ScienceMind

JANUARY 2021

KING'S College LONDON

STAFF

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THIS ISSUE

Dear Reader,

New year, new us! This release marks the expansion of the soon-to-be society to around 18 members and with more members, that means more articles! We have a new section about final year projects so have a read if you're interested in the type of work that final year students do! Also, be sure to read our article featuring Jon Robbins' research and our interview with Honorary Clinical Lecturer Eromona Whiskey from King's College London who were kind enough to give us an insight into their research.

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

CONTENTS

DEEP DIVE

Green tea: A POSSIBLE 'SHIELD' AGAINST HEART DISEASE?

WRITTEN BY ZETA IOANNOU

Green tea is found to contain a chemical compound called Epigallocatechin Gallate (EGCG). The amounts of EGCG contained in green tea however, are not sufficient to induce a pharmacological effect. A higher concentration of EGCG could potentially aid in breaking up hardened plaques in blood vessels, leading to the reduction in the occurrence of heart attacks and even strokes . Recent research has turned its focus on utilising Epigallocatechin Gallate (EGCG) to maximise its cardiac health benefits.

Research has been focusing on altering the chemical structure of EGCG, making it easier for the pharmacokinetic effects to take place (e.g. easier absorption and more resistant to metabolism), as well as finding newer and more innovative methods of delivery (e.g. IV). To understand exactly how EGCG produces its pharmacological effects, we should elaborate on the pathology of the disease it affects.

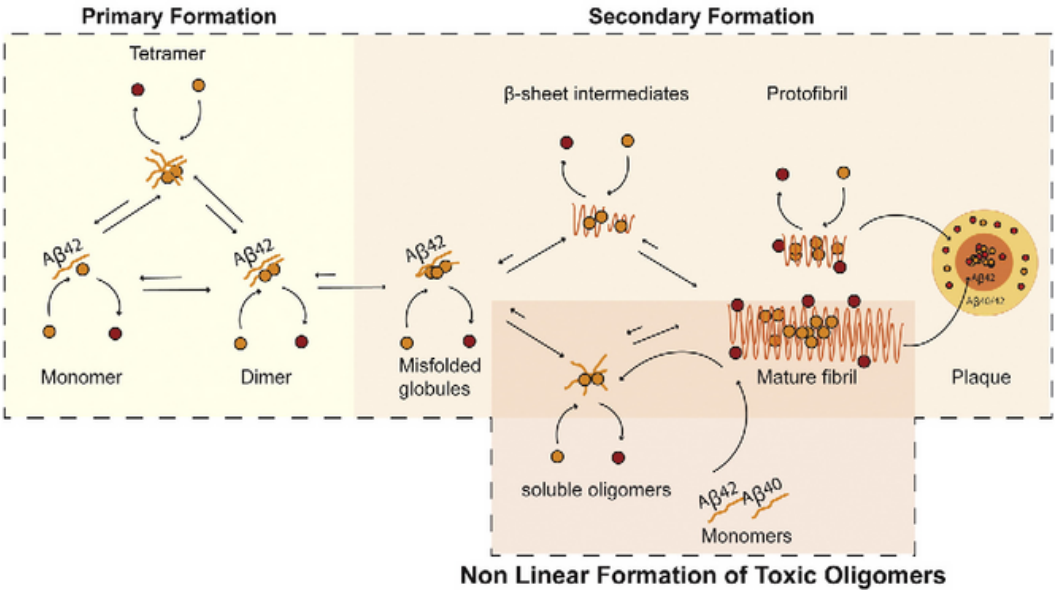

Figure 1. 'The Linear Formation of Amyloid Plaques' (Peters et al., 2015).

Atherosclerosis is the build-up of fatty material inside our arteries that may restrict blood flow to the cardiac muscle and/or the brain leading to heart attacks and strokes. In advanced atherosclerosis, a protein called apolipoprotein A-I (apoA-I) forms amyloid deposits that accumulate within the plaques formed. Amyloid deposits are composed primarily of amyloid fibrils as well as several non-fibrillar constituents such as lipids, proteoglycans, glycosaminoglycans and serum amyloid P component (SAP) (Alexandrescu, 2005; Pepys, 2006). Amyloids develop when proteins lose their native conformation and are primarily converted into a β-sheet form, which increases their proclivity to aggregate. As a result of these amyloid aggregates, the size of the plaques increases, restricting blood flow even further, as well as reducing the stability of the fatty plaques themselves.

This combined effect increases the likelihood of myocardial infarction and stroke.

EGCG binds to the apoA-I amyloid deposits, reducing their size significantly to a form that is less likely to induce blood vessel damage.By using CD analysis, solid-state NMR spectroscopy, and transmission EM, a surprising cooperative effect of heparin and EGCG on apoA-I fibrils has been documented. The fibrils formed in the presence of heparin were remodelled into soluble 20-nm-diameter oligomers with a largely α-helical structure that were more stable and nontoxic to human umbilical artery endothelial cells (Townsend et al., 2018). Human trials however, have not been reached yet and lab derived information has been inconclusive, leaving the science community in a grey area regarding the matter.

Recent research has suggested that the isolated EGCG could be a promising compound upon its successful implementation into medication. It could prove to be very promising in offering new treatments for atherosclerosis, improving people's quality of life via reducing the incidence of cardiovascular failure. Introduction of human clinical trials would investigate this potential further, concluding on the therapeutic use of EGCG.

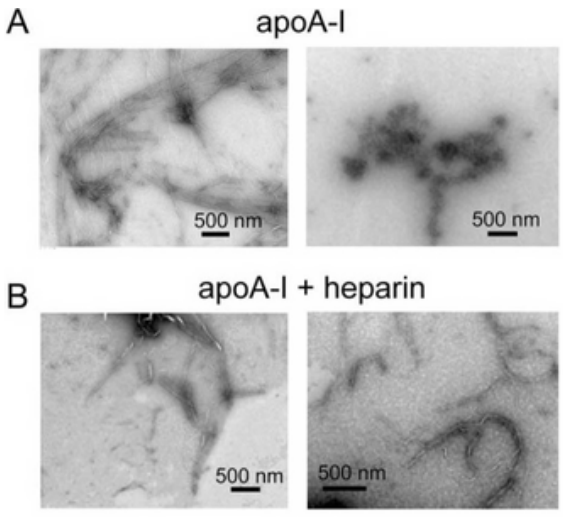

Figure 1. ApoA-I fibril formation in the absence or presence of heparin. A) Negative stain TEM images of apoA-I aggregates formed at pH 4 in the absence of heparin. B) TEM images of apoA-I fibrils formed in the presence of 14–15 kDa of heparin. (Adapted from Townsend et al., 2018).

ABOUT THE AUTHOR

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

KCL PHARMACOLOGY SOCIETY

Welcome Back! We hope you had a lovely break.
Next month we're hosting several exciting events!

5th Feb
Negotiation in the Pharmaceutical Industry
Speaker Panel, a Collab with KCL Negotiation Society

17th Feb 5PM (UK time)
Cooking with Slice!
Interactive cooking class with special guest Sliced_yt, demonstrating simple budget friendly recipes!

22nd Feb 6PM (UK time)
Speed Meeting with Oxford University and St George's University Pharmacology Societies

Check for updates on our socials!

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THREADING WATER

COULD TARGETING BRAIN-DERIVED NEUROTROPHIC FACTOR TREAT DEPRESSION?

