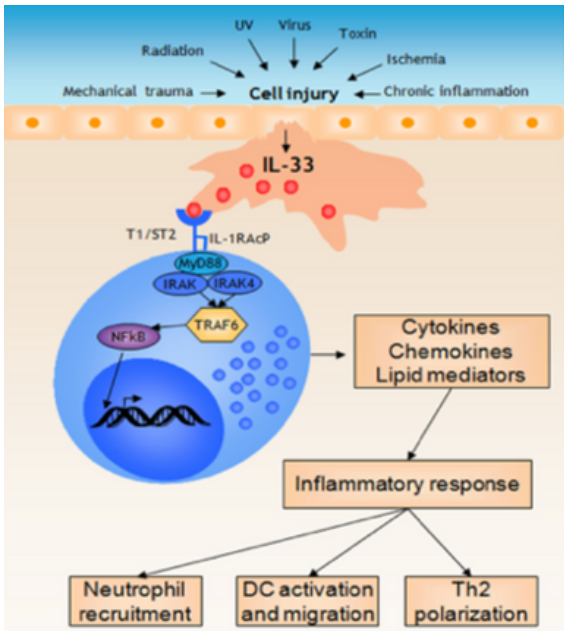

Figure 1. Interleukin-33 (IL33) is responsible for immune responses.

To reduce the risk of severe side effects, it has been suggested that a new antibody drug called Etokimab (previously known as ANB 020). It could improve the symptoms of atopic dermatitis after just a single dose. This could potentially be administered as an alternative to the current treatment.

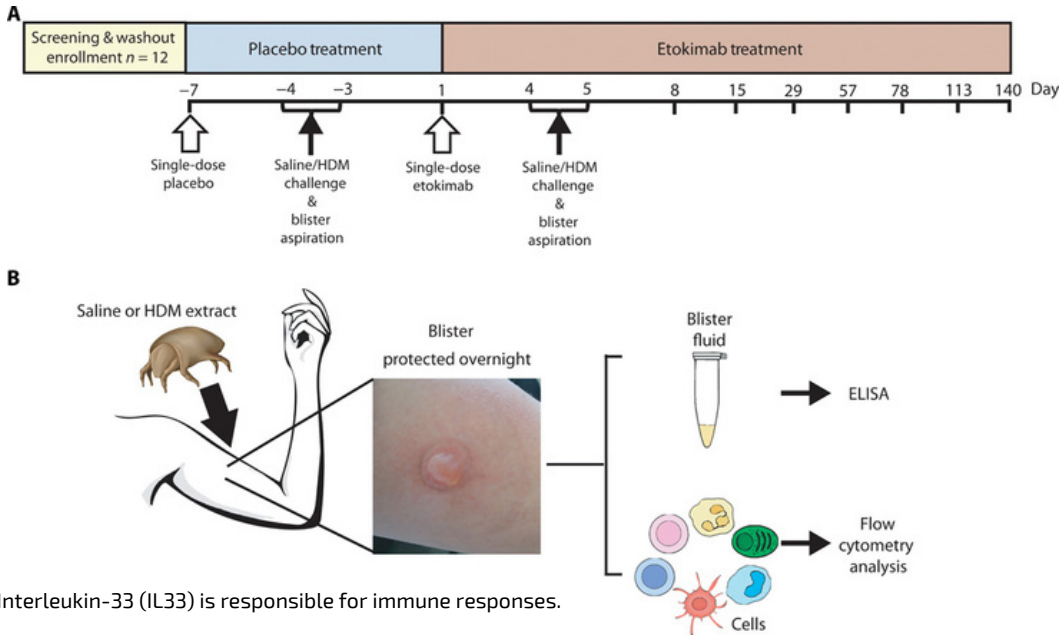

Figure 2. Interleukin-33 (IL33) is responsible for immune responses.

Etokimab achieves the desired effect by targeting and blocking the signalling molecule interleukin 33 (IL33) which is responsible for immune responses. It was also observed that blocking IL33 interfered with the neutrophil recruitment and reduced inflammation. Researchers in the university of oxford led an experiment where 12 participants were administered single doses of Etokimab. It was observed that after about 29 days 83% of the participants had significant reduction in their physical symptoms to half its severity. By the end of the study period, the count of a certain type of white blood cell known as eosinophil had reduced significantly, which indicates a positive response to the therapy. Although eosinophils help in defending against parasitic infections, a high count could indicate an allergic reaction, and this can lead to a bigger inflammatory response. Researchers are testing the same Etokimab therapy in a larger double blind randomised group of participants with atopic dermatitis due to the previous results being preliminary. Antibody therapies like these have a huge benefit for people struggling with severe conditions such as atopic dermatitis and researchers are hopeful to obtain the most appropriate treatment to improve the patient's quality of life.

About the Author

Chetana Prabhu is a 1st year BSc Pharmacology student interested in neuroscience, genetics and pharmacology.