WRITTEN BY CHARLINE HENDRICKX

Antidepressants have been around since the 1950s, yet it can take up to four weeks for the current treatments available to exert their therapeutic effects. The monoamine hypothesis, the basis for current antidepressant drugs, states that the aetiology of depression is due to a depletion of monoamines, but it has failed to explain this delayed onset of action and therefore research for novel antidepressants has moved away from the monoamine hypothesis. Studies have accumulated showing that patients suffering from major depressive disorder have a decrease in hippocampus and prefrontal cortex volume due to a decrease in neurogenesis and synaptic plasticity. The chronic stress that occurs in depression can cause these structural changes by diminishing brain-derived neurotrophic factor (BDNF) levels.

It has been observed in animal models of stress and patients suffering with depression that there is indeed a reduction in BDNF levels. Consequently, there has been a surge in research investigating the role of BDNF in the pathophysiology of depression.

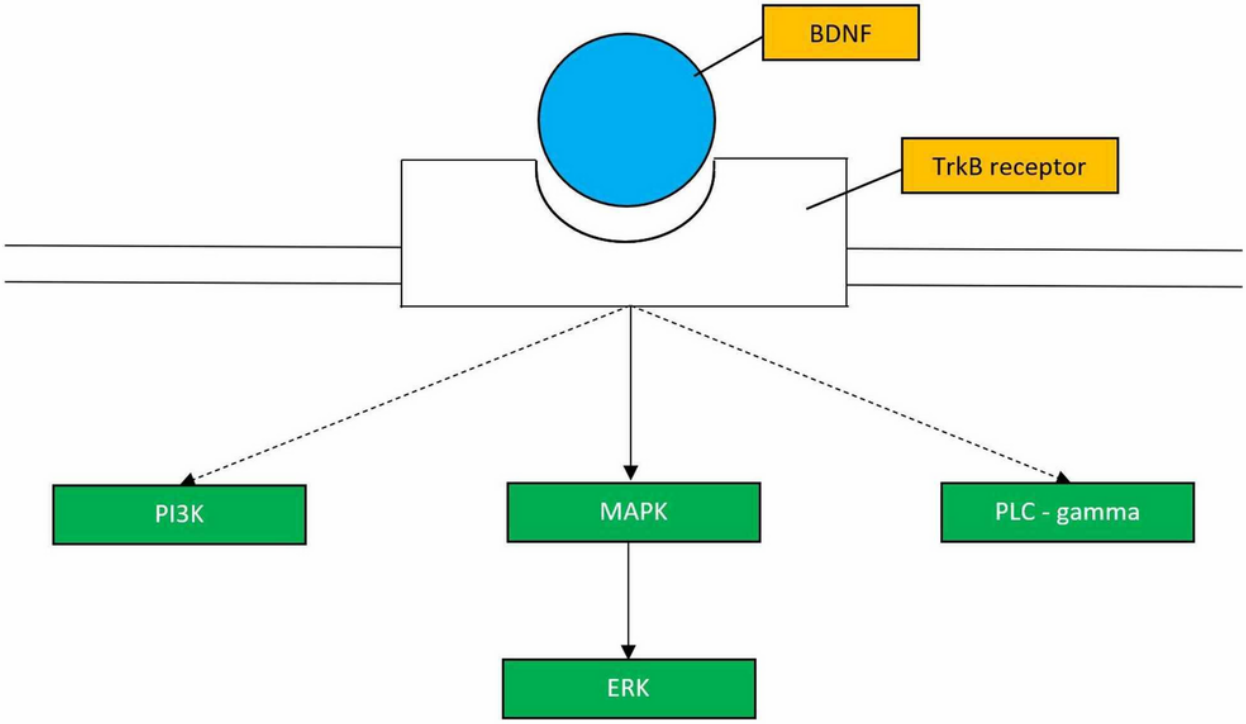
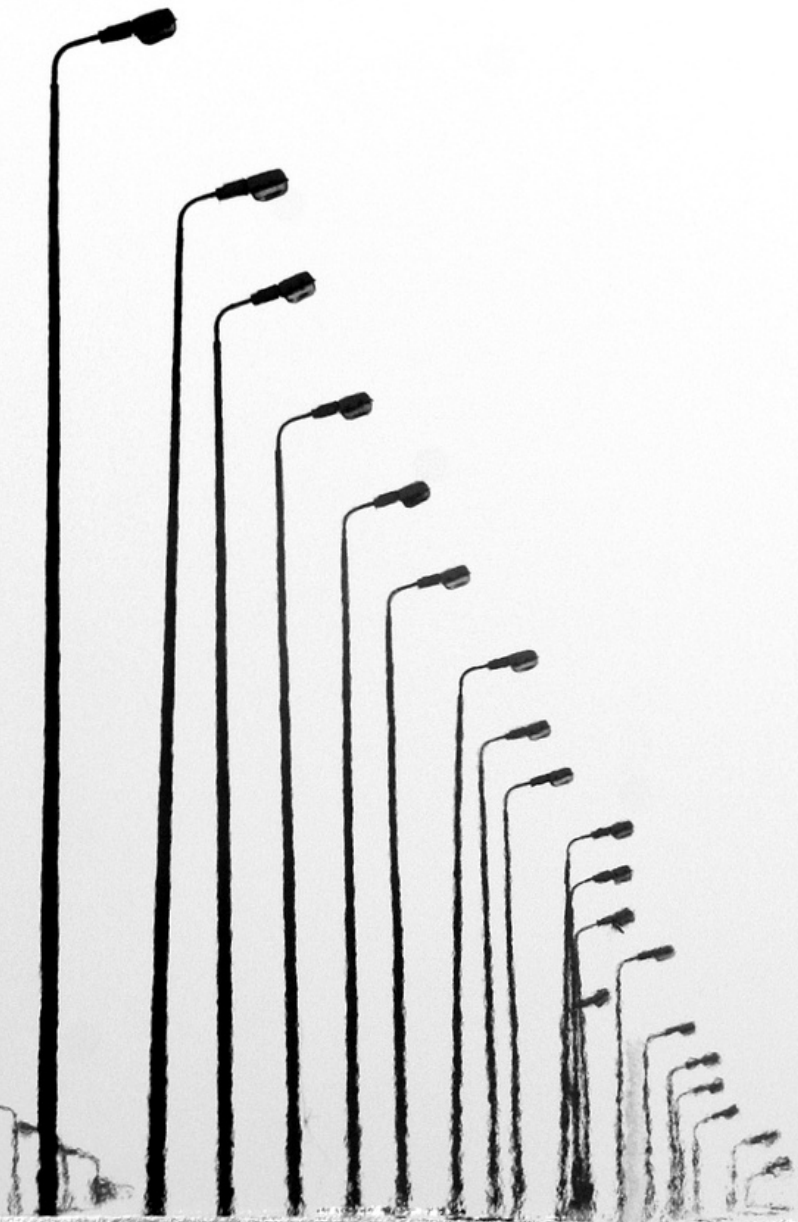


Figure 1. BDNF—brain derived neurotrophic factor, TrkB—tropomyosin receptor kinase B, Pi3k— phosphatidylinositol 3-kinase, MAPK—mitogen-activated protein kinase, ERK— extracellular signal-regulated kinase, PLC-gamma—phospholipase C-gamma



BDNF is a growth factor part of the neurotrophin family that binds to tropomyosin receptor kinase B (TrkB). The binding of BDNF to TrkB initiates the activation of several signalling pathways that lead to an enhancement of neurogenesis and neuroplastic actions important for the improvements of depressive symptoms. A decrease in BDNF can therefore result in glial and neuronal loss and diminished neurogenesis in the hippocampus and prefrontal cortex. When antidepressants were understood to produce their therapeutic effects through initiation of neurogenesis, it was investigated whether BDNF was necessary for these effects to occur.

Studies were conducted to investigate this with mice lacking BDNF, and indeed, without BDNF, neurogenesis was unable to occur. It was investigated further in mice without TrkB in hippocampal neural progenitor cells, and again, without this receptor, there was no evidence of antidepressant effects. Therefore, BDNF is necessary to initiate neurogenesis and bring about the therapeutic effects of antidepressants. It has also been postulated that a possible explanation for the delayed action of antidepressants is due to the time it takes for the drug to initiate neurogenesis with a slow release of BDNF.

Along with neurogenesis, BDNF is involved in the capacity of neurons to initiate synaptogenesis which is crucial for synaptic plasticity. Synaptic plasticity and synaptogenesis signify the changes that occur intracellularly as a result of synaptic activity and is key for adaptive changes. BDNF's role in its contribution to synaptogenesis has been studied in mice using a mutation in the BDNF gene. It has been shown that administering the antidepressant fluoxetine in these mutant mice fails to express an antidepressive response, which suggests an inability to stimulate synaptic plasticity. These studies have allowed a better understanding of how antidepressants produce their beneficial effects and how BDNF stimulating neurogenesis and improving synaptic plasticity is chief.

These findings have had insightful implications in the treatment of depression, directing research towards a BDNF analogue that can produce these neurogenesis and synaptic plasticity changes in the regions of the brain affected by chronic stress to produce rapid antidepressants.

ABOUT THE AUTHOR

Charline Hendrickx is a 3rd year BSc Pharmacology student with an interest in oncology and depression in neuropharmacology.

STUDENTS FOR SENSIBLE DRUG POLICY KING'S COLLEGE LONDON

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SHALLOW DIVE

HOW DO WEIGHT-LOSS SURGERIES REGULATE TYPE II DIABETES?

WRITTEN BY SOUMIYA DRIR SADAOUI

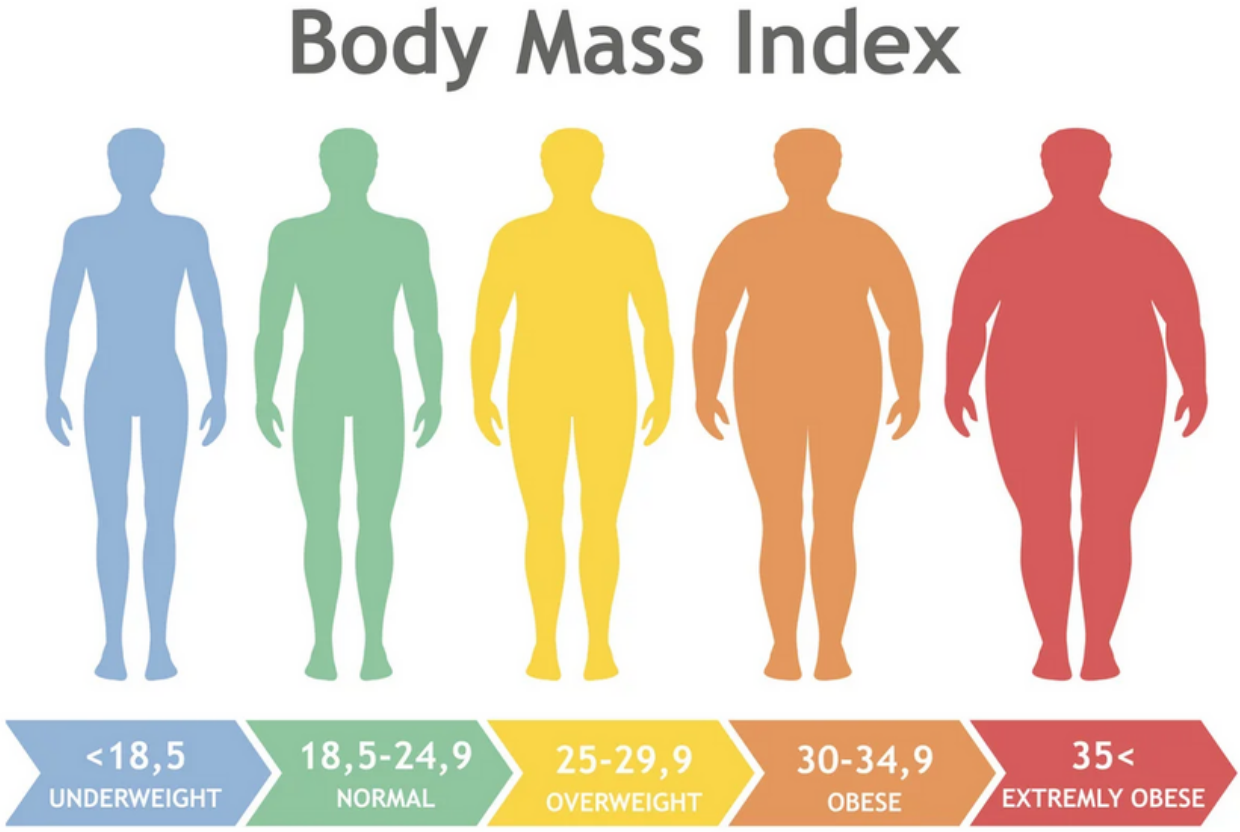

Figure 1. Body Mass Index (BMI) scale in kg/m2. Source: Dr Melvin Look (Mount Elizabeth Hospital).

Diabetes is known to be a chronic condition that is characterised by elevated blood sugar levels. According to the International Diabetes Federation it accounts for over 460 million cases worldwide. Weight-loss surgeries, also known as bariatric surgery, such as gastric bypass, are lately being considered as an effective treatment for people who have type II Diabetes.

However, follow-up data after surgery in diabetic patients is limited, and for this reason, the prevalence of Diabetes relapse is still unknown. An essential factor to consider is that 90% of type II diabetic patients are overweight ([BMI]> 25 kg/m2) or obese ([BMI]> 30 kg/m2). Obesity increases their difficulty maintaining normal blood glucose levels due to insulin resistance.

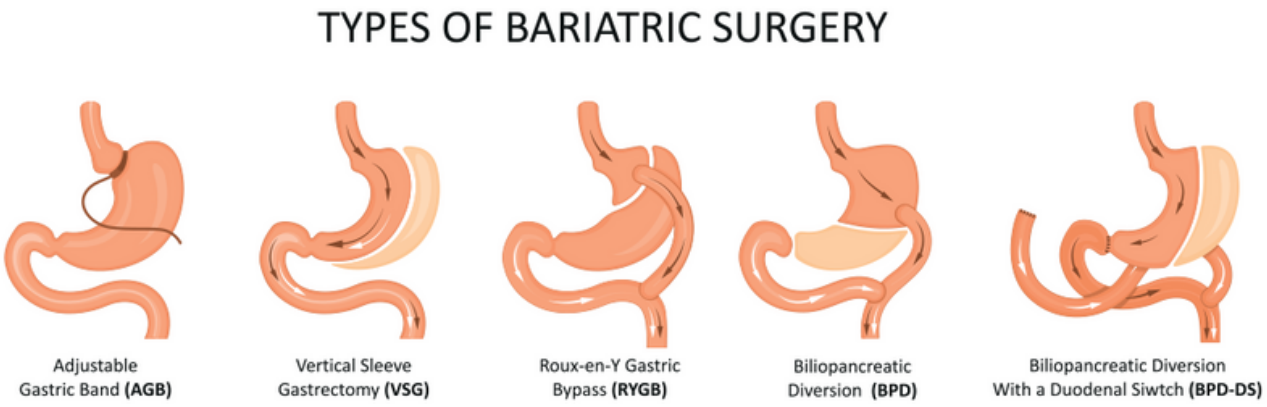

Figure 2. Schematic showing the types of bariatric surgery.