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SHALLOW DIVE

CAN WE USE ANTIHISTAMINES TO TREAT COVID-19?

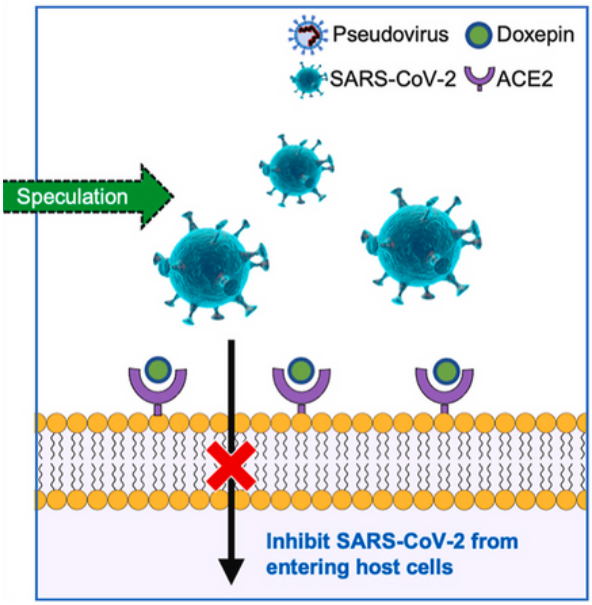
WRITTEN BY FATIMAH PATEL
EDITED BY JABARI LAMBERT

It has been more than a year since the first few COVID-19 cases have been confirmed in China. Ever since, the number of positive cases has grown at an alarming scale to approximately 112 million cases worldwide and has subsequently resulted in the deaths of more than 2.4 million individuals. Research dedicated to control the spread of the virus has been pushed immensely in the scientific community, resulting in the exciting roll out of novel vaccines from Pfizer and AstraZeneca. Alongside this, thousands of drugs already in clinical use are being re-tested to measure their ability to reduce SARS-CoV-2 infection of cells in the human body. One class of drugs that holds such potential are antihistamines, commonly used to treat allergies.

Scientists in China used Cell Membrane Chromatography to investigate if antihistamine drugs can bind to proteins that are vital for virus entry, with the protein in question being ACE-2.

About the Author

Fatimah Patel is a 3rd year BSc Pharmacology student with a strong interest in neuropharmacology.



It has been found that five different H1 antagonist drugs: Doxepin, chlorpheniramine, doxylamine, tripinamin and pyramine, showed interaction with ACE-2. This suggests that antihistamines could have an effect on SARS-CoV-2 cell entry. To see if these drugs can stop SARS-CoV-2 cell infection, the scientists mimicked the infection process of the live virus using a Pseudovirus Neutralisation Assay. An altered form of the SARS-CoV-2 virus was produced, incubated with human cells and one of the aforementioned drugs. It was found that tripinamin and pyramine did not reduce the infection rate too much, hence, these drugs would not be suitable candidates for COVID-19 treatment. However, chloropheniramine, doxylamine and doxepin were much better at reducing infection rates to 56.91%, 56.75% and 25.82% respectively.

Doxepin was the strongest inhibitor for SARS-CoV-2 virus entry which could be due to Doxepin showing better interactions with the ACE-2 protein compared to the other four drugs, which makes it more difficult for SARS-CoV-2 to enter the host cell. Researchers went a step further to see if the dose of doxepin has an effect on its activity, by repeating the Pseudovirus Neutralisation Assay with different doses of Doxepin. The results showed that increasing the dose of Doxepin results in greater inhibition of virus entry.

Repurposing drugs such as antihistamines helps skip the time-consuming drug discovery and development phases, which means we can get quicker clinical treatment for fast-spreading diseases, like COVID-19. Additionally, one of the underlying issues of novel drugs would be that we don't know about any side effects which could potentially harm individuals. With antihistamines currently on the market, their safety has been closely monitored over the years, hence there is greater confidence to prescribe these drugs to children and adults. Although more clinical trials would need to be done to measure how effective H1 antagonists in treating patients with COVID-19, the current study brings hope into using antihistamines to reduce COVID-19 infection.