In most cases, it is not enough to treat patients with intensive lifestyle changes, such as diet or exercise. Bariatric surgery provides a significant improvement in normalizing glucose levels for patients, although there can be a relapse of type II diabetes 3 to 15 years post-surgery in 30% to 50% of patients. Type II diabetes relapse usually requires lower-dose medicines to treat it, which is most beneficial for patients as it improves their life-quality.

As with all surgeries or medical treatments, weight-loss surgeries are associated with a very low mortality-risk of less than 1%. With a frequency ranging from 7.8% to 12% regarding acute surgical complications such as bleeding, vomiting, or lack of minerals and vitamins. If patients develop severe conditions such as anaemia after surgery, they will require lifelong monitoring by healthcare professionals.

Overall, bariatric surgery can improve blood glucose levels by food intake restriction and food-hormones action, which are ligated to the reduction in food intake. Future studies are needed to clarify whether bariatric surgery provides an effective medical cure for people who have type II diabetes. Currently, there is a lack of long-term data. However, advanced electronic medical recording systems may allow long-term data collection for patients who undergo weight-loss surgeries for the post-surgery stage.

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

SHALLOW DIVE

Clozapine Dilemma: Why is One of the Most Promising Antipsychotic Drugs being Underprescribed?

MR EROMONA WHISKEY TALKS CLOZAPINE AND PSYCHOPHARMACOLOGY WITH PETR BORODAVKIN

"If I knew exactly how clozapine works, I would be getting the Nobel Prize!"

MR EROMONA WHISKEY

ISSUE 4 | 2021

Eromona Whiskey is a Consultant Pharmacist at the Trust and an honorary Clinical Lecturer at Kings College London Institute of Pharmaceutical Sciences. His research interest is the treatment of refractory psychotic disorders.

Psychosis is a syndrome that makes a person lose touch with reality, with the main symptoms being hallucinations and delusions. The following may alter perception of one's surrounding world and result in a severe decline in the quality of life. Although affecting only 1% of the UK population psychosis is also a marker of mental disorders such as schizophrenia and bipolar disorder, of which the latter has been diagnosed in 1.4 million UK residents alone. More importantly, the exact causal physio- and neurological mechanisms of psychosis are not fully known, which manifested itself in a large proportion of patients unable to respond to currently existing antipsychotic drugs, reaching almost 40% for patients suffering from schizophrenia.

Mr. Eromona Whiskey is at the heart of the research group at King's College London, which investigates the management and treatment of treatment-resistant psychosis. Over the past couple of years, their work has been in the centre of attention of patients and academics both in the UK and worldwide. **"We see a lot of different patients, sometimes even from abroad. In most cases the patients have tried three types of antipsychotic drugs without any success"** he says.

The reason for such enthusiasm is an antipsychotic drug called clozapine, which appears to alleviate psychotic symptoms even in severe cases, when no other drug was able to do the same. **"In my experience, we see improvements in nearly half of the patients"** says Mr. Whiskey, further explaining that clozapine's potential has been well known in academia for a long time: **"A trial in 1988 showed that clozapine is 30% more effective [in reducing symptoms of treatment resistant schizophrenia] than chlorpromazine [commonly used antipsychotic drug]".** This begs the question why the substance with such high therapeutic potential as clozapine has been neglected by psychiatrists over the last 30 years instead of entering directly onto the frontier of the combat against psychosis and schizophrenia.

"It all comes from its' side effect profile. When clozapine was just put on the market, people had complications like neutropenia and agranulocytosis, which weakened their immune system and 50 patients died as a result, so it was removed from the market immediately" explains Mr. Whiskey.

Fast forward 3 decades, the impact of this notorious tragedy has mapped right onto the prescription rates of clozapine, despite the novel methods of ensuring that the drug does patients no harm. The most recent data report suggests that clozapine is still being severely under prescribed in the UK, with only 40% of patients having access to the drug in some areas of the country.

Mr Whiskey, however, thinks that such reluctant prescribing pattern is understandable given how much is still unknown about the drugs' pharmacodynamic profile: **"If I knew exactly how clozapine works, I would be getting the Nobel Prize!"** he laughs. **"The main hurdle are the effects on the white blood cells, so blood tests have to be done every day for the first couple of months [of treatment] to make sure they are under control, so psychiatrists go for other drugs because it's easier [to monitor their side effects]".** Besides this, Mr. Whiskey explains there are also other contributing factors at play, which are often overlooked by prescribing specialists. An example would be benign ethnic neutropenia- a condition, in which the number of neutrophils in the blood is lower due to the ethnicity of the patient, while the threshold for the clozapine prescription does not account for this difference, further minimizing the number of people, who are able to benefit from the drug.

On the other hand, Mr. Whiskeys' group has been approaching this issue with extreme caution and claim to have developed succinct methodology to use clozapine safely: **"We process the cases on an individual basis and look at the blood tests of every patient before and during treatment. The cardiologists and psychiatrists on our team have decades of experience with the drug and managing its side-effects and [they] know how to proceed. If neutropenia or agranulocytosis happens, then they always have compounds like granulocyte colony-stimulating factor that they can administer to the patient to eliminate the risk of serious side effects".**

Despite the observed under-prescription of clozapine amongst the psychiatrists in the UK and worldwide, academics are optimistic about the prospects of the future use of the drug and claim that it all comes down to experience and awareness, which can be developed by collaboration between the fields. In fact, the latest research outputs by Mr. Whiskey and his group suggest that the better understanding of the clinical nature of treatment resistant psychosis is key to ensuring the wellbeing of patients burdened with the condition: **"Over the past 20 years, we have discovered a lot about where the treatment resistance comes from. Four out of five patients we have are successfully put on clozapine and almost half of them did not respond to clozapine before."** concluded Mr. Whiskey, as he supported the notion that specialist training could tremendously bolster their confidence to prescribe and monitor the wellbeing of their patients: **"We have been organizing training and support hubs for specialists across the country and got a lot of positive responses. I believe that education is the most important thing that will give them [the clinical psychiatrists] confidence and use clozapine more often."**

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BRITISH PHARMACOLOGICAL SOCIETY

DEEP DIVE

WHY DOES THRUSH ITCH?

BY SEAN CRAWFORD, BASED ON FINAL YEAR BSC RESEARCH PROJECT WITH DR JON ROBBINS.

Research from KCL shows that a toxin produced by the thrush causing fungus: C.albicans can act on neuronal cells. This discovery suggests the toxin, named Candidalysin, might act on sensory neurons or nerves to activate the nervous system which could be how thrush causes its troublesome symptoms. Until now, there was no suggestion as to how the common fungal infection caused symptoms.

Thrush is the common name for candidiasis, a fungal infection affecting the vaginal and oral mucosa caused mainly by the yeast-like organism Candida Albicans. Presentation of the disease consists of soft white plaques which are associated with itching, irritation, soreness and burning. C.albicans is usually a commensurable organism which resides on the skin, the genitourinary and gastrointestinal tracts. Up to 60-80% of people are asymptomatic carriers.

As a single celled yeast C.albicans doesn't cause any harm. However, in response to changes in the local environment the dimorphic fungi can switch to their hyphal forming, disease causing state. This can occur when the immune response and the microbiome become disrupted and no longer hold C.albicans growth in check. Hypha are filaments used by fungi to scavenge for nutrients in their environment. They are the root like structures seen when a mushroom is pulled up and make up the 'fluff' seen when mould is growing on food.

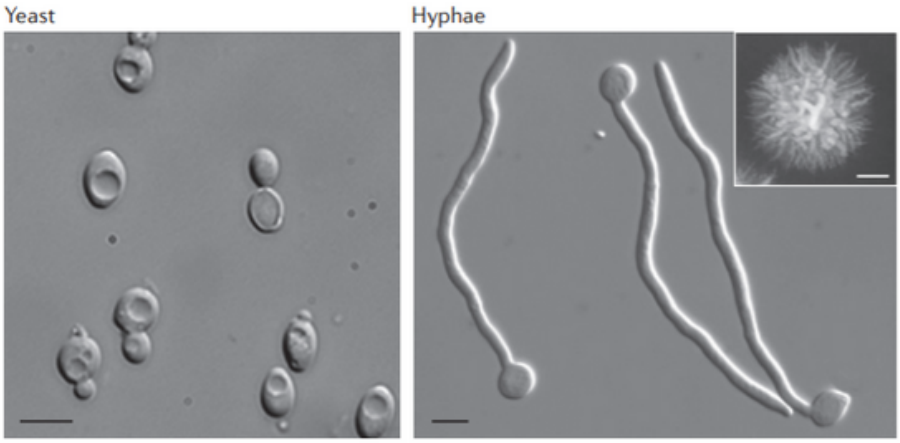
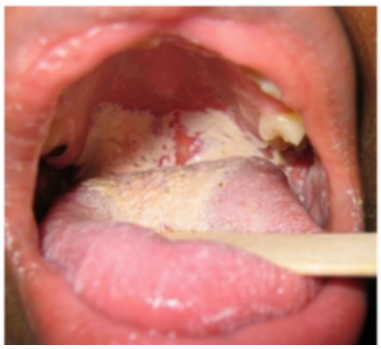


Figure 2. Scan depicting the morphology of yeast compared with hyphae.

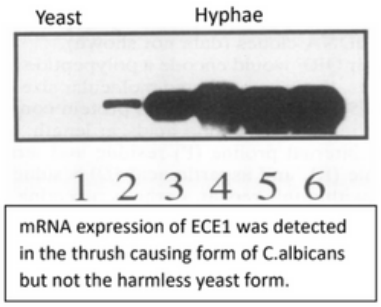
Vulvovaginal candidiasis, also known as vaginal thrush or a yeast infection, is the most common form of thrush. It affects 3 out of 4 women at least once in their lifetime with 5% of women experiencing recurring thrush when use of an antifungal pessary or cream is ceased after 2 weeks. The white patches of thrush infection are associated with intense itching and a white discharge from the vagina resembling cottage cheese is common. Whilst superficial, thrush can lead to time off work or study and recurring infection can provoke anxiety and depression. Changes in the menstrual cycle and alteration of the microbiome by antibiotics are likely causes. While not an STD, a change of sexual partner or receiving oral sex can alter the microbiome and provoke presentation of a thrush infection.



Despite C.albicans residing in the mouths of up to 80% of people, oropharyngeal candidiasis or oral thrush tends to only arise in those who are immunocompromised. The condition was accurately termed a 'disease of the diseased' by Hippocrates for this reason. The condition presents in around 1 in 5 cancer patients receiving chemotherapy, individuals whose HIV infection is progressing to AIDs and those on long term immunosuppressant therapy. Oral thrush in children strongly suggests a genetic immunodeficiency. Presentation consists of soft white plaques on the tongue, palate and buccal mucosa. Bleeding from dislodged thrush plaques can leave a bad taste which can make eating uncomfortable. Oral thrush plaques are associated with soreness, burning and sometimes pain.

The Action of Candidalysin Toxin Could Explain How Thrush Causes Symptoms.

In 1993, scientists at the University of California found that a particular gene is expressed in the hyphal, thrush causing form of C.albicans but not the harmless yeast like form. The gene was termed Extent of Cell Elongation or ECE1 because of its strong association with cell elongation/hypha formation. The scientists were intrigued that when the ECE1 gene was knocked out hypha formation was unaffected. This suggested that the gene contributed to causing disease in some other way than forming thrush hyphae.



mRNA expression of ECE1 was detected in the thrush causing form of C.albicans but not the harmless yeast form.

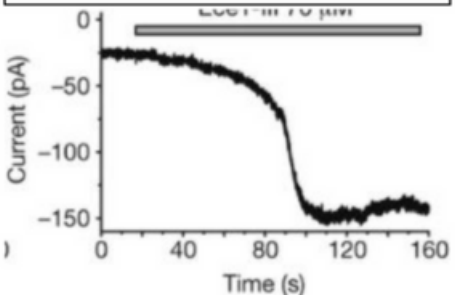
The study was the first to reveal the existence of a virulence factor of fungal origin. Virulence factors are peptides secreted or wielded by bacteria or viruses to specifically colonise and damage human cells and enable the pathogen's growth and reproduction.

The study was the first to reveal the existence of a virulence factor of fungal origin. Virulence factors are peptides secreted or wielded by bacteria or viruses to specifically colonise and damage human cells and enable the pathogen's growth and reproduction.

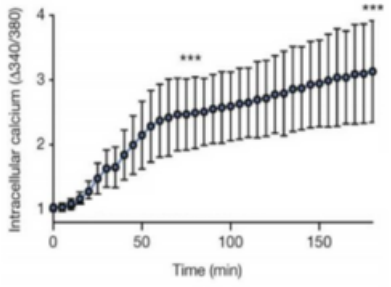
Key Discoveries were:

1. Liquid chromatography – mass spectroscopy revealed C.albicans secretes a particular peptide (candidalysin) in the presence of epithelial cells. The peptide secretion was dependent on the ECE1 gene being intact.

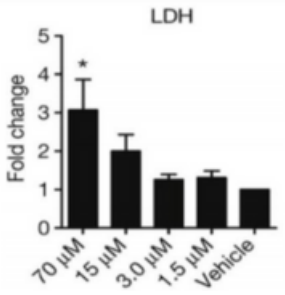
2. Incubation of oral epithelial cells with the secreted peptide was associated with charge influx.