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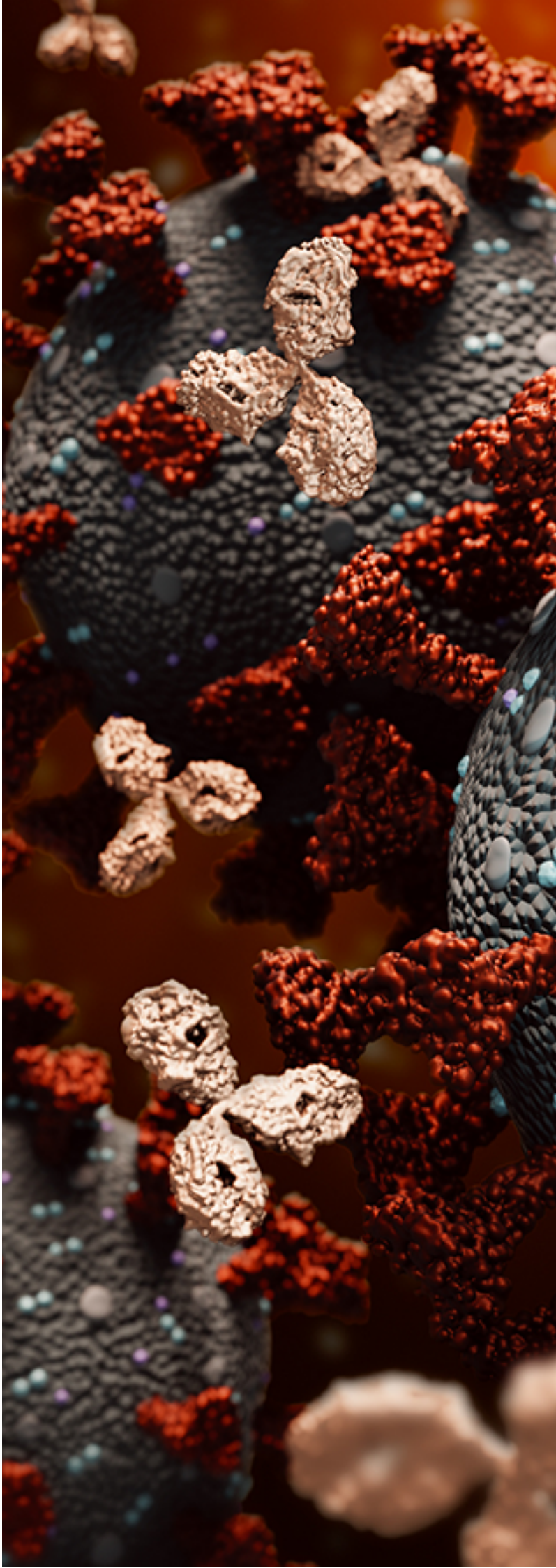

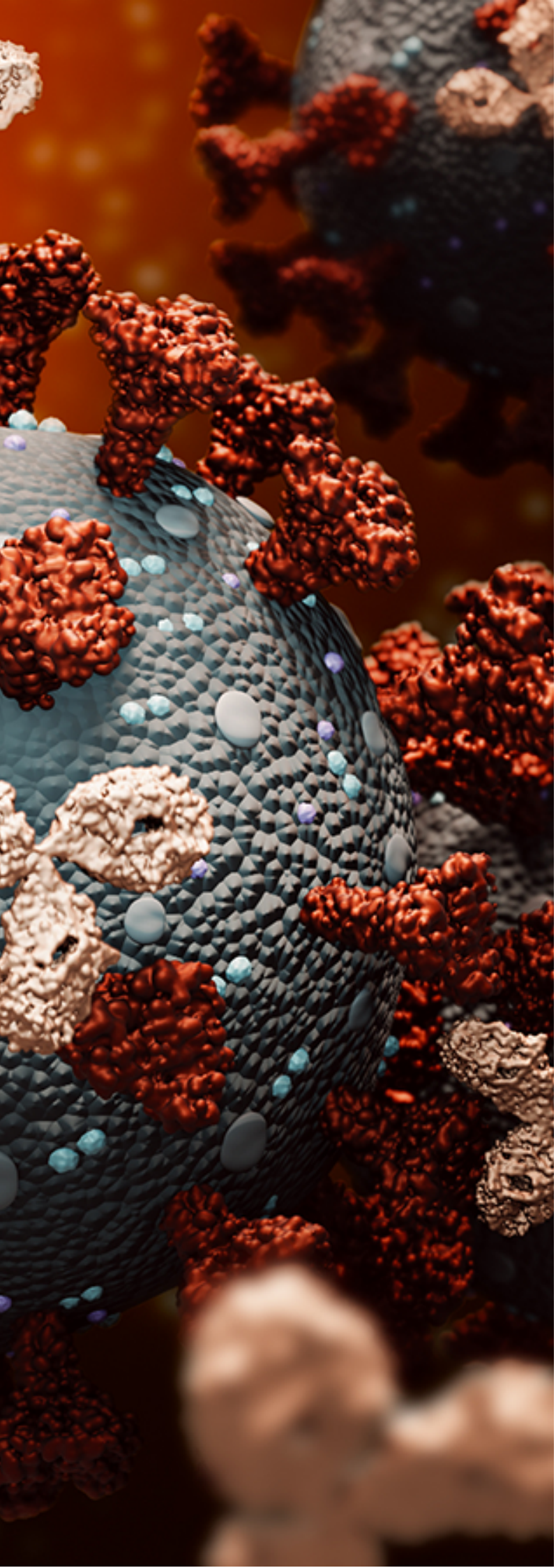

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