3. Charge influx was associated with a rise in intracellular calcium.



4. As well as leakage of the intracellular enzyme LDH out of the cells.

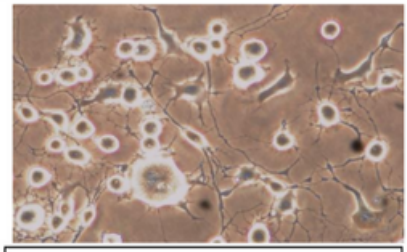


The entry of charge associated with calcium influx as well as the release of a cellular enzyme suggested that the peptide produced by C.albicans causes generalised membrane permeabilization resulting in cytolysis. Candidalysin as a peptide toxin is 31 amino acids long with a-helical structure, with hydrophobic and hydrophilic components. These physical properties are similar to melittin toxin, a pore forming toxin which is the major active component of honey bee venom. Damage to epithelial cells through candidalysin mediated membrane permeabilization appeared to be essential for the fungus to infect mucosal surfaces. C.albicans with the candidalysin encoding ECE1 gene knocked out failed to colonise mouse tongue mucosa. It is likely candidalysin must first damage the epithelial barrier for C.albicans hyphae to penetrate the mucosa and the white plaques of thrush to present.

Candidalysin also permeabilises neuronal cells and could activate sensory neurons to cause symptoms

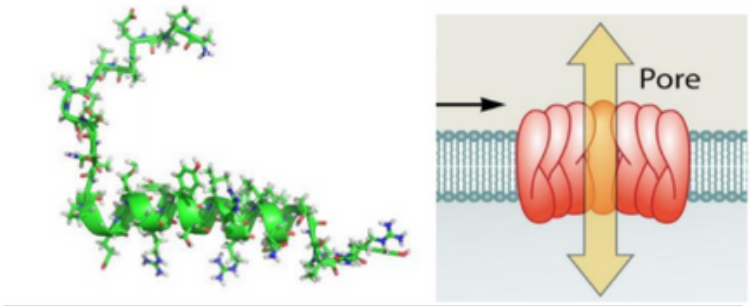
While the 2016 study showed that the secreted peptide toxin and its associated damage to the epithelial barrier was essential for the visible manifestations of thrush to present, it did not account for the symptoms experienced by those with a thrush infection. Itching and burning suggest the nervous system might be involved.

In 2020 researchers at KCL decided to investigate the possibility that candidalysin might act directly on sensory neurons to activate the nervous system. Researchers wanted to test if the effect of candidalysin was due to a special interaction with epithelial cells or if candidalysin does more generally permeabilise cell membranes. As it was still unknown how thrush causes symptoms it was decided that candidalysin should be tested for an effect on neuronal cells. The researchers set out to observe the effect of candidalysin on the concentration of calcium ions in the cytoplasm of neuronal cells.



NG108-15 neuronal cells. For scale, the diameter of the largest cell is about 50µm or 0.05mm.

The scientists at KCL obtained neuronal cells from an immortal tumour cell line. The non-specialised cells were differentiated to cells resembling neurons, with fine and long axonal processes. This source avoided sacrificing an animal unnecessarily. The neuronal cells were then incubated with a fluorescent dye called Indo-1 that binds free calcium ions in the cytosol. Changes in cytosolic calcium was measured by the amount of Indo-1 fluorescence recorded under a fluorescent microscope and relayed to a computer.



Candidalysin toxin has distinctive a-helical or corkscrew structure. This structure allows toxin molecules to congregate in cell membranes and form a channel. Candidalysin closely resembles melittin toxin found in bee venom which definitely acts on sensory neurons!

Cytosolic calcium was recorded in neuronal cells before and after the application of candidalysin. Some of the cells were bathed in calcium containing buffer to see if candidalysin promotes calcium influx into the cell while other cells were bathed in a calcium free buffer to see if candidalysin promotes release of calcium from intracellular stores such as the endoplasmic reticulum. KCL scientists discovered that the candidalysin thrush toxin was able to significantly increase the concentration of calcium ions in the cytosol of neuronal cells. However, the toxin was only able to do this when calcium was present in the extracellular environment. This provides further evidence for candidalysin acting to permeabilise the plasma membrane, rather than toxin action inside human cells. As candidalysin has been shown to affect epithelial cells and now neuronal cells it is unlikely the toxin requires a special receptor to cause its effect but rather has a general pore forming action.

As the data from KCL scientists shows that candidalysin also affects neuronal cell types it is plausible that candidalysin would also activate sensory neurons in the vicinity of a thrush infection. A therapeutic that inactivates the candidalysin toxin or protects neuronal cells from its effect could be investigated for potential symptomatic relief of thrush infection. This has the potential to improve the wellbeing of most women at some point in their lives while also bringing relief to those who are the most medically vulnerable.

ABOUT THE AUTHOR

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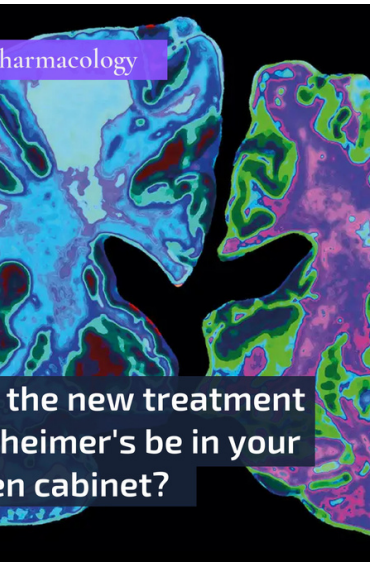
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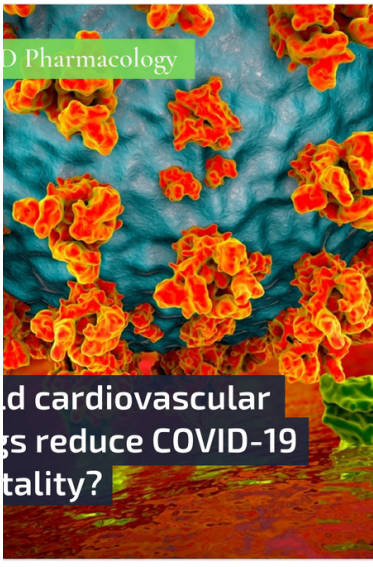
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DEEP DIVE

WRITTEN BY AAIMAN BHARMAL & ZAHRAA BHATTI

THE TRENDING NANO-SIZED DRUG DELIVERY SYSTEM: LIPOSOMES

Anti-cancer drugs are cytotoxic, indiscriminately harming both healthy and tumour cells and have poor bioavailability at tumour sites. The numerous side effects and the high doses required to reduce tumour growth stimulated the development of nano-carriers for the medication which can be used to target actively or passively to the affected tissue. One such nano-sized drug delivery system is the liposome. Liposomes are artificially designed vesicles and consist of phospholipid bilayers (lamella) that can be unilamellar or multilamellar. The core of the lamella is formed of hydrocarbon tails making it hydrophobic and can be used to carry hydrophobic drugs. The hydrophilic head groups which line the surface of the liposome allow them to solubilise and travel in the aqueous environment of the blood plasma. The charge density of the polar heads can be varied by varying the lipid composition for lamellar stability under physiological conditions. Most of the approved formulations use phosphatidylcholine, phosphatidylglycerol, phosphatidic acid and phosphatidylserine. Cholesterol is added to regulate the fluidity and diameter of the lamella in order to prevent drug leakage.

Liposome Formation

The size, shape and stability of the liposome determines which method of preparation to use. The most common method is solvent removal. First, the lipids are dissolved in a solvent, either methanol or chloroform. The solvent is then removed via rotary evaporation. This produces a thin film of lipids, which is dehydrated, followed by rehydration. This method gives rise to multilamellar vesicles, which are cleaved into small unilamellar vesicles by sonication. The size of the small unilamellar vesicles depends on its lipid composition, as well as the sonication, time and energy. Other methods of liposome preparation include detergent removal, emulsion removal, ethanol injection, etc.

Pharmacokinetics

The concept of using liposomes to deliver the drug depends on their accumulation at the site of action. This requires a longer circulating time and a lower clearance rate. The size of the liposomes are 50-200 nm so they cannot penetrate through normal vasculature which has pore sizes of 40-60 nm.

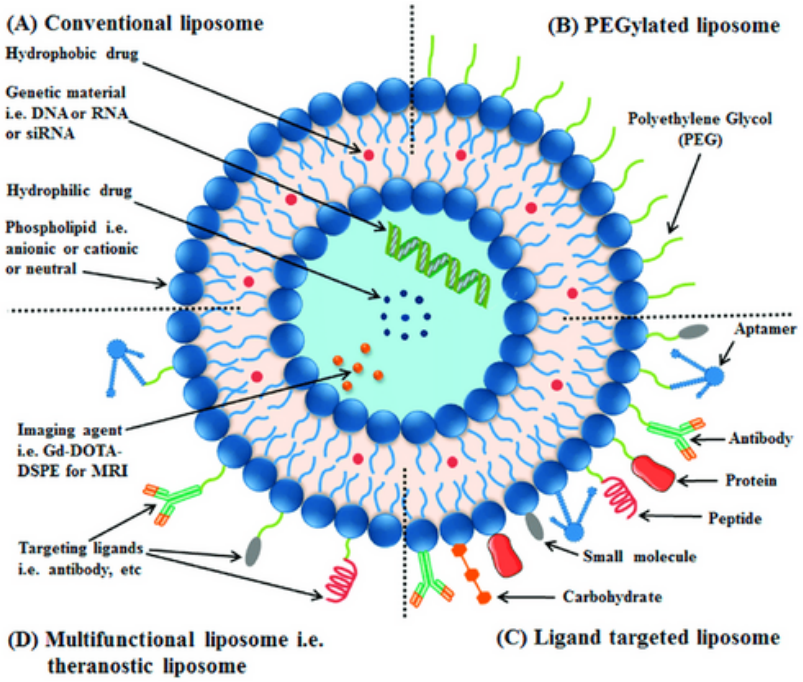


Figure 1. Structure of a conventional liposome (A). Hydrophobic drugs are surrounded by the hydrophobic fatty acid tails. Hydrophilic drug embedded within the hydrophilic centre.Structure of a PEGylated liposome (B). Liposome is modified by containing an outer layer of polyethylene glycol.Structure of ligand targeted liposome (C).Structure of a multifunctional liposome (D).

The exceptions to this are hepatic and splenic vasculature (the reticuloendothelial system) with large pores (150 nm in size) through which liposomes can be cleared from the bloodstream and engulfed by macrophages. To evade clearance, the liposomes are coated with polyethylene glycol which increases the circulation time.

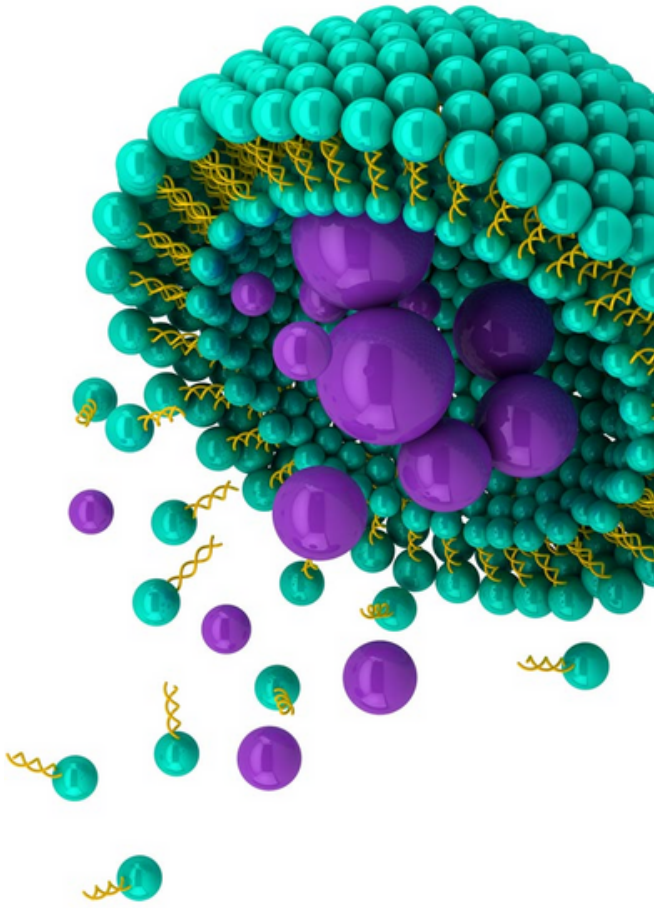
Tumour microvasculature has an additional feature called the enhanced permeability and retention effect (EPR). The pore size of the capillaries supplying blood to tumour cells are much larger than the tighter formations in the normal capillaries. Hence, more fluids can leak out and large liposomes can be administered, leading to their accumulation at the tumour site. Due to the reduced fluid drainage into lymphatic vessels, the liposomes can be retained at the tumour site.

Liposomes can also be actively accumulated at target sites by attaching antibodies specific to antigens on the tumour cells. These are called polyethylene glycol coated immunoliposomes. The subsequent antigen-antibody reaction will help "dock" the drug containing liposomes onto the surface of the tumour cell and release the encapsulated drug to kill the tumour cell. For example, in the case of breast cancer, the growth factor IL-6 is overexpressed. Diacerien encapsulated liposomes embedded with Tyr-3-octreotide are used to bind to IL-6 on the tumour cells. The effect is increased cleavage of enzymes Caspase 3 and poly ADP ribose polymerase leading to subsequent reduction in angiogenesis (formation of new capillary beds) and tumour cell proliferation.

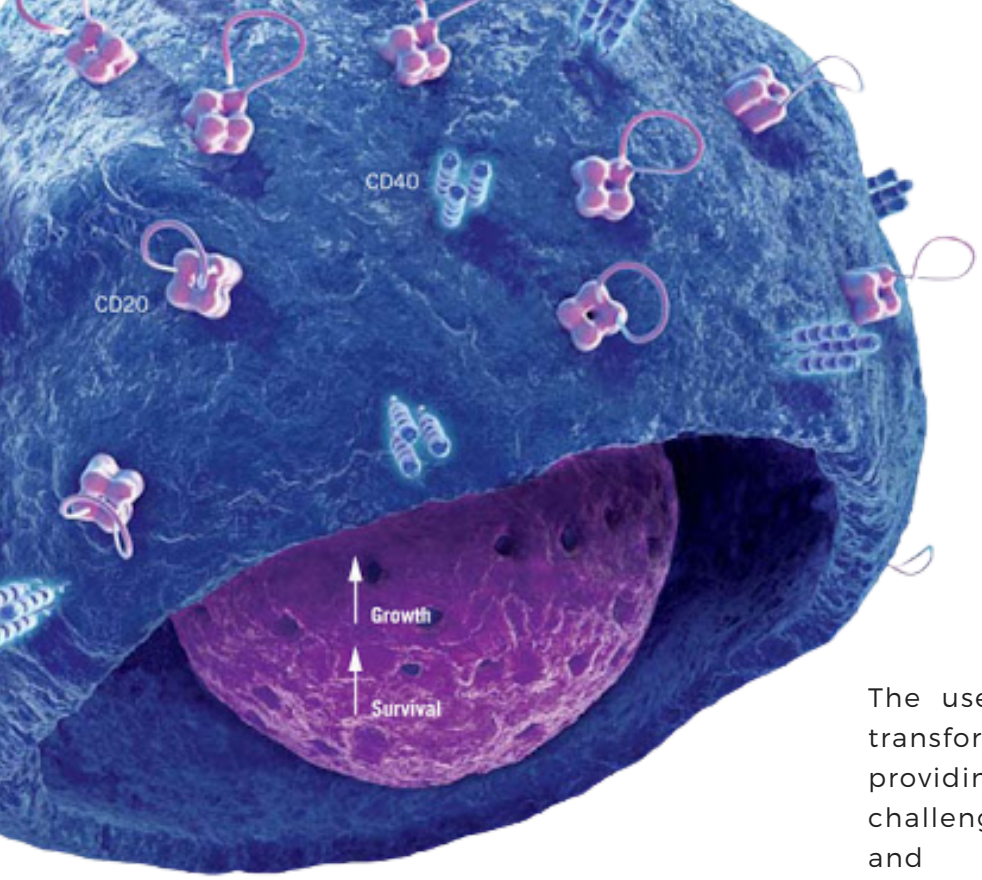
How are the drugs released?

Furthermore, liposomes can be designed to release drugs in response to environmental stimuli. The stimuli can be either endogenous by enzymes or acidic pH, or exogenous by heat treatment. Magnetic liposome-mediated unit chemotherapy has a self-controlled hyperthermia effect. For example the anti-cancer drug Placlitaxel is encapsulated in liposomes which are coated with dextran and biphasic suspension of La3SrMn4O12 (LSMO) and iron oxide nanoparticles. The in-vivo results showed a 2.5-fold decrease in tumour size after a single dose.

The formulation- Doxil also follows this approach. It is used to treat colorectal cancer where the drug doxorubicin (dox) was loaded onto magnetic citric acid coated liposomes. The PEGylated liposome offered a combination of drug release by hyperthermia at the tumour leading to chemotherapy, killing 56% of tumour cells. Doxil was also approved for AIDS-related Kaposis's sarcoma with a lamellar composition of DSPE-PEG200, hydrogenated soy phosphatidylcholine, cholesterol and in a ratio of 5.3 : 56.4 : 38.3. The release of drug in this case is mediated by a transmembrane gradient of ammonium sulphate and has a high melting point so the drug will only leak out at the tumour sites which are exogenously stimulated to be at increased concentration.



Liposomes can also be made responsive to high concentrations of extracellular enzymes present at the tumour site. These can include phospholipase A2, matrix metalloproteinase (MMP), urokinase plasminogen activator and elastase. For example, in the case of phospholipase A2 hydrolyses phospholipids leading to dissociation of the liposome subsequently releasing the anti-cancer drug. Liposomes can also be designed to have MMP sensitive peptides which act as linkers between anti-uptake polymer and lamellar lipids. Cleavage of the peptide by MMP will lead to detachment of the polymer and the liposome can then be engulfed by the tumour cell leading to necrosis.



Other Anticancer Drugs

There's ongoing research for the use of liposomes in cancer immunotherapy, by activating a humoral or cellular immune response. The design of liposome-based antigen delivery systems can improve antibody delivery to antigen presenting cells (specifically dendritic cells) or T cells, which was a previous challenge in cancer immunotherapy. The liposomes' surface can be modified by pH-sensitive materials to allow cytoplasmic delivery of the antigen. The liposome fuses with endosomal or lysosomal membranes, introducing the antigen into the dendritic cells' cytosol. The pH-sensitive material impairs the lipid bilayer, so the liposome can successfully undergo cytoplasmic delivery to activate a cellular immune response.

Conclusion

The use of liposomes has radically transformed cancer therapy by providing solutions for previous challenges involving chemotherapy and immunotherapy. By understanding the action of this nanotechnology, side effects can be minimised, thus improving patients' quality of life. The continuous research of liposomes can be potentially used in cancer immunotherapy by vaccination.

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SHALLOW DIVE

COULD CHINESE HERBAL MEDICINES CURE COVID-19?

WRITTEN BY RACHEL BRADY

In the wake of the global coronavirus pandemic, scientists have endeavoured to find novel therapies to treat COVID-19. The Chinese government heavily endorsed the use of traditional Chinese medicine (TCM) in hospitals to treat COVID-19, and surprisingly, data shows that up to 70,000 patients administered TCM recovered from COVID-19. Naturally, without evidence of its efficacy or safety profile, western medics are unlikely to endorse TCM for COVID-19 treatment. A new study used network pharmacology to identify the mechanism by which the compounds found in herbal medicines treat COVID-19. TCM involves a range of treatment including herbal remedies, tai chi and acupuncture. Unlike TCM, western drugs have a single active ingredient that targets a specific pathway to eliminate the disease's effect.

In contrast, Chinese herbal remedies comprise a wide range of ingredients; some are inactive, while others may counteract beneficial ingredients. Supporters of herbal remedies suggest that more complex disease states cannot be treated using a single active ingredient to target a single disease pathway, as complex diseases involve a series of pathways. The herbal lung cleaning and toxicity excluding (LCTE) soup is one of the many treatments used by Chinese medics to treat COVID-19 and was of interest to the scientists in this study.

Scientists refined the list of LCTE ingredients to eliminate those that were not water-soluble or orally active. LCTE is first boiled then administered orally to patients, therefore compounds insoluble in either the mouth or water would be useless.

Computer analysis of the compounds showed that only 10% of LCTE ingredients were orally active and water-soluble. Raw gypsum is a key ingredient found in LCTE, which reduces body temperature and inflammation by downregulating interleukin 1 beta: an inflammatory cytokine. Kaempferol and quercetin were found in many of the plants used to make LCTE and were two of the most prevalent compounds. Scientists believe these compounds inhibit papain-like protease and 3C-like protease; two enzymes that are integral to SARS-CoV-2 replication.

The scientists then used network pharmacology to identify the compounds found in LCTE that may be responsible for symptomatic relief of COVID-19. The basis of network pharmacology relies on the idea that "the effects of a drug containing multiple active ingredients can be predicted by a network of constructed linkages between multiple components and their targets" (Zhang et al., 2020).

Network pharmacology identified the essential compounds found in LCTE that target proteins responsible for cough and fever, which are early symptoms of SARS-CoV-2 infection. Compounds that have been shown to target the β2-adrenoceptors are believed to relieve cough, whilst compounds that target the prostaglandins are believed to relieve fever.

It is important to note that herbal remedies are heavily criticised due to their lack of efficacy and safety. So, although these results sound promising, a series of clinical trials would need to be conducted with these compounds before they can be approved for use in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA). Also, the large number of active ingredients may lead to many undesirable side effects, resulting in the soup being an unappealing treatment. Despite doubts about its safety and efficacy, LCTE soup may contain compounds useful for the treatment of COVID-19.

ABOUT THE AUTHOR

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

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